Antiviral and Antimicrobial Coatings Based on Functionalized Nanomaterials

Design, Applications, and Devices

Edited by
Shahid Ul Islam
Chaudhery Mustansar Hussain
Sudheesh K. Shukla

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DESIGN, APPLICATIONS, AND DEVICES

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Preface

In recent years, the emergence and spread of infectious diseases have become a major global concern. From the Ebola virus outbreak to the COVID-19 pandemic, the world has witnessed the devastating impacts of viral and microbial infections on public health and the economy. Despite significant progress in developing vaccines and treatments, the need for effective preventive measures remains critical. One promising approach is the use of antiviral and antimicrobial coatings based on functionalized nanomaterials.

Nanotechnology has emerged as a powerful tool in the fight against infectious diseases. Nanomaterials have unique physical and chemical properties that make them effective in preventing the spread of viruses and bacteria. By modifying their surfaces with specific functional groups, nanomaterials can be designed to selectively target and destroy pathogens, without harming human cells.

The development of antiviral and antimicrobial coatings based on functionalized nanomaterials has gained significant attention in recent years. These coatings can be applied to various surfaces, including medical devices, personal protective equipment, and public spaces, to prevent the spread of infectious diseases. The use of such coatings has the potential to significantly reduce the transmission of viral and microbial infections, particularly in high-risk environments.

Antiviral and Antimicrobial Coatings based on Functionalized Nanomaterials provides a comprehensive overview of the latest research and developments in the field of antiviral and antimicrobial coatings based on functionalized nanomaterials. It covers a wide range of topics, including the synthesis and characterization of functionalized nanomaterials, their mechanisms of action against viral and microbial pathogens, and their applications in various settings. The book also discusses the challenges and opportunities associated with the use of these coatings, including their safety, efficacy, and regulatory issues.

This book should be very useful for researchers, academicians, engineers, and healthcare professionals working in the fields of nanotechnology, materials science, microbiology, and public health. It provides a valuable resource for those interested in the development and application of antimicrobial coatings based on functionalized nanomaterials, with the

ultimate goal of preventing the spread of infectious diseases and improving global health.

We would like to thank all the authors who have contributed their valuable insights and expertise to this book. Their hard work, dedication, and commitment to producing high-quality content have been instrumental in the completion of this project. We would also like to thank all the reviewers who have provided constructive feedback and suggestions, which have greatly improved the overall quality of the book. We are particularly grateful to the project editors, production editors, and copy editors for their tireless efforts in managing the manuscript, ensuring that it meets the highest standards of quality, accuracy, and readability.

Shahid ul Islam

SECTION 1

Functionalized nanoparticles-based antimicrobial and antiviral coatings: Design and development

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CHAPTER 1

Recent advances in the designs and development of functionalized nanoparticles

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1. Introduction

Surface-functionalized nanoparticles have flourished greatly due to recent research through their applications in the healthcare sector and many other areas of daily life. The rise of drug resistance among several bacterial species poses a serious threat which can be tackled using the antimicrobial properties of functionalized nanoparticles (FNPs). Improved uptake efficiency and superior biocompatibility of FNPs will enable them to play a significant role in future medicines. Surface functionalization includes thiol/amino thiol conjugation, biofunctionalization by attaching of amino acid groups, attaching of polyethylene glycols to surfaces, etc. Other than for their antimicrobial properties, FNPs have been used for bio-imaging and biosensing. Nanoparticles-based drug-delivery platforms use surface functionalization to provide a cell-specific delivery method of drugs using glycosidic moieties or small molecules such as folate. From the surface functionalization of zinc nanoparticles with bovine serum albumin for enhancing biocompatibility to boosting the antimicrobial effect of silver nanoparticles by polydomanine, nanotechnology has achieved innumerable milestones. Apart from these developments of surface-modified nanoparticles, they have been provided an efficient treatment strategy for cancer. The goal of new advances in nanotechnology is to enable people to switch to a healthier lifestyle with better prevention to diseases. Interdisciplinary research of food technology and nanotechnology has attained great progress by developing new food packaging methods to enhance food protection and minimize spoilage. With the increase in industrialization, water pollution has become an integral problem. FNPs have been used in water treatment for the removal of toxic industrial pollutants. Surface functionalization of nanoparticles can be seen as a boon to modern science which

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has opened a range of possibilities. This chapter focuses on the recent advances of surface-functionalized nanoparticles and their multitudinous applications.

2. What is surface functionalization of nanoparticles?

Nanoparticles display distinct physical properties varying across different size ranges with several biomolecular and cellular systems. These features make them attractive materials for therapeutic and diagnostic applications. Surface functionalization is the act of modifying the surface of nanoparticles by means of conjugation with chemicals or biomolecules like peptides, antibodies, etc., to enhance the properties and targeted delivery [1]. For surface functionalization various organic and inorganic materials are assembled in the nanoscale, harnessing both covalent and noncovalent interactions [2]. Surface functionalization is immensely important for the application of nanoparticles in biological systems, for example functionalization of nanoparticles with cellular receptors for targeted drug delivery [3]. Surface-functionalized nanoparticles are being utilized for imaging, sensing, and delivery applications [4].

3. Approaches for the synthesis of nanoparticles

3.1 Physical methods

In order to reach to the nanoscale of a material, two approaches can be adopted: the top-down approach, in which larger particles are broken down into smaller pieces, and the bottom-up approach, in which materials from an atomic level are clustered to produce materials in the nanoscale range [5]. Nanoparticle synthesis is achieved using physical, chemical, or biological methods. Physical methods usually employ the top-down approach, while chemical and biological methods are usually bottom-up. Top-down methods involve the fabrication of larger materials to produce smaller materials and ultimately to produce nanoscale particles [6].

3.1.1 Milling techniques

High-energy ball milling has been widely used for the synthesis of different nanomaterials in top-down techniques, including mechanical milling (MM) [7]. In MM a powder charge (usually a blend of elements) is fed into a high-energy mill, together with a suitable milling medium. The goal of milling is

to break down the powder charge material into nanoparticles and blend the particles in a separate phase [8]. The main event in MM is the collision of ball–powder–ball. The powder material is placed between the collision balls and, with the rapid movement of the balls, the particles are fragmented into defined structures [7].

3.1.2 Anodization

Anodic oxidation, also known as anodization, is an electrochemical process in which a metal is polarized anodically in an electrochemical cell to generate an oxide layer on a metal substrate [9]. Ghafar Ali et al. reported the synthesis of TiO_2 nanoparticles on carrying out the electrochemical anodization of titanium wire. The process involved a cathode made of platinum plate and an anode of Ti wire. The electrolyte used for anodization was 1M KCl aqueous solution and ethylene glycol mixed with NH_4F and de-ionized water. On application of a voltage difference of 12–15 V, NP synthesis occurred at the anode. The NPs were recovered by centrifugation and annealed at 450°C for 2 h. After 2 h heating at a rate of 3°C min^{-1}, the NPs were cooled down to room temperature. Characterization of NPs was done using ultra-high-resolution FESEM and high-resolution TEM [10].

3.1.3 Laser ablation

In the laser ablation method, a sheet of silver immersed in aqueous solution or surfactant is irradiated by pulsed laser [11]. Mafuné et al. reported the synthesis of AgNPs by ablation of a silver sheet by laser dipping it in an aqueous SDS solution. The intensity of the laser governs the size distribution of NPs. A higher intensity of laser produces a larger size of NPs. The mode used for laser ablation influences the shapes of NPs formed, for instance, the formation of spherical NPs follows a vapor-liquid-crystal condensation process [12].

3.1.4 Vacuum sputtering

Vacuum sputtering makes use of two electrodes held in a vacuum chamber and applied with a potential difference. When an inert gas is released in the chamber, it becomes ionized. The metal target is bombarded with argon plasma, as a result of which atomic clusters accelerate from the target and are deposited on the surface or in the liquid medium [13]. The vacuum sputtering method is a relatively new method of NP synthesis, the research

of which was pioneered by the Kuwabata group. On direct sputtering on the surface of 1-ethyl-3- methylimidazolium tetrafluoroborate, AuNPs with 5.5 nm diameter and deviation of 0.9 nm were produced [14].

3.2 Chemical synthesis

Most of the chemical methods of NP synthesis adopt the bottom-up approach. This involves reducing agents such as sodium citrate, ascorbate, Tollen's reagent, hydrazine, ammonium formate, and gallic acid, which reduce silver salts to silver ions [15–17]. Capping and stabilizing agents like alkanethiols, alkylamines, and long-chain carboxylic acids stabilize the silver nanoparticles [18]. Teodoro et al. produced spherical 15 nm AgNPs by adding the reducing agent sodium borohydride to a boiling solution of aqueous silver nitrate [19]. Mohamed Hasaan Hussain et al. demonstrated the formation of colloidal gold NPs with the addition of $HAuCl_4$ to a reducing agent solution of L-ascorbic acid in presence of the stabilizer, polyvinylpyrrolidone [20].

3.2.1 Sol–gel process

In this method metal alkoxide is dissolved in water or alcohol and the resulting solution is heated and stirred by hydrolysis to produce a gel. [21]. The gel is dried by various methods such as thermal drying, freeze drying, or supercritical drying to produce xerogel, cryogel, and aerogel, respectively. The final product is obtained by calcination of dried gel [22–26]. The sol–gel process is advantageous in producing uniform nanostructures at low temperature and products of high purity. Metal nano-oxides are synthesized by the sol–gel method [27–29].

3.2.2 Pyrolysis

In pyrolysis the metal precursor is burned at high temperature and pressure to produce NPs [30]. Alternatively, plasma or laser can be used for rapid evaporation due to high temperature [31].

3.2.3 Chemical vapor deposition (CVD)

Chemical vapor deposition is a popular bottom-up approach for NP synthesis. In this method, a thin film of gaseous precursor is allowed to deposit on a substrate [32]. Although the process produces NPs with a high degree of purity and uniform size, the requirement for special equipment and production of toxic by-products reduces the overall value of this method [33].

3.2.4 Spinning

In the process of spinning, the precursor molecule is fused by spinning and then precipitated. The NPs produced are collected and dried to be stored for later use. Various factors such as disc surface, rotation speed, liquid flow rate, and location of the disc influence the characteristics of the NPs formed. The NPs synthesized by this method are in the range of 3–12 nm. For spinning, a spinning disc reactor that constitutes a rotating disc is used to synthesize NPs. Physical parameters such as temperature can be manually controlled [34].

3.2.5 Atomic/molecular condensation

Many scientists are interested in the gas phase condensation (GPC) approach for plasma creation of metal nanoparticles because of the enormous potential it offers. These methods are particularly appealing for large-scale production and applications in high-tech industries, where keeping contamination levels to a minimum level is essential [35–40]. In this process the precursor material is evaporated under an inert environment which also acts as a cooling agent for condensation of the material forming nanoscale particles.

3.3 Biological methods

The biological synthesis of nanoparticles is also termed as "green synthesis." Green synthesis is preferred over other methods of nanoparticle synthesis as it is more reliable, eco-friendly, and sustainable. Biological synthesis adopts a bottom-up approach [41]. Biological synthesis using plant materials is more feasible and hence preferred over other materials like fungi, bacteria, etc. The nanoparticles obtained from biological/green synthesis are called biogenic nanoparticles. The phytochemicals obtained from plant extracts like ketones, flavonoids, terpenoids, phenols, carboxylic acids, aldehydes, etc. are capable of reducing metal salts into their corresponding metal nanoparticles [42]. The fundamental properties of these nanomaterials have been studied for applications in biomedical diagnostics, antimicrobials, molecular sensing, biological system labeling optical imaging, and catalysis [43]. The physical and chemical synthesis methods adopted for nanoparticle synthesis result in the release of high radiation, highly toxic reductants, and stabilizing agents, which are harmful to humans and aquatic life. Metal NPs synthesized by green synthesis are safer to use. Green synthesis is a single-step eco-friendly bio-reduction approach that requires relatively little energy to initiate. This method of reduction is also cost effective [44–50].

3.3.1 Synthesis from bacteria

Based on research it has been found that these cells play a key role in the conversion of heavy metals to metallic NPs. The synthesis of metallic NPs is facilitated by the presence of multiple types of interacting pathways within bacterial cells [51].

Green synthesis mediated by microorganisms has gained popularity among the many biological sources for the green synthesis of metal nanopaticles (MtNPs) due to their rapid growth rate, ease of cultivation, and capacity to grow under ambient temperature, pH, and pressure conditions [52].

Metal nanoparticle synthesis from microorganisms offers various advantages including cost-effectiveness, ecological sustainability, nontoxicity, and cleaner alternative. The nanoparticles synthesized using this method show a wide range of sizes, shapes, physicochemical properties, and compositions [53,54]. However, the main problem with this method is of the requirement for complex steps including microbial sampling, isolation of microbes, culturing, and their storage. Furthermore, the necessity for downstream processing for the recovery of MtNPs produced by this approach makes it cumbersome [55].

The biosynthesis of MtNPs in microorganisms can be accomplished by capturing target metal ions from the surrounding environment and converting them into an elemental form through an enzyme reduction pathway [52]. The microbes living in metal-rich habitats can tolerate the metals due to the presence of intracellular and extracellular proteins for their chelation and uptake. As a result, this method could prove to be a promising strategy for the production of MtNPs since it mimics the natural biomineralization process [56]. Essam K. F. Elbeshehy et al. synthesized silver nanoparticles from a new isolate of *Bacillus* spp. by adding silver nitrate to the bacterial culture. The pH used for the synthesis was 7.5. On incubating the flask in an orbital shaker for 72 h in dark, at 25°C under 120 rpm agitation, AgNPs were synthesized [57]. Shiying He et al. used *Rhodopseudomonas capsulate* for the synthesis of gold nanoparticles of various sizes and shapes. The bacteria cultured in pyruvate, yeast extract, NaCl-, NH_4Cl-, and K_2HPO_4-containing media were resuspended in aqueous $HAuCl_4$ solution. The AuNPs formed were analyzed by UV-vis spectrophotometry, TEM, and electronic diffraction [58]. To cope with pressures such as the toxicity of heavy metal ions or metals, some bacterial species have evolved the ability to use specialized defense mechanisms [59].

Some of these were shown to be able to survive and grow in high metal ion concentrations (e.g., *Pseudomonas stutzeri* and *Pseudomonas aeruginosa*) [60,61].

3.3.2 Synthesis from algae

Algae's propensities to absorb metals and reduce metal ions make them a popular contender for nanoparticle biosynthesis. They utilize both live and dead dried biomass to generate metallic nanoparticles, and hence are also called "bionanofactories" [62]. Algae are photosynthetic organisms that are classified under the kingdom Plantae. There are two broad classes of algae: microalgae and macroalgae [63]. Various species of microalgae are known to reduce metal ions. Compared to larger plants, algae are characterized as primitive tiny plants with added advantages shown in the synthesis of nanoparticles such as growth rate and nutritional requirements [64]. Algae are known for their ability to hyper-accumulate heavy metal ions and transform them into other malleable shapes [65]. Various biomolecules found in the cell walls of many seaweeds have been discovered to operate as biocatalysts in the reduction of precursor metal salts to nucleate metal and metal oxide nanoparticles [66–69]. F. Arockiya Aarthi Rajathi et al. reported the synthesis of gold nanoparticles from brown alga, *Stoechospermum marginatum*. On the addition of aqueous hydrogen tetrachloroaureate ($HAuCl_4$) to dried, powdered *S. marginatum* fronds, a change in color of the medium from brown to ruby red within 10 min was observed, indicating the synthesis of AuNPs [70]. The bioreduction of $AuCl_4$ ions in solution was authenticated by monitoring the UV-vis spectra of the solution with a UV-vis spectrophotometer over a wavelength range of 400–600 nm to obtain the absorbance peak [70]. Similarly, Perumal Balaraman et al. demonstrated the synthesis of AgNPs from marine algae *Sargassum myriocystum*. UV-vis spectroscopy analysis based on a band of surface plasmon resonance appearing at 420 nm was used to confirm the creation of AgNPs [71]. Factors like pH, temperature, illumination, incubation time, biomass, and precursor concentration affect the biosynthesis of AgNPs by algae. Despite its many advantages, algae-based silver nanoparticle manufacturing is currently limited due to a lack of knowledge regarding the actual mechanism of synthesis. To build large-scale bioreactors for commercial-level production, more research is needed to tackle problems including kinetics, yield, and cell survival [72].

3.3.3 Synthesis from fungi

The use of fungi as reducing and stabilizing agents in the biogenic synthesis of silver nanoparticles is appealing because of the huge amount of proteins produced, excellent yields, ease of handling, and residues with low toxicity [73]. In addition, the extracellular proteins produced by fungi help in the stability of nanoparticles [74–76]. Fungi mycelial mass is more resistant to agitation and pressure than that of plants, making it a more preferred material for large-scale synthesis [77]. Fungal metabolism is easy to manipulate by adjusting temperature, pH, quantity of biomass, and incubation time, helping to obtain the desired size and morphology of the nanoparticles [78].

Biosynthesis of nanoparticles using fungi can be achieved through intracellular or extracellular mechanisms. In intracellular synthesis, the metal precursor is introduced to the mycelial culture and internalized in the cell. As a result, after the synthesis, the nanoparticles must be extracted using downstream processing by chemical treatment, centrifugation, and filtration to disrupt the fungal cell and release the nanoparticles [79–81]. In contrast, extracellular synthesis involves the addition of a metal precursor to aqueous filtrate of fungal biomolecules. The nanoparticles are obtained in the dispersion. This method is widely used as downstream processing is not very complex [82–85].

Absar Ahmad et al. synthesized AgNPs by an extracellular method using the fungus *Fusarium oxysporum*. *F. oxysporum* biomass was added to aqueous $AgNO_3$ and incubated in dark for 24 h. Small reaction samples were periodically extracted and analyzed by UV-vis and fluorescent spectroscopy. The excitation wavelength of 260 nm was selected for maximum optical transition, as shown by Trp and Tyr residues of fungal proteins. The formation of silver nanoparticles was indicated by a change in the color of the medium from pale yellow to brown [86].

Molnar et al. reported the synthesis of AuNPs of different sizes (6–40 nm) by three different methods of nanoparticle biosynthesis [81]. In the first method, the supernatant containing extracellular proteins and other biomolecules is used for the synthesis of AuNPs [87,88]. In the second method, AuNPs are synthesized intracellularly and recovered by disruption of the fungal cell [89,90]. In the final method, the fungal mycelia is suspended in aqueous extract and the aqueous extract is used for the biosynthesis of AuNPs [91,92]. Fungi-derived chemical compounds can be used to synthesize AuNPs; however, caution should be exercised when processing mycelia further, since the effect of the growing conditions can contribute to the formation of NPs [81].

3.3.4 Synthesis from plants

Chemical and physical methods of NP synthesis are not eco-friendly, and also are expensive and hazardous. Hence researchers have been paying increased attention toward other ecologically sustainable alternatives. Green synthesis via plants comes as a remedy to these problems. Although extensive research has been conducted on the assessment and testing of plants for metal NP synthesis, the principles governing the synthesis of NPs remain rather underexplored [93,94].

AgNPs can be synthesized from *Salacia chinensis* barks, leaf extracts of *Semecarpus anacardium*, *Brassica rapa*, *Glochidion lanceolarium*, *Bridelia retusa*, and *Enicostemma axillare* and *Cannabis sativa* extracts [95–98]. The secondary metabolites produced by plants like polyphenols, terpenoids, steroids, tannins, and alkaloids may be responsible for the reduction of $AgNO_3$ to AgNPs [95,99,100]. Major research works have explored the ex vivo synthesis of NPs using plants. Alternatively, *Brassica juncea*, *Medicago sativa*, and *Helianthus annuus* have been used for the in vivo synthesis of ZnNPs, NiNPs, CoNPs, and CuNPs [101].

Md. Mahidul Islam Masum et al. used *Phyllanuthus emblica* fruit extract to synthesize silver nanoparticles. The fruit extract of *P. emblica* was added to an aqueous solution of $AgNO_3$ and boiled for 20 min. The mixture was incubated at room temperature. A change in color of the mixture to dark brown indicated the reduction of Ag ions. The AgNPs were collected by centrifugation at 10,000 rpm for 10 min. The optimum volume of fruit extract for synthesis of AgNPs was set at 15 mL. Further characterization of the NPs was done by Fourier Transformed Infrared (FTIR), X-ray Diffraction (XRD), Transmission electron microscopy (TEM), Scanning electron microscopy (SEM), and Energy dispersive X-ray (EDX) spectroscopy [102].

AuNP synthesis was reported by Alaa A. A. Aljabali et al. from leaf extract of *Ziziphus*. A mixture of 5 mL plant extract and 1 mM aqueous $HAuCl_4$ was prepared and boiled for 5 min. UV-vis spectroscopy was used to detect the reduction of $AuCl_4$ [103]. Recent studies have shown that apart from the nature of the plant extract and concentration of bioactive compound, factors like temperature, pH, and electrochemical potential also affect the process of reduction of NPs [104].

Plant-mediated synthesis of metal nanoparticles offers a number of advantages over chemical, physical, and microbiological approaches, including the fact that it is a fast, reproducible, eco-friendly, and economical procedure that can be scaled up to industrial levels [105–107].

Although the concept of using living plants is ground-breaking, purifying the intracellularly generated nanoparticles has proven to be a tough undertaking [108]. Hence, the extracellular synthesis of NPs mediated by plants is alternatively used [109]. The extracellular approach of nanoparticle synthesis is preferable, not only because of the ease of purification, but also because of the higher production rate [110]. Although downstream purification procedures are not required for extraction, centrifugation or filtration are commonly used to purify nanoparticles after the one-step production technique [92]. Different methods employed for chemical synthesis and green synthesis of NPs through the bottom-up approach have been summarized in Fig. 1.1.

4. Advances in functionalized silver nanoparticles

Silver nanoparticles (AgNPs) have been reported to have potent antibacterial effects. Researchers have claimed that AgNPs induce ROS generation

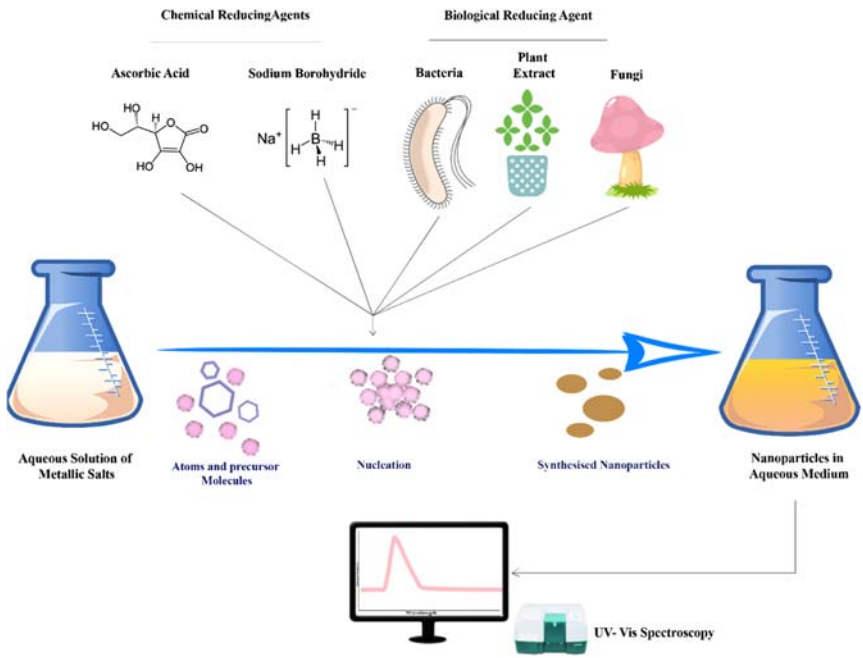

Figure 1.1 *Methods for synthesis of nanoparticles:* Ascorbic acid and sodium borohydride constitute the chemical reducing agent. Green synthesis of NPs can be obtained by using bacteria, plants, and fungi as reducing agents.

and alter bacterial membrane permeability, making the cellular contents leak out [111]. Functionalization of silver nanoparticles with antibiotics to study the antibacterial efficacy has been studied previously. Kanamycin and tetracycline adsorbed to AgNPs have been found to kill *B. subtilis* and *P. fluorescens*. Daptomycin-conjugated silver nanoparticles cause DNA damage in *S. aureus* and disrupt cell membrane with potent antibacterial efficacy [112,113]. Synergy in antimicrobial activity has been found in conjugating antimicrobial peptides to AgNPs. Several antimicrobial peptides like porcine protegrin-1, hen egg-white lysozyme, salmon protamine, or calf thymus histones, bovine indolicidin, conjugated to AgNPs have been proven to amplify the antimicrobial reaction with a lower minimun inhibitory concentration (MIC) value of conjugates in comparison to unconjugated AgNPs. The formation of stable AMP—AgNP complexes enables them to attack the bacterial cells with a higher local concentration [114]. Inhibition of biofilm formation has been accomplished by silver nanoparticles functionalized with cyclic peptide bacitracin and a natural plant product, namely isothiocyanate, against *P. aeruginosa*, *S. aureus*, and *B. subtilis* [115]. The synthesis of mupirocin-adsorbed silver nanoparticles and their efficacy against *S. aureus* has been assessed. Mupirocin is an antibacterial compound commonly used in ointments. The synthesis of AgNPs was carried was using trisodium citrate tannic acid, para amino salicylic acid, and sodium borohydride as reducing agents. The nanoparticles showed synergetic antibacterial properties [116]. Silver nanoparticles functionalized with citrate mediate antibacterial activity and regulate silver release. Such nanoparticles were effective against *E. coli* by excessive ROS production and an increase in the NAD^+:NADH ratio [117]. The synthesis of borohydride-reduced silver nanoparticles stabilized with cellulose whiskers obtained from common white cotton resulted in the formation of spherical nanoparticles with high homogeneity in size and shape. Owing to these factors, such nanoparticles possessed distinct antibacterial activity against *S. aureus* and *E. coli* resulting in MICs of 7.1 and 14.2 ppm for *E. coli* and *S. aureus*, respectively [118]. Overusage of silver nanoparticles can confer resistance to the treatment, thus methods have been developed to interfere with the quorum sensing and inhibit biofilm formation. Endolichenic fungus-derived anti-QS chrysophanol-functionalized AgNPs could inhibit *Pseudomonas aeruginosa* and *E. coli* adhesion and colonization of urinary catheters far better than citrate-capped AgNPs by inhibiting quorum sensing [119]. Biosensing applications of AgNPs include sensing of L-cysteine in milk using ionic liquid

functionalized AgNP probes by a visible color change and shift of the adsorption band from 395 to 560 nm [120]. Another colorimetry-based detection mechanism includes sensing of thiram pesticide in water. Several capping agents were evaluated for functionalization of AgNPs, among them amine-functionalized NPs showed higher sensitivity toward thiram pesticide [121]. Surface-functionalized silver has been actively used in cancer therapeutics research. Chemotherapeutic drugs in cancer treatment often suffer due to a low uptake rate in the target cells. These issues can be solved with nano-conjugation approaches. Silver nanoparticles conjugated to hyaluronic acid engineered to target CD44 receptor showed a good response by arresting cell cycles at the G0/G1 phase when loaded with paclitaxel [122]. Methotrexate-bound AgNPs obtained by sodium borohydride and citrate as reducing agents exhibited a lower IC50 value, ranging from 88, 38, and 23 μg/mL at 12, 24, and 48 h, in contrast to free methotrexate where values ranging from 1051, 169, and 70 μg/mL were obtained in colorectal cancer and lung carcinoma cell lines. Besides this, methotrexate-bound AgNPs showed lower toxicity than free methotrexate [123]. Reports regarding *Azadirachta indica* reduced graphene-oxide AgNPs which were functionalized with polyethylene glycol to increase the circulation time in the bloodstream and coupled with doxorubicin to study its efficacy against cancer cell lines. These nano-conjugates showed a higher drug release potential in acidic pH, which could have a phenomenal effect in the acidic tumor microenvironment and less cytotoxicity in normal HaCaT keratinocyte cell lines [124].

5. Recent advances in functionalized gold nanoparticles

Gold nanoparticles (AuNPs) ranging in diameter from 1 to 100 nm have distinct antibacterial properties. Gold nanoparticles can disrupt the binding of tRNA to ribosome and cut the ATP level by inhibiting ATP synthase, thus harnessing the antimicrobial effects [125]. In addition, gold nanoparticles have good biocompatibility and serve as excellent drug carriers [126]. Several methods have been employed in their synthesis, such as reduction of chloroauric acid with trisodium citrate which results in gold nanoparticle formation. Side by side methanol extract from medicinal plants has been used for green synthesis of gold nanoparticles. Functionalized gold nanoparticles have shown immense utility in various fields [127]. The synthesis of a nanoconjugate of *trans*-cyclooctene functionalized BSA with

gold nanoparticles has been accomplished where the complex has been functionalized by Ontruzant, a humanized IgG against HER2 antigen. The nanoconjugate was utilized for the detection of biotinylated HER2 antigen using a polystreptavidin-coated lateral flow assay where it was found that the nanoconjugate had a clear higher binding affinity in comparison to gold nanoparticle—Ontruzant complex [128]. Research has been carried out on PEGylated AuNPs functionalized with anti-CD133 antibody and tested for their efficacy against colorectal cancer cell lines. Such nanoparticles were found to be nontoxic and they could accumulate in nuclear regions. When loaded with 5' fluorouracil, the nanoconjugate could lower HCT116 cell viability in contrast to lower potency nanoconjugates synthesized without anti-CD133 [129]. Encapsulation of gold nanoparticles with RBC membrane significantly reduced their uptake by macrophages owing to membrane-bound CD47 molecules. Such nanostructures will help to develop biomimetics which require to be shielded from immune attacks [130]. Soy isoflavone genistein-loaded gold nanoparticles were prepared using 10 and 12.5 mg genistein dissolved in 5 mL DMSO which was added to 45 mL of 0.1 and 0.2 mM $HAuCl_4 \cdot 3H_2O$ with a genistein loading efficacy of 46% and 48%. Such nanoparticles were shown to confer antiproliferative effects in PC3, DU 145, and LNCaP cell lines [131]. Monodispersed β-cyclodextrin functionalized AuNPs were synthesized by chemical reduction methods which were employed for the detection of copper in water. Side by side, these nanoparticles were found to inhibit the bacterial growth which was prevalent in water [132]. PEGylated graphene oxide-coated cetyltrimethylammonium bromide (CTAB)-capped AuNPs bound with anti-*Salmonella* and *E. coli* antibodies provide a remarkable strategy to detect food pathogens by colorometric and spectroscopic methods. Such complexes were obtained by harnessing EDC-NHS chemistry for attaching antibodies. Visible colorimetric changes were obtained at up to 10^3 CFU and up to 10^2 CFU using spectrophotometry on incubating the antibody—PEG—graphene oxide-coated AuNPs with bacteria in 1:1 volume for 5 min [133]. Several previous reports have shown gold nanoparticles used for nanocoating in textiles. Self-assembled nanogold in silk fabric was shown to have antibacterial efficacy when tested against *E. coli* and *S. aureus* using turbidimetric methods [134]. A significant decrease in bacterial growth of up to 99.9% for *S. aureus* and 96% against *E. coli* was observed on AuNP soybean knitted fabrics. Such fabrics were pretreated with chitosan and showed a better antibacterial activity than untreated ones [135].

6. Recent advances in ZnO nanoparticles

ZnONPs are among the Food and Drug Administration (FDA)-approved agents to be used as food additives, unlike other nanoparticles. ZnO nanoparticles have antibacterial properties and are nontoxic in low concentrations [136]. ZnONPs generate ROS by reacting with O_2 when irradiated with light [137]. The synthesis of BSA-functionalized ZnONPs has been achieved using 2-oxo-2H-chromene-3-carboxylic acid (3-CCA). Agar disk diffusion data illustrate that these nanoparticles can inhibit the growth of *S. aureus*, *E. coli*, and *Salmonella typhimurium* as well as the fungus *Candida albicans* [138]. *Mucuna pruriens* seed extract functionalized ZnONPs yielded particles with 60 mm diameter as shown by SEM analysis. The growth kinetics data provided display a decline of *Bacillus subtilis* growth after treatment with functionalized ZnONPs [139]. A novel zinc oxide (ZnO) nanoparticle having antioxidant properties has been prepared by immobilizing caffeic acid (ca) on the surface of micro-dielectric barrier discharge (DBD) plasma-treated ZnO nanoparticles. These nanoconjugates inhibited the growth of *E.coli*, *S. aureus*, as well as a clinical isolate of MRSA. Higher inhibition was observed in Gram-positive bacteria than Gram-negative as more potent killing was observed for MRSA strains. Higher potency was observed in ZnO−Ca nanoconjugates than free ZnO [140]. ZnONPs functionalized with gallic acid displayed a two−four-fold higher antibacterial activity than unbound ZnONPs. Antibacterial assay results show that these nanoparticles are particularly targeted toward MRSA strains and more potent killing is observed than with *S. aureus* [141]. A summary of recent advancements in surface fuctionalization of Gold, Silver and ZnO Nanoparticles and their respective applications is provided in tabulated form in (Table 1.1) after the Section 7.1.2.

7. Functionalization of nanomaterial-based sensor surfaces

A biosensor consists of two components, one that is biological, and the other nonbiological or physicochemical. The biological part serves as a primary transducer while the physicochemical part serves as a signal conversion unit. The two components collectively provide the detection of an analyte of interest including drugs, hormones, toxicants, and neurotransmitters [142,143]. Receptor-based nanobiosensors are made from immobilized cells, enzymatic proteins, antibodies, nucleotides, and some artificial receptors like aptamer [144−146].

Table 1.1 Summary of recently developed surface-functionalized nanoparticles and their biomedical applications.

S. no.	Nanoparticles	Surface functionalization	Application	References
1.	Gold nanoparticles	Polyethylene glycol with biotin moieties	Targeted drug delivery, colloidal sensing system	[155]
		PEG	Increased platelet biocompatibility, anticancer agent	[129,156]
		Peptide	Diagnostics and therapeutics, biosensors, antiviral	[157–160]
		Glutathione	Detection of trace inorganic arsenic, lead	[161,162]
		Oligonucleotide	Delivery of theranostic radionuclide	[163]
		Folate	Anticancer nanomedicine	[164,165]
		Trans-cyclooctene functionalized BSA	Detection of breast cancer	[128]
		RBC membrane	Biomimetics	[130]
		β-Cyclodextrin	Detection of Cu in water	[132]
2.	Silver nanoparticles	Thiobarbituric acid or 11-mercaptoundecanoic acid	Cytotoxic effect in cancer cells	[166]

Continued

Table 1.1 Summary of recently developed surface-functionalized nanoparticles and their biomedical applications.—cont'd

S. no.	Nanoparticles	Surface functionalization	Application	References
		Glutathione	N-linked glycopeptide enrichment, antibiofilm formation and antibacterial agents, antimicrobial activity against *E. coli*	[167−169]
		PEG	Increased antithrombic and antimicrobial properties, detection of heavy metal ions	[170−172]
		Ascorbic acid	Detection of glutathione in the system	[173]
		Citrate	Antimicrobial agent	[117]
		Low-molecular-weight chitosan	Increased biocompatibility and better efficacy against meticillin-resistant *S. aureus*	[174]
		Lipoic acid	Antimicrobial activity, biocompatibility, and reduced nonspecific cytotoxicity	[172]
		Antibiotics	Antimicrobial agent	[112,113]
		Antimicrobial peptides	Antimicrobial agent	[114,115]

3.	ZnO nanoparticles	Functionalized bovine serum albumin	Antibacterial, antifungal, and anticancerous agent	[138]
		N-(trimethoxysilylpropyl) ethylenediamine triacetic acid	Biosensor	[175]
		Gallic acid	Antioxidant and antibacterial activity against meticillin-resistant *S. aureus*	[141]
		Caffeic acid	Antioxidant and antibacterial	[140]
		Polyaniline	Antimicrobial agent	[176]

7.1 Immobilization strategies for receptors

Immobilization of the biological component on the transducer surface is essential for maintenance of specificity. The immobilization strategy is selected to preserve the structure, function, and activity of the receptor biomolecule [145]. The two main strategies applied for immobilization are physical and chemical. The physical method is also reversible, while the chemical method is irreversible. The kind of strategy chosen depends on many factors such as the nature of the transducer, biosensor material, properties of the analyte, and the physico-chemical environment [147,148].

7.1.1 Physical/reversible method

In the physical method the enzymes are attached to the transducer surface without formation of a chemical bond. The forces responsible for immobilization are purely physical. The physical method of immobilization includes adsorption and entrapment.

(i) Adsorption

In physical adsorption the main forces resulting in immobilization are weak attractive forces such as van der Waals forces, weak electrostatic forces, and hydrogen bond. Immobilization by adsorption is reversible and does not affect the activity or conformation of the receptor biomolecule. There are some disadvantages to this method such as sensitivity toward change in pH and temperature, the interacting forces are weak, and storage and operational stability is poor [147,148].

(ii) Entrapment

Entrapment refers to physical trapping of receptor biomolecules within 3D matrices through either covalent or noncovalent bonds. The 3D matrices used for entrapment are activated carbon and porous ceramic materials or polydimethylsiloxane, gelatin, alginate, cellulose, acetate phthalate, modified polypropylene, photopolymer, and polyacrylamide. Entrapment can be done using electro-polymerization, sol—gel, or microencapsulation techniques. In electro-polymerization, polymerization of monomeric molecules and entrapment of the biorecognition elements in that polymer is carried out by applying electricity in the presence of an electrolyte. Polymerization occurs due to the formation of reactive radicles that ligate to each other. In the sol—gel method, a nanoporous material is used for the entrapment of receptor biomolecules. This method is advantageous in providing chemical and thermal stability, ease of synthesis, and easy encapsulation of a high concentration of receptor molecules under milder conditions. In the microencapsulation

technique, receptor biomolecules are encapsulated in semipermeable lipoidal, polymeric, or lipoproteinaceous membrane [149–152].

7.1.2 Chemical/irreversible method

In the chemical method, as the name suggests, there is the formation of a chemical bond, such as a covalent bond, between the receptor biomolecule and the surface of the transducer. This is an irreversible association. Depending on the chemical bond, this method can be either covalent binding, cross-linking, or affinity immobilization.

(i) Covalent binding

In direct covalent binding, the receptor biomolecule is covalently bonded to the inert matrix or to the transducer surface. General immobilization through covalent binding follows two typical steps, first the polymerization process and then immobilization. The immobilization of receptor biomolecules on the transducer surface occurs due to the interaction between the functional groups present in the active sites of the receptor and reactive groups present on the surface of the transducer. Covalent binding is preferred due to the added advantage of resistance to physical and chemical changes, small loss of biomolecules due to leakage, and strong bond formation between the two entities. The use of toxic and hazardous chemicals and the fact that the developed matrix cannot be reused, make this process unfavorable to use [152].

(ii) Cross-linking

In the cross-linking process, there is formation of intermolecular cross-links between the receptor and the transducer. Chen et al. demonstrated the use of the cross-linking technique for immobilization of urease enzyme. A selective membrane from polyvinyl chloride (PVC) and polyurethane was prepared. Gelatinized urease enzyme was entrapped on this membrane. For initiation, cross-linking glutaraldehyde solution was used [153].

(iii) Affinity immobilization

In the affinity immobilization technique, antigen–antibody affinity, avidin–biotin affinity, and lectin–carbohydrate affinity are exploited. The affinity between the pairs is due to noncovalent interactions which provide oriented configurations. One of the advantages of affinity immobilization is the regeneration of the matrix by denaturation and so the surface can be reused for loading of fresh receptor biomolecules [154].

8. Conclusion

In this chapter, different approaches for nanoparticle synthesis and their functionalization have been summarized. Several types of nanoparticles, such as ZnONPs, AgNPs, and AuNPs, and their enhanced effects upon functionalization have been elucidated. Apart from antimicrobial activities, their role in bio-sensing has also been discussed. Researchers have shown interest in functionalization of the nanoconjugates because of advantages such as better navigation through biological barriers, site-specificity with better localization, long-term stability, and less off-target toxicity. Functionalization of NPs with drugs has been shown to increase the potency of the applied drug, and lower IC50 values were obtained upon functionalization. Apart from harnessing the antibacterial and anticancer properties of functionalized NPs, they have been utilized for the detection of pathogens in food. In the near future, active nano-formulations of drugs, metals, and nonmetals are hoped to play a major role in healthcare, food technology, and environmental science. More research to enhance the biocompatibility of nanoparticles needs to be undertaken. The progressive trend of effective nanoparticle usage will encourage further innovation of new-generation sensing devices, drug development, and delivery systems for better on-site effects at the disease microenvironment with a higher safety profile.

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CHAPTER 2

Recent advances in the synthesis and functionalization of carbon-based functional nanomaterials

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1. Introduction

For the last two decades, the field of nanoscience and nanotechnology has grown at an exceptional speed, in turn finding applications across various fields such as information processing, biomedical science, optoelectronics, electronics, energy conversion and storage, advanced defense technologies, catalysis, and environmental science. Nanomaterials have been extensively investigated owing to their potential uses in the fields of science and technology. Nanomaterials of different sizes, various morphologies, and several compositions facilitate a large number of surface-active sites for chemical reactions and catalysis [1]. They possess distinct physicochemical properties from the bulk material, resulting in an exceptional transformation in terms of their properties and applications. To create the nanostructure, the synthesis process plays a crucial role, with a separate branch of synthetic chemistry having been devoted to the synthesis of nanomaterials. In the initial period, the focus was mainly on developing nanomaterials by adapting different physical and chemical techniques. However, extensive research has been conducted in the development of various synthesis techniques for nanomaterials over the past few decades [2]. With the support of these techniques, one can control the size, shape, composition, structure, and surface properties of nanomaterials. Subsequently, laboratories and industries have standardized the synthesis process and slowly progressed to the development of methods to scale the production of nanomaterials.

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As this field involves physics, chemistry, and materials science, various approaches to synthesizing and characterizing nanomaterials have evolved over the years, and in particular, a series of characterization tools have emerged to better understand the structure—property relationship of the synthesized nanomaterial. In addition, the structure—property relationship has been fine-tuned with the significant contribution from controlled chemical reactions. The preparation of nanoparticles can be classified into two main approaches: one is the "top-down" or physical approach, and the other is the "bottom-up" or chemical approach. Whereas, the top-down approach involves the reduction of bulk materials into smaller units until they reach a size in the nanometer range., the bottom-up approach involves the construction and growth of smaller units into nanoparticles. This can be achieved by having control over the precursor concentration, choice of a reductant, surfactant concentration, stabilizing agent, and operating conditions [3]. Nevertheless, the top-down approach helps us scale up the production of nanomaterials, whereas the bottom-up approach led to the production of self-assembled monolayers and other structures for specific applications such as device fabrication. With this background, a huge revolution has been witnessed in the field of material science, and a variety of functional nanomaterials have been developed, including graphene, quantum dots, nanowires, nanoparticles, and carbon nanotubes/nanofibers. The systematic follow-up of the structural and morphological changes of the functional nanomaterial is yet another exploration area involved in the construction of nanostructured materials [4]. A high surface-to-volume ratio is a typical characteristic of nanoparticles and is a significant contributor to their specific properties.

As the field has progressed over the last two decades, its areas of application have continued to widen. Meanwhile, the functionalized nanoparticles have attracted the attention of scientists and industrialists toward functionalized nanostructured materials and the functionalization of other materials with nanomaterials, and these have attained significant momentum rapidly. Among the nanomaterials, functional nanomaterials have been developed based on the special physical and chemical properties required for the desired commercial and industrial requisites. Future technologies rely heavily on the synthesis and characterization of novel and new functional nanomaterials with controlled crystalline phases, shapes, sizes, and porosities. Disciplines such as chemistry and materials science play a crucial role in architecting novel nanostructured materials. This involves synthesis, structural modification, characterization, surface manipulation, and device fabrication [5]. Also, functionalized metal nanoparticles, metal-

oxide nanoparticles, and carbon nanomaterials have now found numerous applications. In the context of functionalized nanomaterials, carbon derivatives have attained a special status as one of the parts of the composites used in developing functional nanomaterials. A great deal of research has been conducted in order to enhance the overall efficiency and modality of nanoparticles [6]. The functionalized nanomaterials have been prepared using types of approaches such as the top-down and bottom-up methods and different techniques, including the arc discharge, CVD, flame method, exfoliation, ball-milling, laser ablation, solvothermal, hydrothermal, microwave, pyrolysis, and template approaches. Also, for the functionalization of nanomaterials, several covalent and noncovalent functionalization strategies have been adopted such as oxidation, amination, hydroxylation, hydrogenation, halogenation, acid/base treatment, cycloaddition, diazotization, reduction, radical addition, regioselective reaction, electrostatic bindings, hydrophobic interaction, and $\pi-\pi$ interactions. The development of nanostructures is intended to support areas including micromechanical devices, optoelectronic, optical, electrical, and quantum technologies [5]. Within this scenario, the importance of the synthesis and functionalization of carbon nanomaterials for various applications has been highlighted in this chapter.

2. Graphene

Graphene is a two-dimensional (2D) hexagonal planar structure made up of a single layer of carbon atoms, despite the name graphene being commonly used for materials with stacked-layer structures. This 2D structure has unique physical and chemical properties, and due to its special features after engineering structures, graphene has gained major focus, and derivatives like graphene oxide and reduced graphene oxide have provided a wider scope in terms of its application. Graphene oxide is the oxidized form of graphene, and reduced graphene oxide is the reduced form of oxidized graphene. The oxidized form has a large number of oxygen-containing functional groups, whereas reduced graphene oxide has more defects. Graphene and its derivatives have made significant contributions to photonics, optoelectronics, and catalysis [7].

2.1 Synthesis of graphene

Graphene synthesis can be carried out by various methods that can yield materials with different physical and chemical properties, including different

lateral dimensions, layer numbers, functional groups, chemical residues, and surface charges. Among the two major classes of approaches, a wide spectrum of graphene synthesis methods has been investigated.

2.1.1 Chemical method

Typically, graphene can be synthesized via epitaxial growth and chemical vapor deposition (CVD). In the epitaxial growth method, graphene can be formed on the surface of silicon carbide (SiC) at high temperatures in a vacuum or an inert environment, and growth takes place due to the vapor pressure difference between carbon and silicon [8]. The self-organization of graphene begins with the contributor carbon from the SiC substrate after the sublimation of Si. Also, a monolayer structure can be formed by changing the vacuum to an ultra-high vacuum. The main disadvantages confronted by the epitaxial growth method are poor material quality, differences in layer thickness, and formation of a grain-like structure rather than layers. It is possible to rectify this by annealing the substrate in Si flux and in an inert atmosphere, followed by the deposition of transition metals.

Good-quality graphene with a high surface area appears to be the only option for obtaining repeatability. However, the properties like crystallinity and number of layers of the synthesized graphene depend on the precursors, temperature, catalyst, and gases. In CVD, the precursor is the hydrocarbon gas that is catalytically decomposed by applying high temperatures. During decomposition, reactive carbon radicals are generated that transform into a graphene structure. Some of the commonly used precursors are methane, ethylene, acetylene, propene, benzene, hexane, propanol, ethanol, and methanol. Apart from these gases, solid precursors such as amorphous carbon and poly(methyl methacrylate) (PMMA) can also be employed. Some of the commonly used catalysts are rhodium (Rh), cobalt (Co), nickel (Ni), and copper (Cu). The use of these metal catalysts lowers the activation energy required for precursor decomposition. On the other hand, the need for high temperature and rapid deposition can also be addressed with the help of plasma-enhanced chemical vapor deposition (PECVD), but the disadvantage of this method is that it can generate a large number of defects on the graphene surface in a plasma environment [9].

2.1.2 Physical method

Graphene is synthesized physically from graphite via mechanical or chemical exfoliation methods. The exfoliation of graphene can be carried out by simply breaking the weak van der Waals forces using adhesive tape.

The only drawback of this technique is that it is not scalable. Another simple route is ultrasonication in the presence of a solvent like N-methyl pyrrolidone (NMP) [10]. Further, the ball-milling process is the most commonly practiced mechanical exfoliation method, both in dry and wet forms. However, the problem with ball-milling and ultrasonication is the removal of unexfoliated graphite and the formation of defect sheets and amorphous carbon.

From the viewpoint of scalability, chemical exfoliation is a wonderful alternative. It generally takes place in two steps. First, oxidized graphene is produced, and second, the reduction is carried out to remove the oxygen from the graphene oxide sheets. One such pathway to synthesize graphene oxide is the Hummer's method. To exfoliate graphite, strong oxidizing agents such as potassium permanganate, sulfuric acid, and sodium nitrate are preferred. The oxidized graphene layers are separated with a simple sonication method. To obtain reduced graphene oxide, the chemical reduction process is the preferred route, where various reductants can be employed such as ascorbic acid, hydrazine, hydrohalic acid, and sodium borohydride. On the contrary, green reductants can also be used where the possibility of toxic residues can be neglected. Some of the commonly exercised green reductants are amino acids, plant extracts, microorganisms, and sugars. For example, baker's yeast containing nicotinamide adenine dinucleotide phosphate (NADPH) reduced GO as well as functionalized the rGO [11].

2.2 Functionalization of graphene

Functionalization is a vital synthesis process, as it plays a decisive role in determining the ultimate properties for desired applications. In addition, the presence of defects in the surface is yet another important requisite, as the edge atoms with defects have higher reactivity than the surface atoms [12]. Surface functionalization can be performed through two methods: covalent and noncovalent binding. Covalent functionalization is accomplished through chemical reactions, whereas noncovalent functionalization is accomplished through $\pi-\pi$ interactions and van der Waals forces.

2.2.1 Covalent functionalization

In covalent functionalization, both physical and chemical approaches can be used. The functionalization of graphene utilizing RF-CVD in the presence of a hydrogen atmosphere is one method. However, the chemical route is widely preferred by many research groups. A variety of chemical functionalization methods have been utilized so far, such as birch reduction,

hydrogenation, halogenation, radical addition, cycloaddition, diazotization, Bingel–Hirsch reaction, and regioselective reactions. In a kind of functionalization strategy, azomethine ylides were utilized for covalent functionalization similar to other forms of carbon structures like CNTs and fullerene in the same manner regardless of the surface curvature [13]. In addition, the derivatives of graphene can be functionalized with other molecules easily, as the surface of the GO has reactive groups like hydroxyl, carboxyl, and epoxy. For biological and biomedical applications, GO has been functionalized with a variety of polymer molecules such as PEG, poly(ethyleneimine), poly(acrylic acid), PVA, and poly-L-lysine (PLL).

2.2.2 Noncovalent functionalization

Electrostatic binding, π–π stacking, and hydrophobic interactions are the driving forces in noncovalent functionalization. Electrostatic binding is one of the most effective ways of functionalizing graphene-based materials, as GO possesses a negative charge. The introduction of an anticipated positively charged molecule functionalizes the GO surface. For example, polyethyleneimine (PEI) is a positively charged molecule. In this case, simple mixing of GO solution and PEI can yield GO–polyethyleneimine (PEI) complexes via electrostatic binding [14]. The sp^2 layer of graphene is hydrophobic by nature, so molecules like surfactants, polymers, and biomolecules can be used to functionalize it. For example, in the presence of a surfactant, the hydrophobic aliphatic chains of the surfactant can interact with the hydrophobic graphene, thereby exposing the hydrophilic part of the surfactant for further modifications and reactions. In a report by Assali et al., three different surfactants, namely tween 80, sodium dodecyl sulfate, and cetrimide, were used for the surface functionalization of graphene to obtain a highly stable and dispersible functionalized graphene [15]. To retain the intrinsic electronic structure of graphene by noncovalent functionalization, π–π interaction is a suitable method. The π–π interaction takes place between the aromatic rings and a few molecules to be noted are 1-pyrenebutyrate and pyrene. In one study work, pyrenebutanoic acid succinimidyl ester was used to functionalize graphene through π–π interaction [16].

In the context of the antimicrobial action, functionalized graphene nanomaterials result in the production of oxidative stress or by entrapment, structure destruction, and charge transfer [17]. In addition, the functional nanomaterials are found to have biodegradability in the presence of biological conditions and to have zero genotoxicity in humans [18]. Also, by

varying the size of the functional nanomaterials, the cytocompatibility of the functionalized graphene was enhanced, thereby facilitating tissue regeneration in stem cell therapies. In parallel, the composites of functional nanomaterials have enhanced viral inhibition capacity such as GO−AgNP nanocomposites rather than the individual nanomaterials. The graphene derivatives showed excellent antiviral action for SARS-CoV-2, feline coronavirus (FCoV), and porcine epidemic diarrhea virus (PEDV) [19]. The antiviral action of the graphene derivative in PEDV is due to deactivation by inhibition through destruction of the structure before invading the cells. Also, the fundamental affinity between the functional nanomaterial and the virus was due to the charge clouds via electrostatic interaction [20].

3. Carbon nanotubes

Carbon nanotubes are an allotrope of carbon with a hollow cylindrical shape that exhibits unique noticeable properties such as strength, stability, and dimension, opening up a plethora of applications in fields like mechatronics, environmental and biotechnology, coatings and films, medical, optics, energy storage, and electronics [21]. CNTs can be realized as rolled graphene sheets in a particular direction according to the desired chirality. CNTs are considered to be one of the strongest materials available with lightweight nature. In addition, the biocompatibility of CNTs can be enhanced by performing proper functionalization. The chemistry of CNTs involves synthesis, purification, functionalization, and dispersion.

3.1 Synthesis of CNTs

CNTs are classified into two types: single-walled carbon nanotubes (SWCNTs) and multiwalled carbon nanotubes (MWCNTs). A variety of techniques have been experimented with to produce high-quality CNTs. Among them, three techniques have been predominantly employed: arc discharge, laser ablation, and chemical vapor deposition (CVD).

3.1.1 Arc discharge

Arc discharge is one of the most commonly used methods for the production of CNTs and carbon soot (Figs. 2.1−2.3). In the arc discharge method, plasma is generated by applying direct current between two pure graphite electrodes kept at a distance of 1−3 mm to break down a gas. The method requires high temperatures for the growth of CNTs, triggered by the evaporation and condensation of catalyst and graphite over a period of a

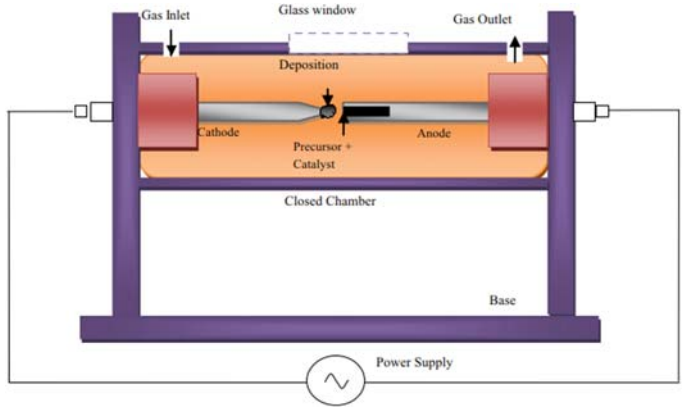

Figure 2.1 Schematic of an arc discharge setup. *(Reproduced with permission from Ref. [24].)*

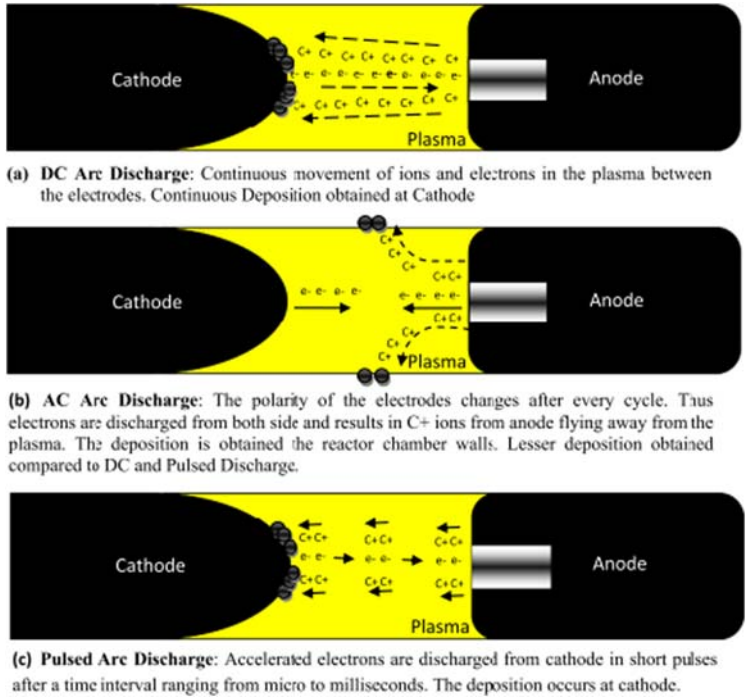

Figure 2.2 Schematics showing the formation of CNTs using different power supplies. *(Reproduced with permission from Ref. [24].)*

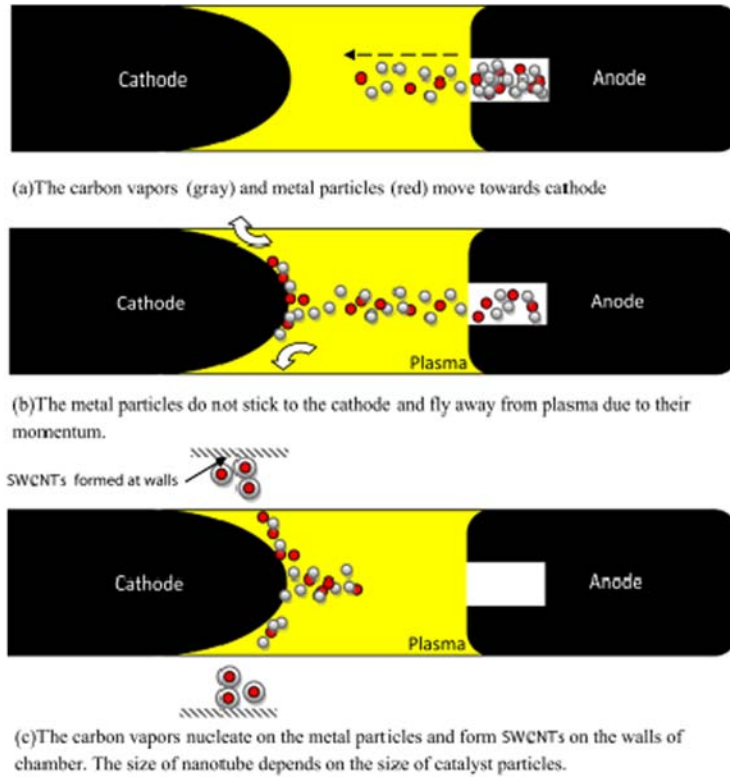

Figure 2.3 Role of catalyst in growth of CNTs. *(Reproduced with permission from Ref. [24].)*

few seconds to 10 min. The experimental parameters such as the metal concentration/catalyst, flow rate, and inert gas pressure can be optimized to obtain a better yield of CNTs. The deposited CNTs and carbon soot materials are properly collected for further purification. Hosseini et al. reported the synthesis of CNTs using Fe and Ni as catalysts and graphite electrodes. The synthesized CNTs had a length and diameter of 100−300 nm and 25−30, respectively [22]. Meanwhile, Maria et al. synthesized SWCNTs using the arc-discharge method based on low-frequency bipolar pulses. The only drawback of this method is that it requires high temperatures and noble gases [23]. The arc-discharge can proceed under hexane, He, NH_3, ethanol, or acetone with metal and alloy catalysts like Pt, Pd, Ag, Fe, Co, Ni, Fe−Ni, Co-Ni, Ni−Ti, Ni−Cu, and Co-Cu.

3.1.2 Laser ablation

One of the most frequently used and controlled methods for the synthesis of SWCNTs is laser ablation (LA). Using the LA technique, high quality with good purity and yield can be obtained. The most commonly preferred laser in the LA technique is the YAG, and synthesis takes place in presence of a catalyst, which is typically a metal or alloy from the transition metal series such as Fe, Co, Ni, Cu, Pt, Rh/Pd, Co/Cu, Co/Pt, Co/Ni, and Ni/Pt at a low concentration. The growth of CNTs takes place when a high-energy laser is focused onto the target through a window with a temperature variation range of 800−1400°C in an inert atmosphere. The high temperature and pressure help to evaporate the target rod and the catalyst. In the presence of the inert environment, the evaporated material is carried away to the collector that is close to the furnace and get deposited as CNTs. The parameters like temperature, pressure, material composition, chemical composition, and inert gas can be optimized for the production of high yield, good purity, and different structures. In 1995, an efficient synthesis method for the production of SWCNTs was developed by Smalley's group [25]. A great deal of research work has been carried out in the investigation of the influence of laser energy pulse and wavelength in producing CNTs having various diameters and different physical properties. Recently, Ismail et al. demonstrated a new pathway for synthesizing polycrystalline MWCNTs in the absence of a catalyst material [26].

3.1.3 Chemical vapor deposition (CVD)

CVD is one of the facile techniques used predominantly for synthesizing different types of materials such as CNTs, powders, and monolithic semiconductors. A variety of CVD techniques have been developed such as radiofrequency CVD (RF-CVD), plasma-enhanced CVD (PECVD), microwave plasma CVD (MPECVD), water-assisted CVD, oxygen-assisted CVD, floating catalyst CVD (FCCVD), and hot-filament CVD (HFCVD). Compared to the other two techniques, CVD is considered as one of the most flexible techniques to synthesize CNTs with high purity and yield at low temperatures by ensuring good control over the synthesis. The growth and morphology of the CNTs depend on the type of catalyst (Fe, Co, or Ni) used, as the chemical composition and size of the metal catalyst ultimately decide the structure of CNTs. Usually, metal catalysts are used for the growth of CNTs with a nanoparticle size of <3 nm. Initially, the catalyst is loaded onto the ceramic boat inside the quartz tube and heated in the temperature range of 500−1200°C [27]. Second, the hydrocarbon source gas (CO, methane, ethane, ortho-xylene, ethylene, acetylene, or alcohols) and inert gas

(Ar, H, or N) are released onto the chamber. Due to the high temperature, the hydrocarbon precursor gets decomposed to generate active carbon atoms that start to grow as CNTs over the catalyst. Finally, the prepared CNTs are collected and sent for purification and surface morphological analysis. The experimental parameters such as the precursor concentration, the nature of the catalyst, flow rate, temperature, pressure, and reaction time can be varied to obtain CNTs of various dimensions and properties [28]. In particular, the diameter of the catalyst dictates the quality and diameter distribution of the CNTs. In addition, the hydrogen content and flow can induce surface modification via catalytic hydrogenation and influence the length and crystallinity of the CNTs. Other than hydrocarbons, waste toner powder has recently been used as a carbon source, but the problem with these conventional techniques is the poor quality of CNTs. Among the three techniques, arc discharge is a physical method, and the desired nanosized particles are also difficult to obtain with this technique. In addition, LA generates toxic by-products and is quite complicated to control the size, structure, and surface chemistry of the nanomaterials, and hence, CVD is a promising technology for the synthesis of CNTs. However, the chemical approach is comparatively better at controlling the size and shape of the nanomaterials. To lower the reaction temperature, the PECVD technique was employed, with the added advantage of producing free-standing, vertical MWCNTs/SWCNTs and nanofibers [29] (Figs. 2.4 and 2.5).

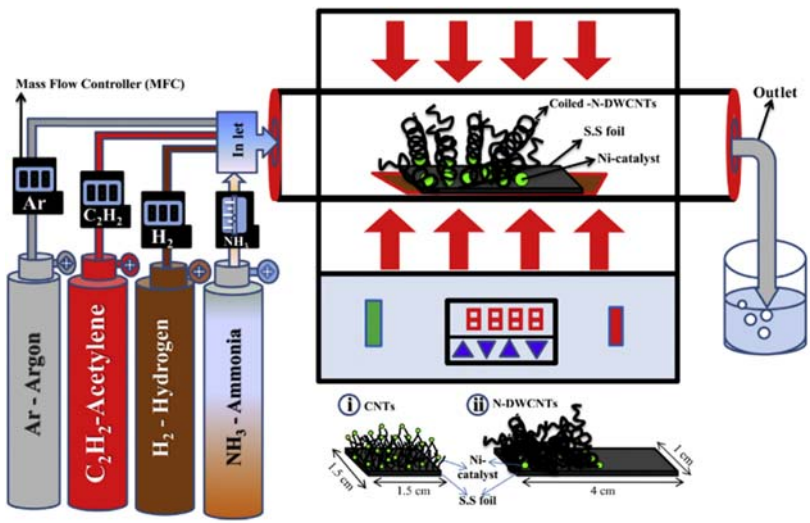

Figure 2.4 Schematic diagram of the T-CVD experimental setup. *(Reproduced with permission from Ref. [30].)*

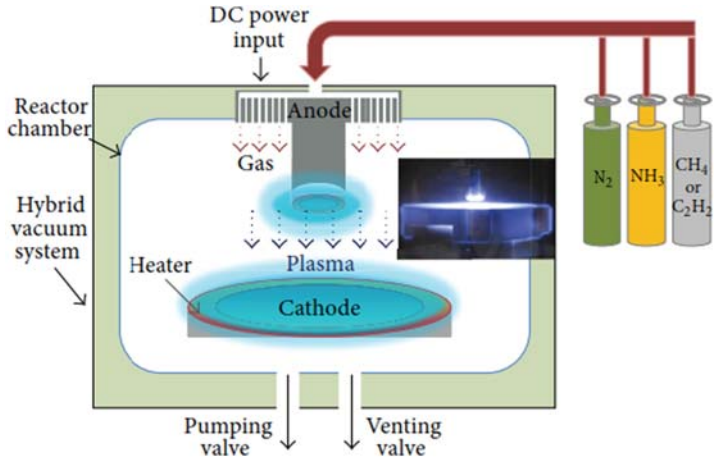

Figure 2.5 Schematic diagram of plasma enhanced chemical vapor deposition and generated plasma (inset). *(Reproduced with permission from Ref. [31].)*

3.1.4 Flame synthesis

Another scalable technique for synthesizing CNTs is flame synthesis. Through the flame technique, controlled synthesis of CNTs over required substrates can be performed using a suitable catalyst, an appropriate precursor, and temperature. During the synthesis process, the catalyst (stainless steel, Fe, Co, Ni) forms nanoparticles when exposed to flame [32]. Generally, hydrocarbon precursor materials are used for the preparation of various types of carbon materials (Fig. 2.6).

3.1.5 Green synthesis

This is a toxic-free chemical approach involving the chemical reduction process using natural products as reducing agents rather than expensive chemicals. The innovation in the green synthesis approach involves the use of green precursors (coconut oil, mixed oil) and green catalysts (plant derivatives). Apart from these, Hakim et al. used coconut shell waste to synthesize CNTs by single-step water quenching. The CNTs produced by this method had an average diameter of 123 nm [34]. Wang et al. produced hollow-structured CNTs by converting polypyrrole-co-polyaniline (PPy-co-PAni) using MnO_2 as an initiator [35] (Fig. 2.7).

3.1.6 Purification

During the synthesis of CNTs, by-products like nanocrystalline graphite, amorphous carbon, fullerenes, and residual metal catalysts are produced.

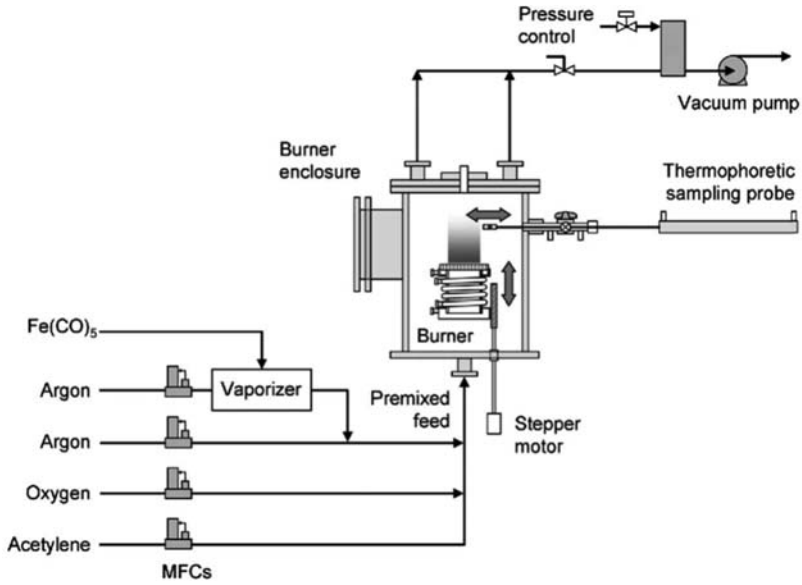

Figure 2.6 Schematic of the premixed flame burner, chamber enclosure, and associated flow metering and pressure control systems. Vertical translation of the burner stage allows sampling at a series of heights above the burner. *(Reproduced with permission from Ref. [33].)*

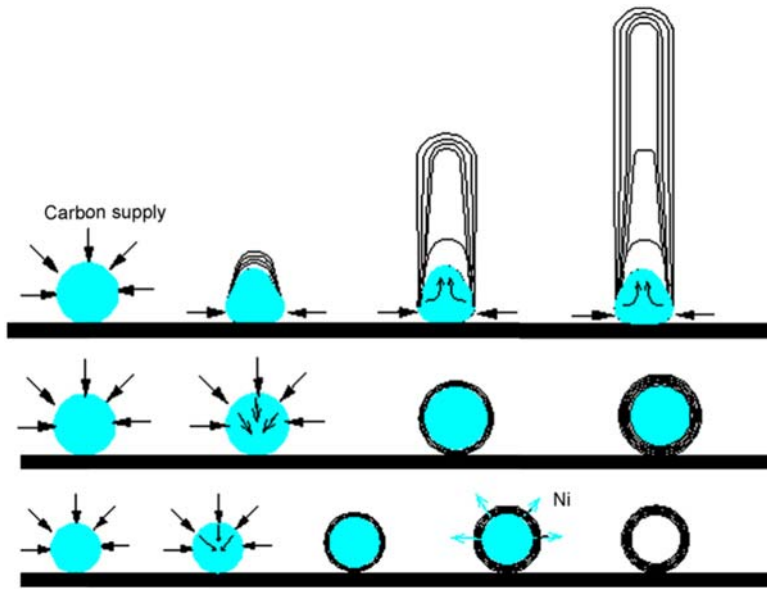

Figure 2.7 Schematic depiction of the growth mechanisms of CNTs and carbon onions. *(Reproduced with permission from Ref. [36].)*

Thus, it becomes necessary to purify the synthesized CNTs to obtain highly pure CNTs. The purification involves the separation of graphitic particles, the removal of metals by dissolution, and performing size-exclusion chromatography and microfiltration for the elimination of fullerene and amorphous carbon [37].

3.2 Functionalization of CNTs

The dispersion or solubilization of synthesized CNTs in aqueous or nonaqueous solvents is very difficult as it contains only a hydrocarbon network. Functionalization is a reliable method to improve the dispersion and solubilization of CNTs. The functionalization can be carried out through two processes: covalent and noncovalent functionalization. Covalent functionalization attach functional groups to the surface of the CNTs with the intention of improving the material's solubilization and dispersion. Nejabat et al. performed covalent functionalization of CNTs using an Fe/Mn bimetallic nanohybrid to improve the catalytic performance of the CNTs [38]. The problem with covalent functionalization is the possibility of rupture of the hexagonal network, which influences the mechanical and electrical properties of the CNTs. In the search for an alternative functionalization strategy, noncovalent functionalization was found to be a suitable method for functionalizing CNTs without damaging the hexagonal lattice, thereby restoring the material properties. Noncovalent functionalization is accomplished via forces like $\pi-\pi$ interactions and van der Waals forces. Alpatova et al. investigated the dispersion of SWCNTs using synthetic and natural dispersing agents to establish noncovalent functionalization by physisorption [39]. Meanwhile, Ghosh et al. developed a noncovalent functionalization technique using nonpolar organic solvents in which donor- and acceptor-rich sites promote noncovalent functionalization via $\pi-\pi$ interactions [40]. In addition to these, surface modification can also be performed through sidewall functionalization, producing defects, noncovalent exohedral polymers, and surfactants. Defect functionalization is the presence of functional groups like hydroxyl and carboxyl at the sidewalls and ends of the CNTs caused during the synthesis and purification processes.

3.2.1 Oxidation and amino functionalization

The purified CNTs can be subjected to acids like H_2O_2, HNO_3, and H_2SO_4 under ultrasonication or with $KMnO_4$, ozone, and reactive oxygen

plasma to attach carboxylic acid groups to the CNTs. The carboxylic acid groups present on the surface of the CNTs through prefunctionalization can be used further for amino functionalization, which is carried out by the oxidative process. Amidation can be performed using free amino groups containing molecules like thionyl chloride and ammonia. Wang et al. synthesized hydrophilic MWCNTs using the precarboxylated MWCNTs through Michael addition with acryloyl morpholine (ACMO), hydroxyethyl acrylate (HEA), and acrylamide (AM) [41]. Mallakpour et al. used microwave irradiation to functionalize amino acid molecules and carboxylic acid. In addition, direct coupling of ethylenediamine via amide formation can also be carried out [42]. Yet, another route is the reduction of the acid to hydroxymethyl for amino functionalization. Amino functionalization through the plasma method is another functionalization pathway that involves particles like radicals, electrons, and ions. These reactive particles destroy the carbon—carbon network for functionalization. This type of functionalization can be performed utilizing RF-plasma activation, CF_4 plasma treatment, or NH_3 plasma treatment. Also, by increasing the power of the plasma, the functionalization of amino groups is increased. However, it is important to retain the structural properties of the CNTs, so it is advisable to maintain the plasma at a low level. Furthermore, the functionalization of amino groups can be manipulated by varying the bias voltage, microwave power, and gas flow rate. In the noncovalent amino functionalization of CNTs, molecules like 1-pyrenebutanoic acid, 1-pyrenemethylamine, 1-aminopyrene, and 4, 4-diaminodiphenyl ether can be utilized for the surface functionalization via radical polymerization [43] (Fig. 2.8).

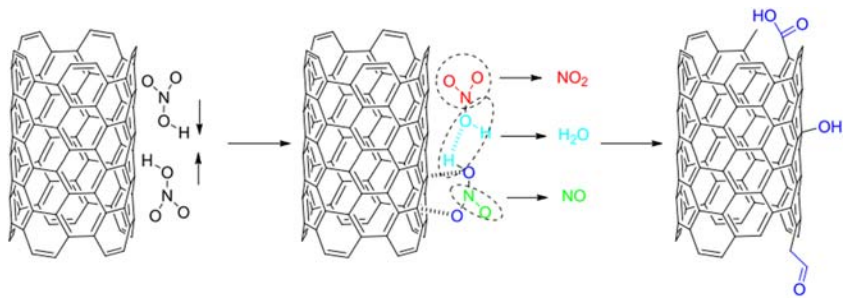

Figure 2.8 The estimated oxidation mechanism of carbon nanotubes using concentrated HNO_3. *(Reproduced with permission from Ref. [44].)*

3.2.2 Halogenation and hydrogenation

Fluorination is another functionalization strategy used for CNT functionalization as it enhances the electrical, structural, and polarization properties. The fluorination of CNTs can be done by the direct method using fluorinating agents like F_2 gas, XeF_2, and BrF_3, and other techniques use RF-plasma with CF_4. The chlorination of CNTs can proceed with oxygen/chlorine gas, $SOCl_2$, and CCl_4 under high pressures and temperatures. Functionalization of CNTs through bromination is another method in which passing bromine vapors at room temperature can perform functionalization. Similarly, solutions like CH_3Br and IBr in CCl_4 are used for the covalent functionalization of CNTs. Moradi et al. have proposed a new route for the bromination of CNTs using Br_2, N-bromosuccinimide, and NH_4 NO_3/N-bromosuccinimide under UV and thermal treatment [45]. The hydrogenation of CNTs is realized by improvements in their physical and chemical properties such as conductivity and electronic behavior [46].

3.2.3 Addition of radicals, nucleophilic carbenes, and sidewall functionalization through electrophilic addition

Radical addition is another pathway to functionalize CNTs. In one such study reported by Umek et al., the functionalization of carbon radicals generated from species like dibenzoyl peroxides (DBP) and diacyl (LP) by decomposition gets attached to the sidewalls of the CNTs [47]. In another work by Vanhorenbeke et al., radical precursors were employed for the covalent functionalization of CNTs [48]. The xanthate precursor reacts with the C—C bonds, resulting in functionalized CNTs and copper(I/II) redox systems. The use of reactive radical species is a common strategy for amino functionalization. Molecules like diamines and p-phenylenediamine give diazonium salts in the presence of nitrous acid or sodium nitrate. The instability of the diazonium salt generates radicals, which can then be functionalized on the CNT sidewalls. A solvent-free approach by Dyke et al. reported the use of sodium nitrite/acid and 4-substituted anilines for the amino functionalization of CNTs [49].

Other functionalization reactions at the side walls include nucleophilic addition of carbenes and electrophilic addition. The carbene functionalized on the SWCNTs and MWCNTs using a diaryl diazomethane derivative can be obtained through the intermediate carbene upon actinic irradiation. The electrophilic substitution was carried out using molecules like diphenyl benzyl chloride, benzene sulfonyl chloride, thiophenol, and ketone. Tagmatarchis et al. demonstrated the electrophilic addition reaction at

SWCNTs followed by a hydrolysis reaction for the preparation of hydroxyl-functionalized CNTs [50].

3.2.4 Direct sidewall functionalization and endohedral functionalization

The direct functionalization of the sidewalls of the CNTs is investigated by the change in the hybridization states due to nucleophilic or electrophilic attack and cycloaddition reactions. The repercussions of the sidewall functionalization collapse the conjugations of the CNTs. The one-electron reduction process facilitates the covalent sidewall functionalization like the transfer of one electron to benzophenone from potassium. In the same manner, sidewall functionalization can be carried out by thermal treatment. However, this can destroy the electronic structure of the CNTs. In addition, by varying the temperature and pressure of the reaction, the solubility of the material can be manipulated. Similarly, molecules like lithium alkynylides and n-hexyl were used to functionalize the sidewalls of CNTs.

The functionalization of molecules inside the CNTs is called endohedral functionalization. As the inner core of the CNT has an inner cavity, that space can be utilized to encapsulate atoms or molecules like organic molecules and fullerenes. Functionalization, on the other hand, is dependent on the inner diameter of the tube [51]. Other molecules employed for the covalent functionalization of CNTs are polyethyleneimine, cyclodextrins, epoxide, polyhedral oligomeric silsesquioxane, and polyether.

3.2.5 Surface modification with surfactants and polymers

Molecules like polymers and surfactants can be employed for the surface functionalization of CNTs. As the surfactant molecule possesses hydrophobic and hydrophilic groups, the hydrophobic ends can react with the CNTs, leaving the hydrophilic end for further functionalization, aiding in the solubilization of the CNTs. Commonly used surfactants for surface modification are Triton X-100, poly(diallyldimethylammonium) chloride (PDDA), dodecyl trimethylammonium bromide (DTAB), sodium dodecylbenzene sulfonate (SDBS), and sodium octanoate (SOCT). Similarly, polymers are employed for the noncovalent functionalization of CNTs without modifying their intrinsic properties. The functionalization proceeds via various polymerization processes and polymerized products, self-polymerization of tannins (TA), and polymerized ionic liquids [52]. Several polymers were grafted onto the CNTs, including poly(acrylic acid), sulfonated polyaniline, (1-pyrene)methyl-2-propenoate (PyMMP),

Zn-porphyrin polymer, methyl methacrylate(MMA), poly(methylene blue), poly-L-lysine, poly(urea-formaldehyde), poly(MMA-co-PyMMP), poly(3-methylthiophene), oligothiophene-terminated poly(ethylene glycol), poly(neutral red), and polypyrrole (Fig. 2.9).

The functionalized CNTs possess surface active sites that have potential applications in the field of electrochemistry for diverse analytes detection. However, it does not essentially indicate that the electroactivity is caused by the functionalized CNT tips but might be from the sensing mechanism pathway of the analyte [54]. On the contrary, the functionalized CNTs can have covalent interaction with enzymes and other biomolecules for the biorecognition of analytes. In addition, drug-conjugated CNTs and carboxylated CNTs exhibit greater antiviral capacity than unfunctionalized

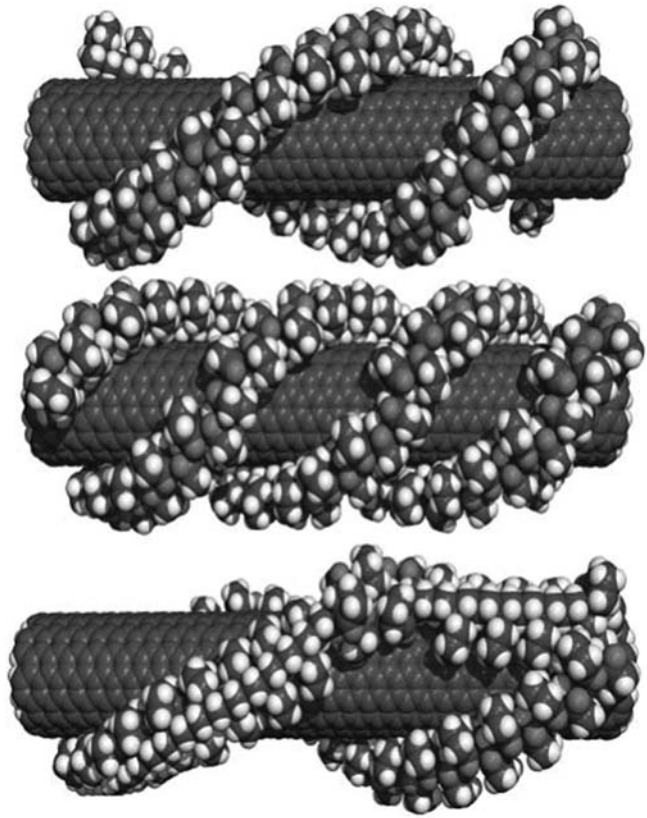

Figure 2.9 Some possible wrapping arrangements of PVP on an 8,8 SWCNT: a double helix (top) and a triple helix (middle). Backbone bond rotations can induce switchbacks, allowing multiple parallel wrapping strands to come from the same polymer chain (bottom). *(Reproduced with permission from Ref. [53].)*

CNTs [20]. The functionalized CNTs showed better bacteriostatic characteristics and the cause for the antibacterial activity was the generation of reactive oxygen species [55].

4. Nanodiamonds

Nanodiamonds (NDs) have the same sp^3 hybridized network as is present in the conventional diamond system. However, they have the crystal size in the nanometer dimension. The conventional diamond possesses tetrahedral symmetry, which provides the extraordinary properties of diamond such as hardness, compression, and high strength. However, when exposed to atmospheric oxygen, diamond gets decomposed into CO_2 and CO, which it is primarily caused by the presence of defect sites in the crystal [56]. While NDs are bulk diamond replicas, their nanoscale dimension promotes their use in a variety of fields such as electroanalysis, catalysis, energy storage, chromatography, mass spectrometry, and tribology.

4.1 Synthesis of nanodiamonds

The detonation process is a commonly used synthesis method that can be divided into three distinct routes. One way to synthesize NDs is through the use of explosives in a closed chamber to detonate carbon precursors. This involves the consumption of shock waves released during detonation as they carry high pressure and temperatures (20−100 GPa and 1700°C), which are sufficient to perform the decomposition process [57]. Another way is the transformation of carbon precursors into NDs under high pressure and temperature (7 GPa and 2000°C) with the help of suitable catalysts [58]. Lastly, an explosion is created using hexagon, cyclotrimethylene trinitramine, and trinitrotoluene in the presence of H_2O, CO_2, and N_2. This leads to the production of high temperatures and pressures (3800 K and 28 GPa) close to the carbon cluster point, where the decrease in temperature results in the formation of NDs [59]. In order to obtain high-purity NDs, CVD plasma is one of the potential synthesis approaches wherein NDs can be obtained by using ethanol as a precursor solution. In the presence of laser-induced plasma, the precursor undergoes decomposition to form NDs. Meanwhile, in typical CVD synthesis, methane and hydrogen are employed to commission NDs in which the presence of hydrogen facilitates the cleavage of hydrocarbons, helps in saturating the dangling bonds, and guides the production of pure crystals by eliminating the graphitic phase [60]. Yet another approach to ND synthesis is pulsed

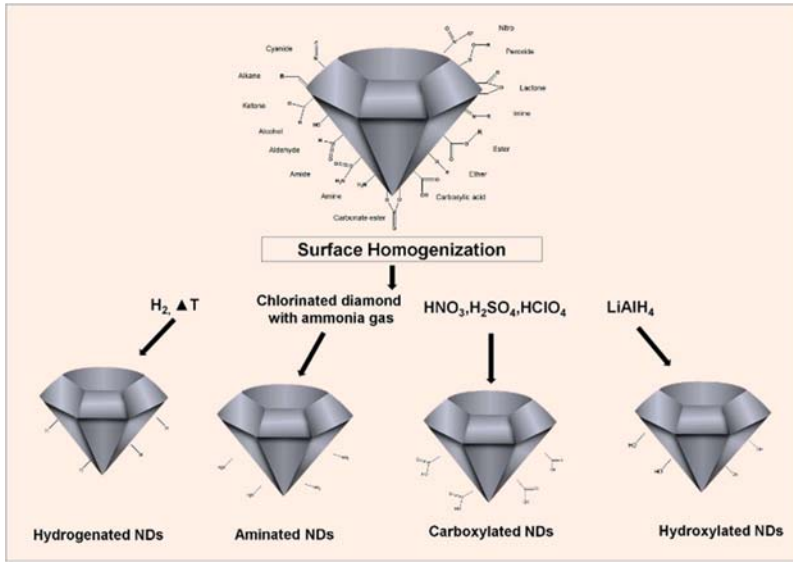

Figure 2.10 Approaches for surface homogenization of NDs. *(Reproduced with permission from Ref. [62].)*

laser deposition (PLD), which utilizes high-power lasers to cause localized vaporization for the deposition of NDs [61] (Fig. 2.10).

4.2 Functionalization of nanodiamond

The diamond's surface can be hydoxylated via mechanical and sonication in water, which introduces the hydroxyl group at the end of the radical reaction. The hydroxylation is performed using the Fenton reagent and borane [63]. On the other hand, using strong acids, supercritical water, and ozone can induce the surface oxidation of NDs. In addition, after PEGylation, the functionality-induced ends can be used to attach additional molecules to NDs [64]. The hydrogenation of NDs can be carried out using a hydrogen atmosphere, but the process is limited to films. Conversely, hydrogen plasma was employed to functionalize NDs at considerably lower temperatures [65]. Noncovalent functionalization takes place via hydrophobic or electrostatic interactions of several nonpolar and polar molecules such as polymeric compounds and DNA. The main disadvantage of noncovalent functionalization is the weak adsorption process (Figs. 2.11 and 2.12).

In terms of the application of functional NDs, the composites of functional NDs have good antimicrobial activity such as ND-supported

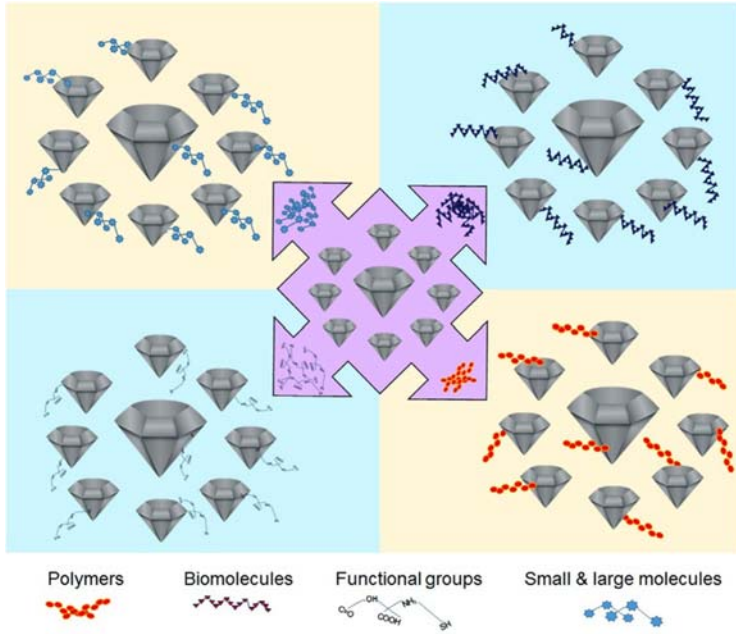

Figure 2.11 Attachment of various surface functionalization moieties on NDs. *(Reproduced with permission from Ref. [62].)*

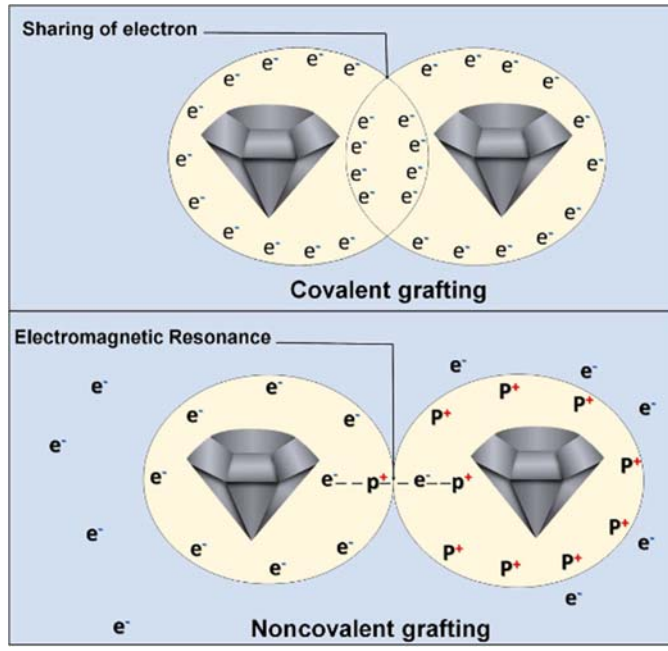

Figure 2.12 Covalent and noncovalent grafting for surface functionalization. *(Reproduced with permission from Ref. [62].)*

AgNPs conjugated with albumin [66]. The cytotoxicity of NDs is insignificant, thus the composite of this functional nanomaterial finds potential antiviral and antimicrobial applications. In addition, NDs incorporated into agar plates were excellent prohibitors of colony construction of *E. coli* by clustering around the bacteria. Also, the amine-functionalized NDs exhibited antibacterial activity against *S. aureus* [67].

5. Carbon onions

Carbon onions are basically spherical or polyhedral carbon in the nano dimension that look similar to a cluster of fullerenes. They are named "carbon onions" due to their multilayered structure. By tuning the synthesis parameters and methods, carbon onions of various phases, sizes, morphologies, and compositions can be obtained.

5.1 Synthesis of carbon onions

Carbon onions (CNOs) can be synthesized via the CVD method by the decomposition of precursors such as ammonia, boron trichloride, and acetylene in the presence of a carrier gas. In the report, CNOs were synthesized with the aid of a Ni/Al catalyst [68]. In addition, CNOs can be produced from NDs by thermal treatment. This happens in a three-stage transformation starting from the graphitic shell, followed by the diamond core, and then into CNOs. Another study highlighted the formation of CNOs from NDs at high temperatures where the purified NDs were heated between 900 and 1400°C, which suggests a three-stage transformation [69] (Fig. 2.13).

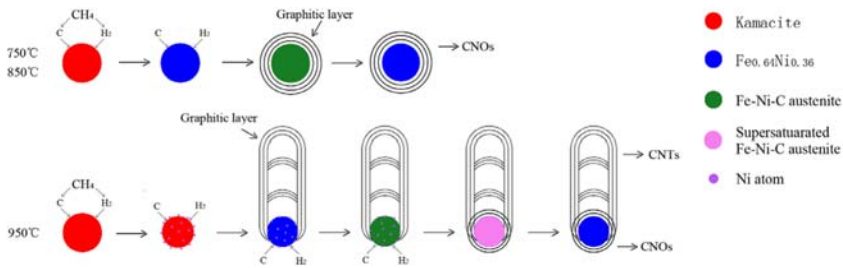

Figure 2.13 Schematic growth model of the carbon products at different temperatures. *(Reproduced with permission from Ref. [70].)*

5.2 Functionalization of carbon onions

The structure of CNOs facilitates a ready pathway for surface transformations. The oxidation of CNOs is achieved using strong acids, but the use of strong acids can damage the structure of the CNOs. A suitable alternative to accomplish functionalization without damaging the CNO structure is by using ozone or nitric acid [71]. The functionalized end of the CNOs can be further grafted with several functionalities. To be more specific, the functionalized CNOs can be used directly for amidation using 1-octadecylamine and diamine-terminated polyethylene glycol [72]. In addition, other modes of amidation of CNOs involve microwave treatment of CNOs in DMF solvent, which can be accomplished via pericyclic reactions. The noncovalent functionalization of CNOs was accomplished using surfactants and polymers, namely poly(ethylene glycol), poly(4-vinylpyridine-co-styrene), and polysorbate 20 [73] (Fig. 2.14).

CNOs are widely used as vehicles in drug delivery due to their biocompatibility and water solubility. In addition, the composites of functionalized CNOs with polymeric compounds find potential applications in the field of tissue engineering. Also, functionalized CNOs can act as a fluorescent probe for bioimaging applications. Furthermore, functionalized CNOs were utilized for sensing analytes such as glucose, human papillomavirus oncogene, and glyphosate [75].

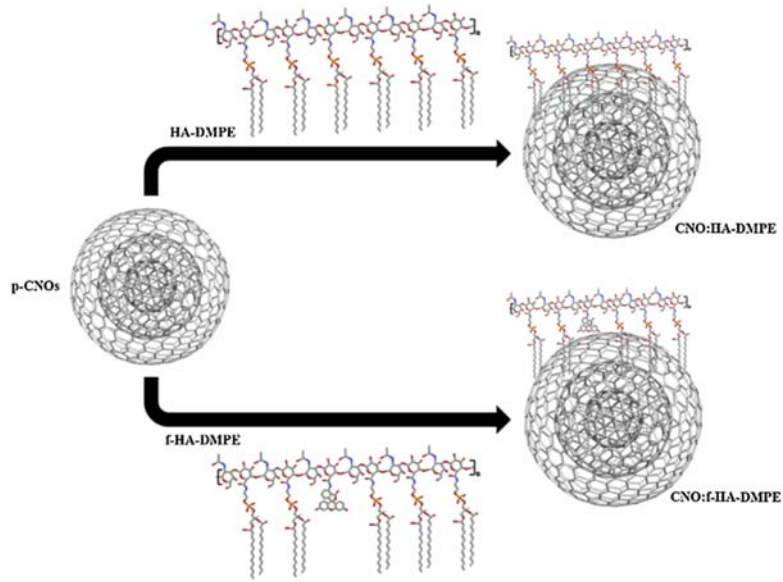

Figure 2.14 Noncovalent approach for the functionalization of p-CNOs with HA-DMPE and f-HA-DMPE conjugates. *(Reproduced with permission from Ref. [74].)*

6. Quantum dots

Due to their versatile synthesis and unique properties, carbon quantum dots (CQDs) have gained enormous interest. CQDs are composed of a carbon network with an oxygen-functionalized surface. Due to quantum confinement, CQDs in the nanometer dimension exhibit good stability and different optical and electronic properties.

6.1 Synthesis and functionalization of CQDs

The synthesis of CQDs can be carried out through physical and chemical techniques. Various methods can be adopted in top-down and bottom-up approaches, namely laser ablation, arc discharge, and acidic oxidation in physical methods by dispersion of macromolecules or breakdown of large carbon materials like graphene, graphite, and CNTs into smaller ones, and electrochemical, hydrothermal, template-approach, and microwave pyrolysis in chemical methods by carbonization and polymerization of small molecules. The surface of the CQDs can be grafted during the synthesis process under a controlled precursor concentration.

6.1.1 Arc discharge

CQDs are produced by the decomposition of carbon precursors in the presence of generated gas plasma in a closed environment between the electrodes at a highest temperature of 4000 K followed by the reorganization of generated atoms [76]. CQDs were found by accident while preparing SWCNTs via acid treatment and were first reported by Xu et al. in 2004. The obtained CQDs were found to have surface functionalities. The only disadvantage of this method is the production of large-particle-sized CQDs of different sizes, as this would greatly affect the specific surface area of CQDs.

6.1.2 Laser ablation

LA involves the irradiation of high-energy laser, e.g., an Nd:YAG laser to generate plasma under high temperature and pressure that was used to form CQDs [77]. The CQDs obtained by this method were found to have a homogeneous size distribution, excellent fluorescence properties, and good water solubility. Basically, carbon precursors dissolved or dispersed in organic solvents were utilized for the synthesis of CQDs. The choice of organic solvent plays a crucial role in determining the surface states and

photoluminescent properties of the desired CQDs. In addition, the width of the laser pulse can be tuned accordingly to enable control over the CQD size. A study reported the use of graphite flakes in organic solvents to obtain N-doped CQDs via laser treatment. In addition, the pulse laser deposition method was also used for the deposition of CQDs from polymeric compounds [78]. The advantage of the LA technique is its simplicity.

6.1.3 Microwave method

Microwave synthesis of CQDs was considered as one of the suitable techniques for large-scale production. This method produces intense energies, as microwaves possess a wavelength range of 1 m and 1 mm that can be utilized for the decomposition of carbon precursors. The advantage of this method is the production of homogeneously distributed CQDs. Moreover, the microwave technique was used in tandem with the hydrothermal method, which employed a variety of sugar precursors, to obtain water-soluble CQDs [79].

6.1.4 Solvothermal/hydrothermal synthesis

The solvothermal/hydrothermal method is considered to be one of the inexpensive environment-friendly carbonization methods. In the hydrothermal method, precursor solutions are made with organic or polymeric compounds mixed with aqueous or nonaqueous solvents. Further, the mixture is transferred and kept inside an autoclave. The relatively high temperature provides the essential energy for the formation of CQDs [79]. Some of the commonly used carbon and nitrogen source materials are chitosan, citric acid, glucose, ethylene diamine, and polyacrylamide. In the solvothermal method, the precursor materials are heated, concentrated, and extracted in organic solvents. Furthermore, the hydrothermal method is a facile technique to obtain uniformly distributed CQDs grafted with several functionalities such as nitrogen, oxygen, and sulfur.

6.1.5 Template approach

This involves the synthesis of nanosized CQDs, where templates like silicon and mesoporous surfaces are predominantly utilized and act as a nanoreactor. Initially, the precursor was subjected to calcination in the templates, and finally, the support material was etched and removed. To remove the support material strong bases and corrosive acids have been utilized and purified to obtain support-free CQDs [80] (Fig. 2.15).

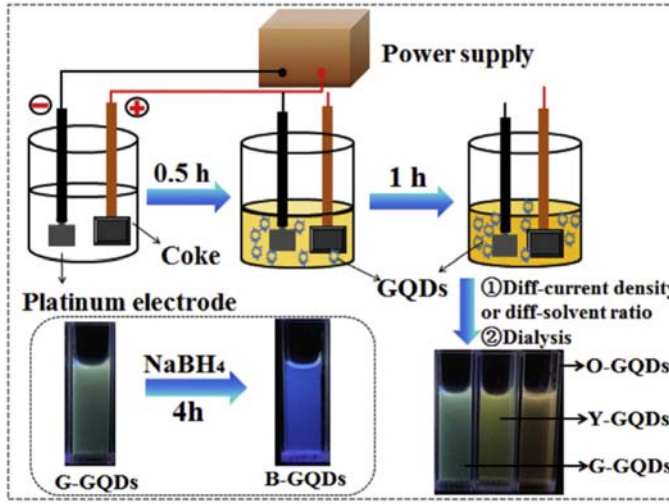

Figure 2.15 Schematic illustration of the synthetic process of multicolor CQDs from coke. *(Reproduced with permission from Ref. [81].)*

Other methods such as oxidation involve the oxidation of graphite electrodes, and ultrasonic treatment is another method used for the preparation of CQDs utilizing various precursors such as glucose and ammonia via the cavitation effect. Yet another commonly used method is the acid treatment of carbon materials like natural derivates of activated carbon. The decomposition of the carbon structures with acidic oxidation yields CQDs with terminal functionalities such as hydroxyl and carboxyl groups. The oxidized CQDs can further be treated with dimethylformamide and sodium hydrosulfide for grating nitrogen and sulfur functional groups. Oxidation can be performed in the presence of various acids like HNO_3, and H_2SO_4. In contrast, the chemical approaches are generally scalable techniques that are involved in the synthesis of CQDs, namely pyrolysis and combustion. This work highlights the use of various amino acids with glucose molecules to obtain a variety of CQDs with different morphologies, sizes, and shapes [82]. A viable synthesis method for CQDs is the electrochemical exfoliation of low-cost graphite or pencil electrodes in the presence of various electrolytes like NaOH, H_2SO_4, and NaCl [83].

The functionalization of GQDs behaved as an antibody for the selective recognition of an antigen because of the carbodiimide covalent linkages between the functionalized GQDs and the antigen [84]. Apart from the

catalysis, bioimaging, and bio/chemical sensors, the functionalized carbon dots have excellent antiviral properties. The acid-functionalized carbon dots have antiviral activity toward human coronavirus and RNA viruses. In another case, in the absence of antiretroviral agents the functionalized GQDs displayed viral inhibition toward HIV. Łoczechin et al. studied the CQDs of various sizes, charges, and functionalities with difference antiviral activities toward HCoV-229E-Luc by interacting with the surface proteins and disturbing the genomic replication [85].

7. Carbon fibers

Carbon fibers (CFs) are polycrystalline materials constructed of 90% carbon and have a graphitic structure with an anisotropic nature. The fibers can be visualized as a 2D hexagonal network, as in graphite, with irregularities from the three-dimensional graphite structure. Due to this structure, the CFs exhibit unique properties such as high electrical conductivity, good mechanical strength, high corrosion resistance, and compatibility.

7.1 Synthesis of carbon fibers

CFs were first synthesized in 1879 by Edison during attempts focused on the preparation of carbon filaments. The experiment involved the preparation of cellulose fibers, followed by carbonization and reinforcement. The current synthesis methodology uses precursors such as petroleum pitch, polyacrylonitrile (PAN), and rayon. The formation of CFs takes place by heating the precursors at high temperatures. In particular, the synthesis of CFs using PAN undergoes dehydrogenation, leading to the construction of heterocyclic rings [86]. Further, the surface functionalization of CFs can be tailored for desired applications, and PAN-involved CF synthesis provides a faster and more scalable route to obtain uniform CFs. Mostly, CFs are used as reinforcement in composite materials to improve the material's properties. Another material in use is rayon, which has good mechanical flexibility, thermal conductivity, and high purity. The only complications are those involved in the production of precursor material. The rayon fibers also show good thermal stability like the PAN fibers but with the disadvantage of a high-temperature requisite (initially 200−380°C) as carbonization via repolymerization needs 300−900°C [87]. With the aid of pitches, two different types of CFs can be produced, however the isotropic pitches show poor properties while the anisotropic pitches provide

good-quality CFs [88]. The formation of CFs proceeds by spinning, stabilization, and carbonization, where the formation of fibers is by melt spinning and stabilization by atmospheric oxidation followed by oxidation at 1500−1800°C.

7.2 Functionalization of carbon fibers

CFs are one of the key reinforcement materials as they offer high specific strength. The physical method of surface functionalization improves surface area and roughness, thereby enhancing the active sites on CFs. On the other hand, the chemical method helps in the formation of strong chemical bonds. Surface oxidation can be performed through liquid-phase, gas-phase, or chemical processes (through strong acid treatment). This facilitates the functionality-grafted CFs with functional groups like phenol, acid, lactone, ester, and quinone. Due to the repercussions of the surface acid treatment, the mechanical properties of the material have been altered, but the surface area and roughness have been found to have increased. However, the argon plasma treatment shows outstanding changes by removing the defects and reducing their size [89]. Similarly, UV/laser irradiation and high-energy gamma-irradiation exhibit surface roughening and functionalization [90].

The functionalized carbon fibers were utilized largely as electrochemical transducers because of the uniformly activated surface without damaging the structure [91]. They find wide application as an immobilization platform for biomolecules. The derivatives of carbon fibers are found to possess antimicrobial agents that can be utilized for the treatment of bacterial infections [92].

8. Fullerenes

Fullerene is one of the allotropic forms of carbon made up of C60 atoms arranged in a cage-like geometry. The football-like cage structure is basically the construction of pentagons and hexagons in alternative positions. The size of the cage differs by the number of carbon atoms among them; the smallest cage is C20. The super-aromaticity of fullerene is limited by the presence of pentagons that restrict delocalization over the entire structure. Fullerene structures makes them strong and is capable to withstand high pressures. However, the dimension of fullerene affects its reactivity and solubility, thus resulting in aggregation of the material, which can then be resolved by functionalization of the material.

8.1 Synthesis of fullerene

Fullerene can be synthesized through various methods such as pyrolysis and arc/plasma discharge/laser ablation. In the pyrolysis method, polycyclic aromatic hydrocarbons are treated at about 1000°C in an argon atmosphere or any other inert gas. At this high temperature, the molecule undergoes decomposition via hydrogen bond cleavage leading to the production of C70 and C60 fullerene [93]. Because the formation of C70 and C60 is primarily dependent on gas pressure, the gas pressure can be changed to either one, depending on the requirements. Another commonly used technique is the arc discharge method; the arc is developed when a high voltage is applied between two graphite electrodes. The discharged graphitic vapors create a plasma that then condenses into fullerene.

8.2 Functionalization of fullerene

Fullerene functionalization is facilitated by the presence of abundant double bonds in the material structure. The functionalization of fullerene can be carried out with solubilizing agents as well as by chemical functionalization. Several surface-grafting reactions can be used, including amination (methylamine, ethylenediamine, diethylamine, n-propylamine, t-butylamine, dodecylamine, 1,6-hexanediamine, l,4-butanediamine, piperidine, and N,N′-dimethylethylenediamine), hydroxylation (NaOH), cycloaddition, PEGylation, acid (strong acids), and base treatment, Diels—Alder reaction. Another notable functionalization reaction of fullerene is the Bingel reaction; this reaction aids in the selective exohedral functionalization of fullerene [94,95]. The reaction proceeds by the grafting of α-halo ketone/ester onto the fullerene structure.

This type of fullerene is highly hydrophilic, making it unsuitable for drug delivery applications. However, the derivatives of fullerene exhibit antiviral properties suitable for drug dispersion [96]. The differently manipulated fullerene derivatives showed differences in their antiviral capacity and toxicity ratio [97]. To be specific, the different fullerene derivatives possessed antiviral activity against the hepatitis C virus, the zika virus, the dengue virus, and influenza with good solubility [98,99]. Also, the fullerene derivatives have antimicrobial property by growth inhibition and membrane destruction via strong electrostatic interaction [20].

Table 2.1 Summary of recent advances in the synthesis and functionalization of functional nanomaterials.

S. No.	Material	Synthesis method	Functionalization strategy	Characteristic property	Motivation	Advances	Application	References
1.	GO	CVD	Oxygen plasma treatment	Enhanced electrochemical characteristics	To overcome the residual contamination from the metal ions and polymer support in the CVD graphene	Without the transfer process graphene layers on the SiO_2/Si substrate	Electrochemical-based glucose sensor	[100]
2.	MWCNTs modified with magnetic magnesium ferrite	NR	Sonication	NR	NR	Simple recovery step with excellent adsorbent nature	Heavy metal ion removal from wastewater	[101]
3.	CNTs-embedded nanofiber	NR	Electrospinning	High elasticity, enhanced surface area, improved active sites, good porosity and stretchability	NR	Flexible multimodal piezoresistive nanofiber-incorporated wearable textile sensor	Textile sensor	[102]
4.	MWCNTs-polyurethane and polyurethane with cellulose nanocrystals	NR	NR	Self-healing capacity, and good temperature sensitivity	To combine multifunction ability and self-healing property	Both temperature and pressure sensor	e-Skin	[103]
5.	MXene-functionalized porous graphene	NR	Nucleophilic substitution reaction	Fast heterogeneous electron transfer rate, good conductivity, and enhanced electrochemical performance	To minimize burden of chronic wounds	Multifunction smart sensor integrated on wound bandage	Chronic wound care management	[104]

6.	PEGylated-GO	NR	Plasma etching	Excellent biocompatibility, high active sites, good photothermal conversion, and stability	Targeted cytotoxic effect for cancer treatment and to improve the photothermal efficiency	Single nano-device containing both drug delivery and photothermal therapy property	Targeted drug delivery and NIR anticancer phototherapy	[105]
7.	Hyaluronic acid and chlorin e6 functionalized SWCNTs	NR	Sonication	Excellent biocompatibility, and nanocarrier ability	To increase dispersibility	Excellent anticancer activity	Photodynamic therapy for cancer	[106]
8.	Functionalized-fullerene nanoparticles	Solvent exchange method	Stirring	Better biocompatibility and large surface area	Dual-amplified sensing system	High discrimination capability	Electrochemical biosensor for cancer diagnostics	[107]
9.	CuNPs-NiNPs@ reduced-fullerene-C60	NR	Electrodeposition	Large surface area and high catalytic nature	To improve sensitivity	Analysis of vitamin D3 in pharmaceutical samples, serum, and urine	Electrochemical sensor for vitamin D3 detection	[108]
10.	Functionalized-CNO	NR	Acid reflux	Ease of manipulation, high chemical versatility, and surface area	NR	Excellent fluorescence	Blue emitting furo[2,3-c] isoquinolines	[109]
11.	Diamond with quantum defects	CVD	NR	NR	Improve molecule-number sensitivity	Femtomole sensitivity	Hyperpola rization-enhanced NMR sspectroscopy	[110]
12.	Fouling-free nanocarbon and nanodiamond	NR	NR	Low fouling property	To avoid surface fouling	Continuous assessment and high sensitivity	Electrochemical sensor for bisphenol A detection	[111]

Continued

Table 2.1 Summary of recent advances in the synthesis and functionalization of functional nanomaterials.—cont'd

S. No.	Material	Synthesis method	Functionalization strategy	Characteristic property	Motivation	Advances	Application	References
13.	N-doped GQDs	Pulsed laser ablation	NR	Enhanced short recombination lifetime	NR	High quantum yield	Potential application in bioimaging, and optoelectronics	[77]
14.	Peptide-based CNTs	NR	Shaking	Improved electrical characteristics	NR	Increase of Δ Ions	DNA detection	[112]
15.	rGO	Hummer's method	Thermal reduction	Increased DC electrical conductivity	NR	Significant influence in the sensing performance due to the pore volume, surface area, and graphitic domains	Chemiresistive gas sensor-based SO_2 detection	[113]
16.	Polyaniline modified MWCNTs	NR	Graft polymerization	High surface-to-volume ratio, good water solubility, fast charge transferability, good electron conduction, and film-forming ability	To improve the electrochromic behavior	Excellent electrochromic, and electrochemical performance	Electrochemical and electrochromic	[114]

17.	Magnetic CNTs functionalized with imidazole groups	CVD	Acid treatment	Improves the reaction speed	To fasten the reaction	Nanocatalyst can be separated, recycled, and reused without any loss in the activity	Pesticide degradation	[115]
18.	O-functionalized CNTs	NR	Acid treatment	Specific surface area, good dispersibility, and enhanced catalytic activity	To improve the catalytic activity	The surface functionalities facilitated immobilization of catalyst, along with capping the active centers and nanocatalyst size reduction.	Catalytic reduction of NO_x with NH_3	[116]
19.	Metal-based NPs=functionalized graphene hybrids	Hummers' method	Microwave treatment	Lowered the flammability of epoxy	To overcome the flammability of epoxy resins	NR	Flame retardant	[117]
20.	Graphene nanosheets functionalized with polystyrene sulfonate	NR	Free radical polymerization	Good barrier effect	To decrease defects	Improved mechanical performance and flame retardancy	Fire safety	[118]

Continued

Table 2.1 Summary of recent advances in the synthesis and functionalization of functional nanomaterials.—cont'd

S. No.	Material	Synthesis method	Functionalization strategy	Characteristic property	Motivation	Advances	Application	References
21.	Graphene/LDH phosphorus-rich triple hybrid	NR	Hydrothermal method	Interrupts the heat exchange and prevents internal combustion overflow	NR	Triple functionalization process facilitates gradual transfer of flame	Flame retardant	[119]
22.	N-, P-, Si-modified GO	NR	In-situ polymerization	Water resistant, flame retarding ability, toughness, shape memory, and self-healing ability	NR	Multifunctionalized composite	NR	[120]
23.	Tannic acid-functionalized graphene	NR	Sonication	Excellent mechanical properties	NR	Flame retardancy and smoke suppression properties	Flame retardant	[121]
24.	9,10-Dihydro-9-oxa-10-phosphaphenanthrene-10-oxide-decorated fullerene	NR	Hydrothermal method	Free radicals trapping capability	To improve flame retardancy, stability, and thermo-oxidative capacity	NR	Antioxidative and flame retardant	[122]
25.	Hyaluronic acid-carbon dot-doxorubicin	Hydro thermal method	NR	Good biocompatibility, hemocompatibility, and serum stability	NR	NR	Targeted drug delivery and breast cancer therapy	[123]

26.	Functionalized ND	Sonication	Stirring	Good biocompatibility	NR	Simultaneous functiona lization and DOX loading	pH-responsive drug delivery	[124]
27.	Isoniazid-functionalized MWCNTs	NR	Acid treatment	High efficacy and less adverse effects	To improve antibacterial activity and obtain appropriate drug dose	Low therapeutic dose and bacterial resistance	Drug delivery	[125]
28.	Silica-coated magnetic FeONPs with GO	NR	Reverse microemulsion method	High stability and saturated magnetization	To separate GO and minimize the weak magnetic force of the material	NR	Protein isolation	[126]
29.	Poly(vinyl alcohol)/GO −Ag NPs	Hummers' method	Sonication	Water resistance, tensile strength, and thermal stability	NR	High bactericidal eflect due to direct interaction with the composite	Potential application in infection prevention and wound healing	[127]
30.	PEGylated GO and Au NPs	NR	Nucleophilic substitution reaction	pH dependency and good drug-loading capacity	NR	NR	Cancer therapy	[128]

NR, Not reported.

9. Conclusion

The need and significance of functional nanomaterials in a variety of research fields are highlighted in the literature (Table 2.1). In addition to synthesis procedure, the functionalization fundamentals, the aspects and attempts that reflect the desired requirements, play a significant role in the production of engineered materials. The physicochemical properties of carbon nanomaterials determine their potential applications. Also, the systematic follow-up of the synthesis and functionalization processes aids in obtaining new or improved characteristics. Moreover, the same material synthesized or functionalized through different strategies influences the material behavior for the target application. Each functionalization strategy carries inherent advantages that affect the chemical versatility, mechanical, electrical, and structural properties of carbon nanomaterials. The importance of functional nanomaterials is purely dependent on obtaining their characteristic performance, which can be observed by manipulating their surface characteristics. This chapter has covered the overall strategies involved in the synthesis and functionalization of carbon-based functional nanomaterials that meet the ground requirements for framing new and novel methodologies. The advantages and limitations of synthesis methods and their impacts on the choice of functionalization routes are described. The development of functional nanomaterials based on the demands of the future can be anticipated, and new pathways can be created for emerging nanomaterials in the fields of material science, nanoscience, and technology. Also, multifunctional carbon nanomaterials can be explored for different applications.

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CHAPTER 3

Therapeutic antimicrobial applications of functionalized nanoparticles

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1. Introduction

Infectious diseases caused by pathogenic bacteria have always adversely impacted health care systems. Antibiotics such as penicillin, ampicillin, and vancomycin, earlier considered as magic bullets for treatments, have nowadays become out-of-date due to their lower potency against common illnesses. Also, the development of resistance against antibiotics adds to the woes of the medical fraternity [1,2]. High doses of antibiotics administered in such cases lead to systemic toxicity and other adverse effects. In this scenario, identifying new antibiotics to fight against infections not only becomes tedious, and labor- and time-consuming, but also becomes an economic burden, thus prompting the development of alternative strategies. Nowadays, with the rapid development of nanoscience and nanotechnology, a new ray of hope has been generated to use such a strategy to tackle the infectious disease risk [2,3].

Nanoparticles (NPs) provide a universal platform for therapeutic applications based on their unique physical and chemical properties that make them alternatives to traditional antibiotics. In fact, antibacterial activity exhibited by nanomaterials such as silver, gold, copper, titanium, zinc oxide, and magnesium oxide could replace the traditional antibacterial drugs owing to their property of the generation of reactive oxygen species (ROS) [4,5]. Also, the large surface-area-to-volume ratio of NPs increases their contact area with target organisms regulating cell membrane penetration, and interfering with molecular pathways. NPs also enhance the inhibitory effects of encapsulated antibiotics following their site-specific delivery. Furthermore, the morphology, size, surface charge, and stability of NPs also play a critical role in determining the antimicrobial properties of nanomaterials. These NPs are also reported to be quite successful in

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overcoming drug resistance and drug-resistant bacteria, although even for them resistance develops following repeated exposure [6,7]. Surface functionalization strategies are nowadays being employed for enhancing the antimicrobial efficacies of NPs by enabling them to better interact with microbial cells.

Engineering surface chemistry for formulating tailor-made nanomedicines has emerged as the perfect way to regulate their biological fate without compromising their in vitro and in vivo colloidal stability. This methodology has also been well implemented for cell labeling and imaging, tissue engineering, cell separation, and cell sensing [8,9]. Moreover, surface-engineered NPs having antimicrobial activities have been found to be quite effective against various diseases (Fig. 3.1). Surface-modified NPs exhibit numerous advantages, such as site-specific delivery, reduction in side effects, dose reduction, and improved therapeutic efficacy. Moreover, they can aid in improving physical and biochemical properties such as preventing aggregation, and enhancing stability and high-water solubility. Similarly, these therapeutic regimes also enhance the pharmacokinetic and pharmacodynamic profiles of the encapsulated drug [4,9]. Biomolecules such as proteins/peptides, lipids, carbohydrates, and nucleic acids can be functionalized on nanoparticle surfaces using proper procedures to enhance the antimicrobial activity of the NPs. This chapter provides an overview of such functionalized nanoformulations and assesses their effectiveness against infectious diseases in a lucid way.

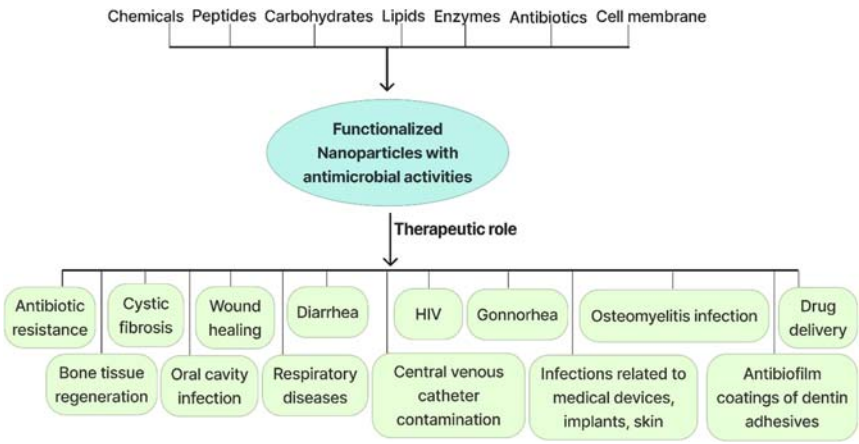

Figure 3.1 A flow diagram showing the therapeutic antimicrobial applications of functionalized nanoparticles.

2. Overview of nanoparticles showing antimicrobial activity

Nanotechnology, based on nanoscale materials, is being widely explored to open up new possibilities in the field of nanomedicine, particularly as a potential strategy for the design of novel therapeutic antimicrobial agents to control infection [4,10]. Nanomaterials, particularly NPs, possess potent antimicrobial activity because of their distinct physical and chemical properties. They use their antimicrobial property to bypass the common antibacterial resistance mechanisms of antimicrobial agents such as enzyme inactivation, decreased cell permeability, alteration of target sites/enzymes, and enhanced efflux through overexpression of efflux pumps as well as eliminating the evolution of multiple drug-resistant organisms (MDROs), thus providing a viable method to combat MDRO-related infections (Fig. 3.2) [11]. Several physicochemical properties of NPs, like ultra-small size (lesser than 100 nm), strong reactivity, low solubility, specific target-oriented actions, and large surface area-to-volume ratio, make them suitable antimicrobial weapons [11,12]. Also, because the size of natural functional units in living organisms is equal to or less than 100 nm (DNA—2 nm, microtubules—25 nm, short RNAs, and ribosomes—20 nm), make the NPs an appropriate material for use in nanomedicine [13]. Antibacterial activity of NPs can be elicited through a variety of mechanisms, including (1) interaction with the bacterial cell wall; (2) biofilm

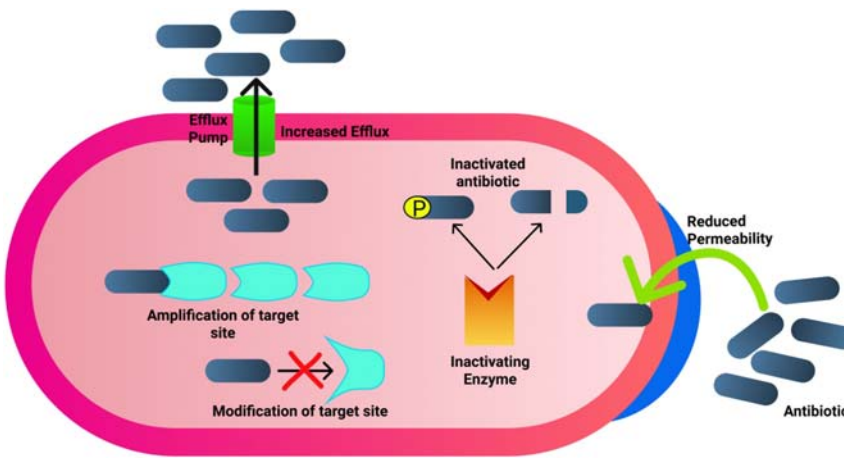

Figure 3.2 Schematic depiction of the mechanism of antimicrobial resistance developed by microbes.

inhibition; (3) stimulation of innate and adaptive host immunological responses; (4) production of reactive oxygen species (ROS) and induction of oxidative stress; (5) metal dissolution from NP surfaces which causes free metal ion toxicity; and (6) activation of intracellular effects like interactions with DNA, enzymatic inhibition, and protein disruption (Fig. 3.3) [6]. The multifaceted antimicrobial activity of NPs improves their antimicrobial efficacy while also preventing the emergence of resistance in microbes.

Furthermore, the antimicrobial property can be actively imparted on a platform utilizing three different methods, as depicted in Fig. 3.4. The first way involves functionalization of NPs or polymers with antimicrobial agents, e.g. quaternary ammonium compounds (QAC). This process employs a contact killing strategy to enhance the antimicrobial activity of different surfaces. Surface-functionalized NPs have recently piqued researchers' interest as a potential strategy to enhance the antimicrobial capacity of NPs to combat multidrug-resistant bacteria. The second method involves adding fillers to synthesize nanocomposites like metal-based nanomaterials (ex-silver NPs). In this method, the type of materials used to synthesize NPs influences their bactericidal properties. The metals like

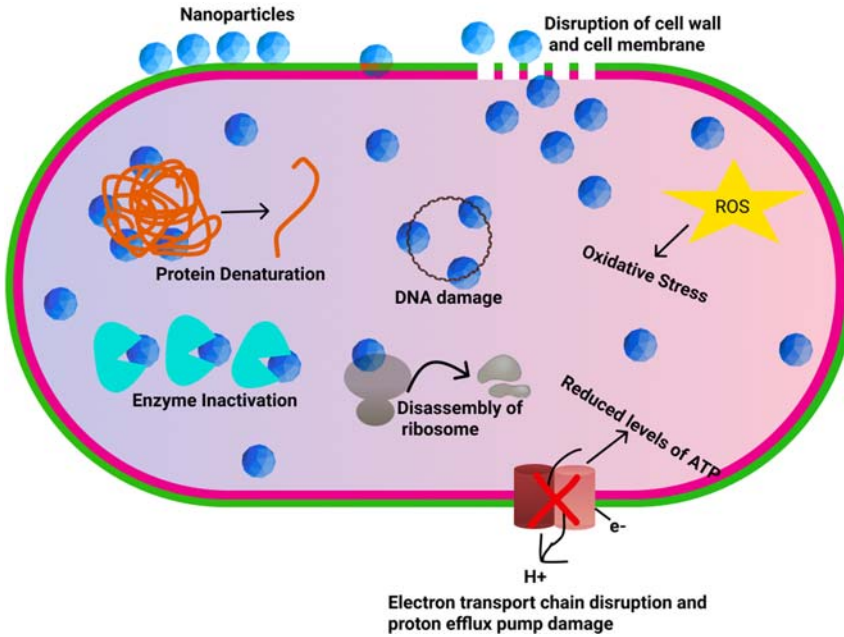

Figure 3.3 Schematic representation of the antimicrobial activity exhibited by nanoparticles.

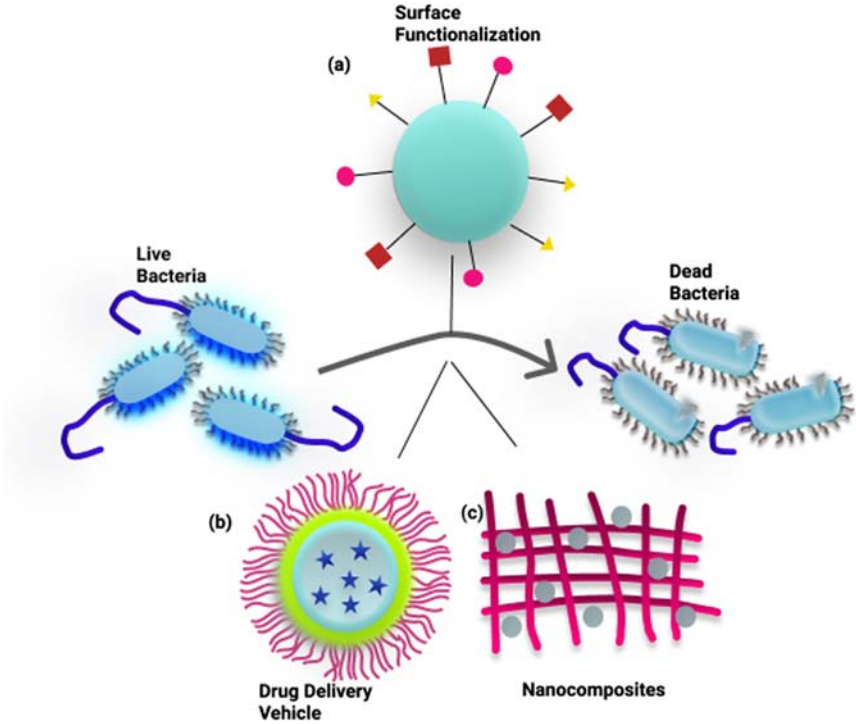

Figure 3.4 Schematic diagram illustrating the different methods of imparting antimicrobial activity on a platform: (A) surface functionalization of nanoparticles/polymers, (B) drug-delivery system, and (C) fabrication of nanocomposite.

Ag, Au, Zn, Cu, Ti, Mg, Ni, Ce, Se, Al, Cd, Pd, or superparamagnetic Fe, and oxides, like cerium oxide, zinc oxide, titanium dioxide, and silicon dioxide that are commonly used to synthesize metallic NPs, are associated with significant antimicrobial efficacy along with a broad spectrum of activity. Among various metallic NPs and their oxides used as active antimicrobial agents, silver or its ionic form is the most potent because of its high toxicity to bacteria. Silver NPs (AgNPs) are used extensively in nanomedicines owing to their multiple antibacterial mechanisms of action, high biocompatibility, better functionalization potential, and ease of detection [11]. The final method involves drug or biomolecule encapsulation inside NPs which enhances their antimicrobial properties significantly [14]. Several favorable features of NPs, such as improved drug solubility and stability, ease of production, biocompatibility with target agents, and modulated release that may be controlled by stimuli like light, pH, and heat, make them suitable carriers for medications to fight against disease-

causing microorganisms. Drug-loaded NPs' penetration into host cells can be accomplished via endocytosis, thus allowing their intracellular entry, which is a major limitation for most antibiotics. NPs can also insert into bacterial cell membranes by interacting with surface lipids. Moreover, the ability to load a combination of drugs into NPs develops an antibacterial mechanism of action that bacteria are unlikely to build resistance to [15–17]. Although NPs are effective antimicrobial carriers, their efficiency can further be improved by surface functionalization to enhance the site-specific delivery, cellular uptake, and internalization, and reduce off-target toxicity [18]. Overall, these properties make NPs suitable alternatives to traditional antibiotics and allow the use of NPs–antimicrobial agent combinations as an effective strategy for combatting the current antimicrobial resistance challenge.

3. Antimicrobial functionalized nanomaterials

The correct functionalizing of NPs with different chemical or biological groups may result in altered physicochemical and biological properties of the particles guiding the development of more standardized applications of the same such as drug delivery (Table 3.1). Many active groups like thiol/dithiol (octane thiol, dodecanethiol, 1,6-hexane dithiol, and 2,8-octanedithiol), aminothiol (2-aminothiol), silanes (mercaptosilane), phosphine (triphenylphosphine), and succinimidyl 4-(N-maleimidomethyl)-cyclohexane-1-carboxylate have been the most frequently used compounds for biofunctionalization. The key principle of functionalization involves an interfacial activity that helps in attachment to a surface [29]. Many molecules can be functionalized onto NPs and such ornamented molecules exhibited better antibacterial activity in comparison to their unfunctionalized counterparts (Fig. 3.5). Some of these are elucidated below.

3.1 Peptide- and protein-functionalized nanoparticles

It has been reported that cationic antimicrobial peptides have been quite effective against drug-resistant bacteria and other microorganisms. TAT peptides when functionalized over NPs or other therapeutic regimes have resulted in better cellular uptake of proteins and genes. For regulating viral multiplication within the brain, TAT-conjugated NPs served as an effective way for delivering anti-HIV-1 drugs [30]. In this milieu, poly(ethylene glycol) (PEG)-b-cholesterol conjugated with TAT in self-assembled core–shell NPs and loaded with ciprofloxacin was found to be very

Table 3.1 Therapeutic applications and mechanisms of action of different surface-functionalized NPs.

NPs	Functionalized materials	Microbes	Antimicrobial properties	Antimicrobial mechanism of action	Application	References
Gold NPs	N-heterocyclic molecule	Multidrug-resistant bacteria	• AuNPs have good biocompatibility and allow for easy functionalization with surface ligands and hence serve as potent antimicrobial agents • N-heterocyclic molecules have antimicrobial properties and possess an −SH group, which allows them to be good protective agents for the synthesis of well-dispersed AuNPs • The functionalization of only one kind of N-heterocyclic molecule on the AuNPs increases the experimental repeatability and makes the antibacterial effect more stable	• The positive charge of functionalized AuNPs allows their easy entry into the negatively charged bacteria via electrostatic interaction • The NPs kill the bacteria by destroying the cell wall and cell membrane	Effective antibiotic against multidrug-resistant pathogens	[19]
Silver NPs	Ampicillin	*E. coli*	• Biologically synthesized and functionalized AgNPs were more stable than chemically synthesized and functionalized AgNPs • Biologically synthesized AgNPs' antibacterial activity is enhanced when functionalized with antibiotics	• AgNPs enter into the bacteria by disrupting the cell membrane and releasing the antibiotic inside the cell • Ampicillin acts by inhibiting bacterial cell wall synthesis	Treatment of external infections of the skin and mucous membranes	[20]

Continued

Table 3.1 Therapeutic applications and mechanisms of action of different surface-functionalized NPs.—cont'd

NPs	Functionalized materials	Microbes	Antimicrobial properties	Antimicrobial mechanism of action	Application	References
Gold NPs	Indolicidin	*Candida albicans*	• AuNPs increases the activity of indolicidin and they maintain their antimicrobial properties by reducing proteolytic degradation inside the cells or biofilm matrix and peptide self-aggregation	• The nanocomplex inhibits biofilm formation by altering the permeability of the fungal membrane, thereby reducing the cell population by accessing the intracellular target • By suppressing the biofilm formation genes such as ALS1, ALS3, EFG1, and HWP1 and the genes encoding for the drug transporter such as CDR1, and CDR2	Treatment against pathogenic *Candida albicans* biofilms infection	[21]
Amino silane-coated iron-oxide magnetic NPs	1,4-Dihydropyridine (1,4-DHPs)	Gram-positive and Gram-negative bacteria and clinical isolates of *Candida* strains	• Improved biocompatibility and higher antiinflammatory properties of the nanosystem • The positive charge of the nanocomplex helps in their interaction with negatively charged pathogenic cells • The nanosystem protects the cell from lipopolysaccharide-induced oxidative stress • The antimicrobial activity of the nanosystem is maintained	• The presence of C-3, C-4, and C-5 substituents in the chemical structure of (1,4-DHPs) and their lipophilicity contribute to their antimicrobial activity • The high affinity of 1,4-DHP derivatives to bacterial membrane and their amphiphilic nature promote penetration into the microbial membrane. This property of	Treatment for life-threatening infections	[22]

			in various body fluids as it can resist various antibiotic inhibitors present in the body fluids • Functionalization of the magnetic NPs broadens their antimicrobial spectrum • The covalent and electrostatic-based immobilization of antibiotics on the magnetic NPs enhances the antimicrobial efficacy of the antibiotics as well as the bactericidal effect of the NPs	1,4-DHP derivatives makes it difficult for the microbes to escape by using an antimicrobial resistance mechanism • The magnetic NPs can penetrate the microbial membrane, generate oxidative stress, disrupt the bacterial electron transport chain and macromolecules like DNA, lipids, and proteins, damage the microbial biofilms, and thus contribute to antimicrobial activity		
Fe_3O_4 amino silane core −shell NPs	Antimicrobial peptide clavanin A (clav A)	*S. aureus, E. coli*, *P. aeruginosa*, and *Klebsiella pneumoniae*	• The coating inhibits microorganisms from adhering to the surface • Fe_3O_4 NPs have also been utilized to combat drug-resistant bacteria	• Clav A of the nanocomplex specifically interacts with the cell membrane, which results in the formation of pores over the bacterial membrane, thus preventing biofilm formation • The nanocomplex application results in the reduction of proinflammatory cytokines locally in infected cutaneous wounds	Prevention of central venous catheter contamination	[23]

Continued

Table 3.1 Therapeutic applications and mechanisms of action of different surface-functionalized NPs.—cont'd

NPs	Functionalized materials	Microbes	Antimicrobial properties	Antimicrobial mechanism of action	Application	References
				• The level of cytokines in the treated site is sufficient for efficient bacterial elimination in cutaneous infection while causing no immune response dysregulation		
Manganese iron-oxide magnetic NPs	Hydrophilic antimicrobial cationic polyacrylamide and usnic acid (UA)	*S. epidermidis*	• Polymer provided basic groups for adsorption of UA • The polymer acted synergistically with UA, enhancing the antimicrobial activity and inhibiting the formation of drug resistance in bacteria • The nanosystem was less aggregated, had better magnetic characteristics, was better in loading and releasing UA, and had strong antimicrobial properties	• The positively charged MNPs via electrostatic interaction bind to negatively charged bacterial cell membrane resulting in disruption of the cell wall and promoting the entry of the released drug into the bacterial cell	Treatment for infections related to medical devices	[24]
Silica NPs	Amine functional polymers	*E. coli*, *S. aureus*	• The biocidal activity of the polymeric NPs with functional amine groups depends on the state of the amine groups rather than their positive charge	—	Antimicrobial activity of polymeric NPs with amino groups	[25]

Silver NPs	L-cysteine (L-cys)-functionalized AgNPs incorporated into graphene oxide (GO) sheets	*E. coli*, *S. aureus*	• GO possess thermal and chemical stability, low cytotoxicity, high mechanical strength, large surface area, electron conductivity, and better water solubility • GO acts as a suitable support for growing metal NPs to stabilize them • GO inhibits the growth of Gram-negative bacteria along with low cytotoxicity by generating reactive oxygen species • In the nanocomposite, GO nanosheets appear to operate as a morphological driver for AgNPs, directing the production of spherical-like particles • The antibacterial activity of GO sheets against *E. coli* cells is influenced by their lateral size, i.e., antibacterial activity is stronger in larger GO sheets than in smaller ones	• GO-L-cys-Ag nanocomposite exhibited antimicrobial effect by disrupting bacterial cell membrane and hence killing the microbe • By interacting with biosystems, cysteine improves the antibacterial activity of AgNPs • AgNPs can bind to sulfur-containing proteins in cell membranes and phosphorus-containing substances in cells, damaging the respiratory chain and causing bacteria to die • When compared to the nonfunctionalized nanocomplex, the functionalized nanocomplex had a longer antibacterial activity and a slower rate of Ag^{+} release • The Ag^{+} from the NPs interrupts cell metabolism and finally triggers cell death by binding to the thiol groups of metabolic enzymes and the phosphorous in DNA	Antibacterial agents to control biofilm formation on medical products	[26]

Continued

Table 3.1 Therapeutic applications and mechanisms of action of different surface-functionalized NPs.—cont'd

NPs	Functionalized materials	Microbes	Antimicrobial properties	Antimicrobial mechanism of action	Application	References
Silver NPs	Hydroxyapatite (HAP) with 5-aminosalicylic acid (5-ASA)	*E. coli*, *S. aureus*	• The antimicrobial activity of AgNPs depends on their morphology, i.e., smaller particles have higher antimicrobial activity • To manage the interaction period between microbial species and antimicrobial agents, and the release rate of Ag^+ ions, it is important to immobilize AgNPs on support in various applications • During five repeated cycles against *E. coli* and *S. aureus*, AgNPs supported by HAP maintained their antimicrobial activity under long-run working circumstances	• Because AgNPs are strongly bonded to the functionalized support, their capacity to interact with bacteria is considerably reduced, hence the antimicrobial action of the nanocomplex is attributed to the released Ag^+ • Ag^+ ions interact with the functional groups of peptidoglycan (amino and carboxyl) resulting in damage to the cell wall	Biocide to modify surfaces of implants	[27]
Chitosan NPs	DNase-I	*P. aeruginosa*	• DNase-I functionalized chitosan NPs loaded with ciprofloxacin inhibited microbial growth significantly and for a long time, prevented biofilm production, and can cause biofilm dispersal without producing toxicity	• DNase-I greatly enhances antibiotic distribution in biofilms by hydrolyzing extracellular DNA, a prominent component of ECM that plays a critical role in biofilm generation, dispersal, and disease progression, thereby reducing	Treatment for *P. aeruginosa* biofilm infection in cystic fibrosis	[28]

			• The freeze-dried NPs were adsorbed on fine-grade lactose powder to acquire stability and pulmonary deposition properties	resistance and increasing the exposure of bacteria to antibiotics • Chitosan NPs increase penetration into the biofilm and facilitate drug release in a regulated manner close to microbial colonies		

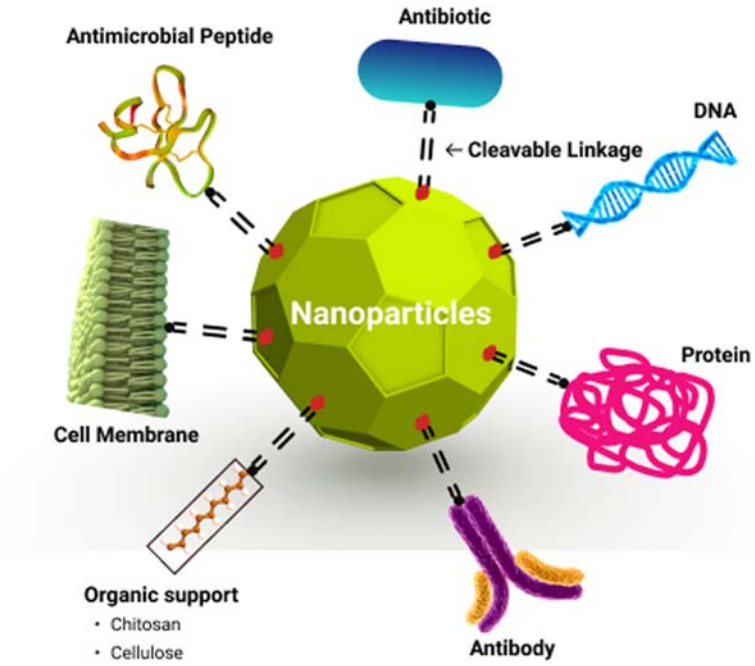

Figure 3.5 Different compounds commonly used for surface functionalization of antimicrobial nanoparticles.

effective against a wide spectrum of bacteria, yeasts, and fungi [31]. Lysozymes when conjugated to positively charged NPs exhibited extraordinary potential against *Micrococcus lysodeikticus* [32]. Another study by Devlin et al. focused on the development of an enzyme-functionalized NP-based antibiofilm treatment method against meticillin-resistant *Staphylococcus aureus* (MRSA) and meticillin-sensitive *Staphylococcus aureus* (MSSA) biofilms. Three different enzymes were individually immobilized on the surface of NPs, namely lysostaphin which causes cell lysis of *S. aureus* bacteria, serrapeptase which degrades protein components, and DNase I that degrades DNA in the extracellular polymeric substances (EPS) matrix, which is responsible for bacterial growth and biofilm formation. The mesoporous silica NPs (MSNs) used as enzyme-carriers were functionalized with amine, to improve enzyme stability and enzyme penetration into the biofilm. The formulated enzyme-functionalized NPs were used in combination as an effective treatment strategy to enhance the eradication of biofilms.

Conclusively, the resulting enzyme-functionalized NPs could broaden the therapeutic choices for the treatment of *S. aureus* infections, primarily those with a biofilm component [33].

3.2 Carbohydrate-functionalized nanoparticles

Functionalization of carbohydrates onto the NP surface has yielded nanostructures with superlative antibacterial properties. Many studies have been conducted worldwide to establish this theory. In this context, glucosamine, an amino sugar, was coated on AgNPs and these nanovehicles displayed superior antibacterial activity against *Klebsiella pneumonia* and *Bacillus cereus* owing to their better penetration power and ability to better interact with bacteria [34]. A previous study examined the antibacterial efficiency of gold NPs (AuNPs) that had been functionalized with aminoglycosides, streptomycin, and gentamycin, to prove the above hypothesis.

Chitosan, a natural polysaccharide, has been extensively studied due to its increased biocompatibility, biodegradability, and metal complexation ability. In this regard, a cross-linked chitosan-coated silver-loaded nanosilicon oxide hybrid was synthesized which demonstrated exceptional antibacterial activity against *Escherichia coli* and *S. aureus* [35]. In an independent study, electrochemically fabricated chitosan—iron oxide nanocomposite film was implemented for the detection of gonorrhea [36]. Similarly, AgNPs coated with chitin nanofiber sheets had an augmented antimicrobial activity against *E. coli*, *P. aeruginosa*, and H1N1 influenza A virus in comparison to their uncoated counterpart [37]. Self-assembled nanogels of luminescent thiolated silver nanoclusters coated with chitosan were effective as a bactericidal agent and bacterial sensor [38]. Functionalization of sponge-originated 3D chitinous skeletal scaffolds over AgNPs magnified their antibacterial ability [39]. Chitosan- and DNase-coated solid lipid NPs loaded with anacardic acid improved the antibacterial activity of the nanosystem against *S. aureus* biofilm [40]. In another study, Li et al. formulated trehalose-functionalized AuNPs as an antiadhesive agent to prevent the attachment of microbes to human umbilical vein endothelial cells (HUVECs), thereby inhibiting *S. aureus* infection, which specifically binds to HUVEC. The study particularly implicated the advantageous substitution position of sugar as an antiadhesive to prevent microbial infection [41].

3.3 Lipid-functionalized nanoparticles

Lipid-amalgamated NPs have been explored as antibacterial agents for treating multiple infections. In this regard studies were undertaken to formulate oleic acid-stabilized AgNPs which were quite effective in controlling the growth of *E. coli* and *S. aureus* bacteria [42]. Likewise, HIV-1-associated dementia is a relatively new neurological disorder. To treat such a condition, Nifedipine-loaded solid lipid NP surfaces coated with Tween 80 were engineered to facilitate enhanced brain drug delivery [43].

3.4 Antibiotic- and chemical compound-functionalized nanoparticles

Nanoconjugated antibiotics are often regarded as high-performance magic molecules owing to their exceptional ability for surmounting multidrug resistance in pathogenic bacteria. In this regard, a novel vancomycin-modified Fe_3O_4@SiO_2@Ag microflower demonstrated exceptional potential against pathogenic bacteria in solutions [44]. Vancomycin-functionalized silver (Ag) @titanium dioxide (TiO_2) NPs showed selective phototoxicity against vancomycin-sensitive bacteria, thus suggesting the development of a novel NP antibiotic conjugate with superlative bactericidal properties [45]. Vancomycin and iron-oxide NPs were successfully joined onto the surface of lanthanum hexaboride NPs with a silica coating and carboxyl functionalization to engineer a unique therapeutic regime for NIR photothermal ablation against *S. aureus* and *E. coli*. [46]. Armenia et al. synthesized teicoplanin-conjugated iron-oxide NPs using (3-aminopropyl) triethoxysilane (APTES). Antibiotic conjugation resulted in the development of more potent antibacterial NPs which exhibited prolonged activity against Gram-positive bacteria [47]. Similarly, ampicillin-functionalized Au and Ag NPs acted as broad-spectrum bactericides against Gram-negative and Gram-positive bacteria. It is noteworthy that functionalization with antibiotics endowed these NPs with the ability to avert antibiotic resistance mechanisms of many drug-resistant bacteria [48]. In the same context, Jana et al. designed AuNPs functionalized with a virstatin-derived ligand (VL) to effectively combat diarrheal diseases caused by *Vibrio cholerae*. The spherically shaped VL-conjugated AuNPs exhibited negligible cell toxicity along with increased antimicrobial efficacy as compared to virstatin against the El Tor biotype of *Vibrio cholerae*, by inducing DNA damage and inhibiting the activity of ATPase enzyme. Furthermore, the study's findings revealed that VL-functionalized AuNPs

can reduce the synthesis of the key virulence factor, cholera toxin, by targeting ToxT, the main virulence regulator of cholera toxin, with substantially greater effectiveness than virstatin [49]. Another study by Jihad et al. focused on the synthesis of polyethylene glycol functionalized flaky graphene oxide NPs encapsulated with *Nigella sativa* seed extract to serve as a novel drug-delivery system with enhanced antimicrobial efficacy. The investigation revealed that the developed drug-delivery system was able to penetrate the bacterial nucleic acid and cytoplasmic membrane, leading to cell wall integrity loss, nucleic acid damage, and enhanced cell-wall permeability, which ultimately leads to bacterial death [50].

4. Different responsive structures of functionalized nanomaterials

Even though NPs have various advantages that make them a good nanocarrier, the ability to control the release of the encapsulated antimicrobial ingredient according to clinical need and target-specific delivery cannot be established. However, coating or capping the NPs or blocking the pores of NPs with different inorganic or organic moieties as gatekeepers with a stimulus-responsive behavior can help achieve on-demand release of the incorporated drugs along with the increased antimicrobial activity of the functionalized NPs [4]. This smart performance can be achieved by attaching different materials to the NPs externally via cleavable-linkages or by employing certain gatekeepers which in response to a particular stimulus undergo certain changes in physical properties and/or chemical structure. In this way, smart nanosystems can be used to load, protect, and regulate the release of antimicrobials to the target site in response to an internal or external stimulus, thereby lowering the off-target toxicity and enhancing the therapeutic efficacy. To this end, several internal (bacteria, pH, bacterial toxins) and external (temperature, magnetic field, light) factors have been proposed to act as efficient stimuli to trigger the release of incorporated antimicrobial agents from the functionalized NPs (Fig. 3.6) [51].

4.1 pH-sensitive nanosystems

Bacterial and viral infected sites are usually linked to a drop in pH values, which is induced by a combination of inflammation mediated by natural host immune response as well as anaerobic fermentation triggered by low oxygen. This fall in pH can sometimes be reduced to values as low as 5.5,

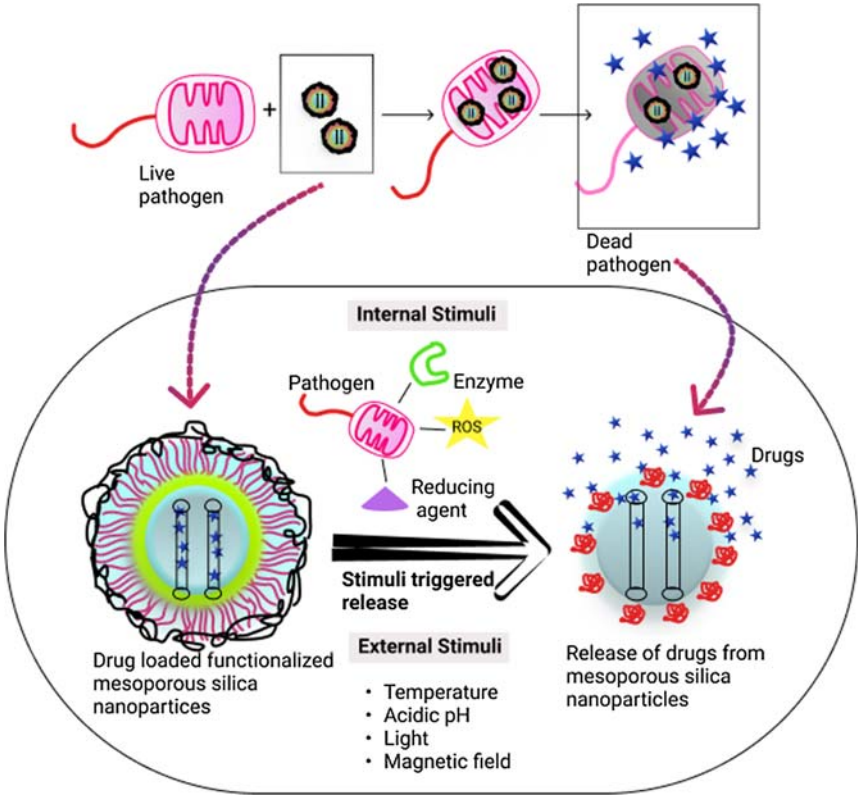

Figure 3.6 Schematic diagram demonstrating the operating mechanism of different stimuli-responsive functionalized nanosystems loaded with antimicrobial drugs. The functionalized layer when exposed to specific stimuli undergoes disruption resulting in the release of payload at the target site.

which can be exploited as an effective stimulus to trigger the release of drug [4]. In this regard, Moreno et al. synthesized a systemically administrable nanocomposite consisting of triblock copolymer poly(D,L-lactic-co-glycolic acid)-b-poly (L-histidine)-b-poly- (ethylene glycol) (PLGA-PLH-PEG)-based NPs and incorporated the nanocomposite with an antimicrobial drug, vancomycin. Owing to the ability to alter surface charges in response to variations in pH, these NPs bind strongly to the bacterial cell wall at acidic condition but do not interact with the nontarget sites at pH 7.4. This pH-dependent, specific bacterial cell targeting occurs due to the presence of an imidazole group containing PLH polymer which under acidic pH undergoes protonation, acquiring a positive charge and thus imparts an overall positive zeta potential onto the NP surface,

facilitating multivalent electrostatic-mediated interactions with the negatively charged bacterial cell wall. Furthermore, this NP drug carrier system acts as an efficient antimicrobial system by inhibiting the therapeutic efficacy loss of the encapsulated drug and modifying the properties of the drug [52]. Similarly, another study by Chen et al. focused on the design and development of a pH-sensitive nanocarrier composed of ampicillin-loaded MSNs and coated with double layers of folic acid (FA) and calcium phosphate (CaP), as an efficient antibacterial nanosystem for enhanced wound healing. MSNs were first altered by grafting FA onto the outermost surface of the NPs via electrostatic interactions, then coated with CaP through biomineralization and again grafted with another FA layer. FA's capacity to localize itself to the site of bacterial infection effectively boosted NP absorption and eliminated the efflux pump effect in *E. coli* and *S. aureus*. Moreover, the sensitivity of CaP to a pH-triggered mechanism controls the release of antibiotic ampicillin from the nanosystem at the infection site. This results in a higher concentration of antibiotics at the infected area, in response to a low pH, thus leading to inhibition of bacterial growth as evidenced by in vitro and in vivo studies. This nano-drug carrier demonstrated efficient antibacterial activity by enhancing the efficacy of ampicillin to inhibit drug-resistant bacteria and preventing the development of bacterial resistance to the drugs, thus promoting increased healing of wounds infected by drug-resistant *S. aureus* [53]. Additionally, in a separate work, Lu et al. reported the development of an MSN-based nanocarrier with a pH/GSH dual-responsive property for the delivery of chlorhexidine (CHX) and Ag^+ ions to treat oral infections. In this study, disulfide-bridged MSNs were decorated with AgNPs, and the mesopores were functionalized with carboxylate groups to allow electrostatic interactions with the positively charged CHX. The pH- and GSH-responsive property of the nanocomposite triggered the degradation of matrix, permitting concurrent release of CHX and Ag^+ ions when subjected to both acidic and reducing conditions. Subsequently, the release of the antibiotic is controlled through the protonation and dissociation of carboxyl functional groups in acidic media. This results in producing the synergistic action of CHX and Ag^+ ions against Gram-negative bacteria, such as *E. coli*, and Gram-positive bacteria, such as *S. aureus*. Moreover, the nanocomposite drug-delivery system is more efficient in inducing bacterial cell death for a sustained period, as compared to free CHX. The developed nanocomposite thus acts as a potent oral biofilm nanoseptic that efficiently reduces the toxicity of CHX in oral epithelial cells [54]. Utilizing a similar approach, topical

pH-sensitive hybrid nanocarriers composed of ZnO functionalized humic acid (HA) NPs and encapsulated with ciprofloxacin have been developed by Murugesan et al. to allow the sustained release of antibiotics at the site of infection. In response to the pH-triggering mechanism, the nanosystem releases antibiotics for a longer period at different pH values ranging from 2.5 to 6.8 and thus exhibits bacteriostatic and bactericidal activity against *Pseudomonas aeruginosa* and *Bacillus cereus* at the site of infection. Moreover, HA addition onto the ZnO surface enhances the drug-loading capacity of the hybrid nanocarrier by providing more ciprofloxacin adsorption sites. The pH-sensitive ciprofloxacin acquires a negative charge at high pH due to its carboxylic group deprotonation, while it becomes positively charged at low pH owing to its amine group protonation. Hence at low pH, the positively charged ciprofloxacin binds to the negatively charged bacterial cell wall via an electrostatic interaction and contributes to the destruction of the pathogen. The drug-encapsulated hybrid nanocarrier exhibited higher antibacterial activity against both Gram-positive and Gram-negative bacteria and is regarded as a potential therapy for bacterial infections, owing to its high biocompatibility, biodegradability, safety, and cost-effectiveness features [55]. In the same context, Maji et al. reported the design and development of novel pH-responsive lipid-dendrimer hybrid (LDH) NPs, derived from oleylamine (OLA) and poly(amidoamine) or PAMAM dendrimer (G3PD) for target-specific drug delivery of vancomycin (VCM) to treat bacterial infections. The fatty amine OLA binds to the succinamic acid group of G3PD via an electrostatic interaction which breaks in response to low pH, due to the protonation of the acidic group of G3PD. This results in the development of a positive charge on the LDH-NPs in an acidic environment which aids in binding the NPs to the negatively charged surface of the bacteria, thus resulting in targeted delivery of the therapeutic concentration of the drug at the infection site. Conclusively, the investigation proved that the LDH-NPs are a stable, biocompatible, potent drug-delivery vehicle with enhanced antimicrobial activity [56]. To overcome the infections caused by MRSA, metal-organic framework (MOF)-coated MSNs were synthesized for the simultaneous delivery of β-lactam antibiotic (carbenicillin) and inhibitor of β-lactamase (sulbactam) at the infection area. Carbenicillin, an organic ligand, forms a coordinate bond with the Fe^{3+} ions to form a biodegradable shell of MOF to block the pores of MSNs. The coordinate bond formation between the carboxyl group of carbenicillin and Fe^{3+} may be cleaved off in response to changes in pH and is thus responsible for the pH-sensitive drug-release behavior of the nanosystem.

The MOF shell on being exposed to a low pH at the infection site undergoes degradation via a pH-mediated cleavage of the coordinate bond, followed by the codelivery of both the β-lactam antibiotic and β-lactamase inhibitor at the site of infection. Furthermore, the core−shell nanosystem demonstrated efficient antimicrobial activity against MRSA infection by facilitating improved penetration of the antimicrobial agents into the biofilm [57]. In a similar line, Sabzi et al. synthesized another pH-sensitive antimicrobial nanocarrier based on poly(vinyl alcohol) (PVA), cross-linked with citric acid, incorporated with AgNPs, and loaded with ciprofloxacin drug. The cross-linking agent, citric acid, possesses a free carboxylic acid group which contributes to the pH-sensitive behavior as well as antimicrobial activity of the PVA-based hydrogel system. In response to variations in pH, the developed PVA-based hydrogel demonstrated a remarkable swelling behavior, thereby controlling the release of drugs from the hydrogel at different pH. The drug release from the hydrogel was more at pH 7.4 as compared to pH 1.2. This difference in the drug-release profile of the hydrogel is because the swelling ratio increases with the increase in pH. Moreover, the free −COOH- groups of CA ionize to $-COO^-$ when the pH value rises above the pKa value of the hydrogel resulting in a net negative charge on the surface of the hydrogel. Consequently, this leads to an enhanced electrostatic repulsion between the negative charges of the carboxylate group, resulting in increased swelling. Furthermore, the hydrogel exhibited a potent antimicrobial activity by facilitating the AgNPs-driven long-term release of the antibiotics at the infection site [58]. Another study by Luo et al. focused on the development of a pH-sensitive liposome-polymer NP to regulate the release profile of antibiotics at the infection site as a therapeutic approach to treat acute lung infection. The liposomal core was encapsulated with the antibiotic spectinomycin and the surface of the liposomes was sequentially decorated with the pH-sensitive polycationic polymer poly(β-amino ester) (PBAE) and polyanionic sodium alginate (NaAlg) via electrostatic interaction using a layer-by-layer approach. The bilayered hybrid NPs control the release profile of the drug in a pH-responsive manner at the infectious microenvironment. This pH sensitivity could be attributed to the NPs' positive surface charge, which is created by protonation of tertiary amine residues in the PBAE layer in an acidic environment, causing bacterial cell wall disruption, bacterial death, and a synergetic effect with the drug. Further, the in vitro and in vivo results confirmed that the bilayered drug-loaded hybrid NPs with improved antimicrobial efficacy were able to induce the death of and

eliminate the invading *S. aureus* and MRSA BAA40 strains along with minimal side effects [59]. Similarly, Akram et al. designed a pH-responsive MSN modified with PLGA and loaded with chlorhexidine (CHX) to coat resin-based dentin adhesives, which can serve as a novel antibiofilm therapeutic agent. The PLGA grafted onto MSN enables a higher amount of CHX to be loaded and shows long-term sustained release of CHX at low pH, resulting in improved antibacterial activity. The resulting MSN-based nanocarriers are of significant importance in resin-based dentin adhesives due to the drug-release behavior of MSNs which is pH-responsive, particularly in response to low pH resulting from the formation of biofilm, along with the activation of dentin-bound proteases as a result of acid etching and acidic composition of bonded resin monomers [60].

4.2 Bacterial toxins/enzyme-sensitive nanosystems

Bacterial toxin/enzyme-sensitive nanosystems change physical properties or chemical structures to control the release of encapsulated cargoes, in response to a high concentration of bacterial toxins in the infected microenvironment. In this regard, Grutzner et al. formulated enzyme-responsive fluorescent molecule tagged hyaluronan nanocapsules containing polyhexanide biguanide as well as octenidine-loaded poly-L-lactic acid NPs to promote wound healing. The developed nanocomposites can be used in a theranostic approach in which following the bacterial enzyme (hyaluronidase and proteases) mediated degradation of the nanocomposites, a visible signal is emitted along with the release of antimicrobial agents present inside the nanocomposites at the infection site. Their degradation by bacterial enzymes facilitates an antimicrobial response to different microbes such as *S. aureus* and *P. aeruginosa*, most commonly found in infected burn wounds. According to the results of the investigation, these nanosystems are biocompatible with primary human endothelial cells and have therapeutic potential for the prophylaxis and treatment of burn injuries [61]. In another work, Ding et al. utilized an innovative approach to overcome *S. aureus*-associated osteomyelitis infections while also promoting bone tissue regeneration. For this purpose, MSNs loaded with AgNPs and coated with a multilayered film of poly(L-glutamic acid) (PG) and cationic polyallylamine hydrochloride (PAH) were developed. The nanocomposite was then used to modify the surface of Ti implants to inhibit infections and promote bone tissue regeneration at the same time. The release of antimicrobial agents (Ag^{+} ions) from the nanocomposites and their target-oriented delivery is induced by a glutamyl endonuclease enzyme-responsive

mechanism due to overexpression of the enzyme at the *S. aureus*-based infection microenvironment. This enzyme-rich microenvironment triggers the cleavage of the amide linkage of PG and hence results in degradation of the outer multiple layered films, leading to the release of the antimicrobial agents from the nanocomposite. The antimicrobial effect of AgNPs and Ag^{+} ions is based on the interaction of positively charged AgNPs with the negatively charged bacterial membrane, and enhanced membrane permeability along with ROS generation [62]. Further, to overcome the infections caused by multidrug-resistant bacteria, Liu et al. fabricated an enzyme-responsive nanocarrier composed of hyaluronic acid-capped mesoporous RuNPs loaded with ascorbic acid. The surface of the nanosystem was then modified by ciprofloxacin precoated molybdenum disulfide (MoS_2) for the effective targeting of the nanocarrier to the infection-specific site. After the delivery of the nanosystem to the infection site, the hyaluronic acid-rich cap was dissolved by the hyaluronidase enzyme released from bacteria, followed by the release of the encapsulated ascorbic acid, which was catalyzed by the MoS_2 to generate •OH. In conclusion, the nanosystem could inhibit drug-resistant Gram-positive and Gram-negative bacteria and remove the recalcitrant biofilm synergistically by utilizing the photothermal action and the generated •OH [63]. Similarly, Gao et al. reported and designed smart biocompatible and biohybrid nanomaterials based on MSNs with enzyme-responsive release behavior of antibiotics that demonstrated improved in vivo and in vitro antimicrobial activity. Hyaluronic acid, lysozyme, and polyglycerol methacrylate modified by 1,2-ethanediamine (EDA-PGMA) were used for coating of NPs by the layer-by-layer method. The NPs were initially loaded with amoxicillin and further functionalized with the carboxylate group for the adsorption of a bactericidal enzyme, lysozyme via electrostatic interactions. To form a hyaluronidase-responsive shell of the NPs, they were subsequently coated with hyaluronic acid. Additionally, a cationic polymer, EDA-PGMA, was used to modify the surface of the nanosystem to enhance the electrostatic interactions with the negative charge of the bacterial membrane. This allows the immobilization of NPs on the surface of the bacteria with the help of multivalent interactions of lysozyme and EDA-PGMA with the bacterial membrane. Furthermore, the disruption of the hyaluronic acid-rich layer facilitates the release of antimicrobial agents from the NPs, in response to the hyaluronidase enzyme secreted by various pathogenic strains of *S. aureus*. The in vivo microbiological studies further demonstrated that the nanosystem inhibited the bacterial growth in the infected wound by

exhibiting synergistic antimicrobial activity [64]. Several researchers have adopted another approach to induce the release of antibiotics from the NPs by taking advantage of other enzymes secreted by bacteria such as lipases, phosphatases, and phospholipases. In this context, Rathnayake et al. fabricated a nanosystem based on MSNs and capped it with a stimuli-sensitive lipid bilayer shell that protects the encapsulated antibiotic from inactivation and early release while fighting against intracellular infections. MSNs are loaded with antibiotics and are functionalized with a peptide that confers the NPs with the ability to target specific bacteria. The liposomal coating of the nanosystem on being exposed to bacterial toxins undergoes degradation, resulting in the release of antibiotics at the site of infection. The results of the investigation revealed that the nanocarrier shows a marked enhancement in antimicrobial efficacy compared to the free antibiotic [65].

4.3 Light-sensitive nanosystems

In the fight against bacterial infection, a synergistic combination of phototherapy with delivery of antimicrobials offers a viable alternative to traditional antibiotic therapies. This strategy motivated Kuthati et al. to develop an antimicrobial nanohybrid made up of curcumin-loaded MSNs infused with Cu (II) and coated with AgNPs. Owing to the synergistic action of curcumin, Ag, and Cu (II) this nanosystem exhibited remarkable photodynamic inactivation of drug-resistant *E. coli* along with an enhanced bactericidal effect under visible light as compared to free AgNPs or curcumin. This enhanced bactericidal effect of the nanohybrid can be explained by the release of Ag^{+} ions under visible light irradiation and excessive generation of ROS induced by both curcumin and AgNPs, which results in bacterial cell death [66]. Similarly, Yuan et al. fabricated a uniform and stable nanocarrier consisting of a core (AuNPs)—shell (AgNPs) structure with excellent optical properties as two-photon excitation bacterial imaging and antibacterial therapy. The aggregation of the positively charged nanosystem on the surface of the negatively charged bacterial cell results in enhanced 2PPL via two-photon excitation under NIR irradiation and this property can be used for bacterial cell imaging. Moreover, this nanosystem has demonstrated outstanding antimicrobial activity with the potential to remove the bacteria present inside the biofilms of *S. aureus* by two-photon excitation under NIR irradiation [67].

4.4 Pathogen-sensitive nanosystems

In this regard, Mas et al. developed N-[(3-trimethoxysilyl) propyl] ethylenediamine triacetic acid trisodium salt (TMS-EDTA)-functionalized MSNs loaded with the antimicrobial drug, vancomycin as a pathogen-sensitive nanodevice, with the ability to release the payload in the presence of bacteria. Further, the mesopores of the negatively charged NPs were capped with a cationic polymer, ε-poly-L-lysine (ε-pLys) via electrostatic interactions, to produce a pathogen-responsive behavior of the nanodevice. The resultant nanosystem releases the antimicrobial agents in response to the presence of bacteria, which induces the uncapping of the mesopores, due to the adhesion of positively charged ε-pLys to the negatively charged bacterial cell wall. Additionally, the attractive forces between positive ε-pLys and the negative bacterial cell prompt bacterial cell membrane disruption which favors the penetration of antibiotics into the cell. This study demonstrates that the combination of the stimuli-sensitive ligand, ε-pLys, and antibiotic into the nanodevice produces synergistic antimicrobial activity against Gram-negative bacteria [68]. Later on, the same research group adopted a similar approach to fabricate a biocompatible histidine kinase autophosphorylation inhibitors (HKAIs)-loaded nanosystem based on TMS-EDTA-functionalized NPs capped with ε-pLys as a stimulus-sensitive and targeting ligand. The antimicrobial mechanism of action of the nanodevice is based on the interaction of the positively charged ε-pLys with the negatively charged bacterial cell wall, which induces uncapping of the mesopores of the NPs, followed by the release of antimicrobial agents and inhibition of bacterial growth. It is also confirmed by the microbiological studies that the nanodevice produced enhanced bactericidal activity against the Gram-negative bacteria *Serratia marcescens* as compared to the free HKAIs [69]. In a similar line, Alsaiari et al. reported the fabrication of a smart stimuli-responsive coating for X-ray dental imaging devices that can detect as well as treat healthcare-related infections. The coating is composed of poly(ethylene oxide)/poly(butylene terephthalate) polymer matrix with nanofillers homogeneously distributed within it. These antimicrobial nanofillers consist of kanamycin-loaded positively charged aminopropyl-modified MSNs and capped with negatively charged lysozyme-functionalized gold nanoclusters. The nanocomposites on exposure to the bacteria-rich microenvironment release the entrapped antibacterial agent kanamycin due to the interaction of lysozyme

with the bacterial cell wall, which ultimately triggers the detachment of nanoclusters from MSNs, thus allowing the drug release. Moreover, the nanocomposite also functioned as a bacterial detection nanoplatform. According to the findings of the current investigation, this smart coating has the potential to effectively detect and inhibit the growth and colonization of bacteria on a photostimulable phosphor plate, a common radiographic dental imaging device that is prone to contamination by microbes in the oral cavity [70].

4.5 Magnetic field-sensitive nanosystems

Multifunctionalization of NPs, or their combination with other types of NPs, has resulted in the development of various types of nanosystems with magnetic properties that can be used for the detection of different pathogens and to improvise the existing diagnostic techniques. These NPs exhibit macromolecule-like diameters, as well as high surface-to-volume ratios and superparamagnetic properties. The NPs are functionalized to improve their inherent qualities and/or introduce new ones, despite having therapeutic effects. In this regard, Geilich et al. synthesized a biocompatible multiple-compartment polymerosome formulation encapsulating both hydrophobic superparamagnetic iron-oxide nanoparticles (SPIONs) and the hydrophilic antibiotic meticillin for the treatment of infections associated with medical devices. The coencapsulation of multiple hydrophobic SPIONs into a single nanocarrier confers improved relaxivity and magnetism, thus facilitating penetration of the antibiotic into the biofilm, rendering drug-resistant biofilms sensitive to treatment. Synthesizing IOPs containing a sufficient concentration of SPIONs allowed these particles to be pulled with high efficiency into biofilms on physiologically relevant time scales. Both meticillin and SPIONs are known to potentiate ROS generation, and this may account for the high degree of therapeutic efficacy achieved here. These novel iron oxide-encapsulating polymersomes demonstrate that it is possible to overcome antibiotic-resistant biofilms by controlling the positioning of nanocarriers containing two or more therapeutics [71]. As an antibiofilm weapon, Wang et al. synthesized magnetic NPs coated with multilayered films composed of gentamicin, tannic acid, and AgNPs by electrostatic interactions and capped with a responsive shell of hyaluronic acid. The hyaluronic acid shell made the nanocomposite biocompatible and controlled drug release when exposed to the infection microenvironment, while also preventing nanocomposite component

leakage under normal physiological pH. The magnetic NPs via magnetic field guidance facilitate deeper penetration of the nanocomposites into the *S. aureus* biofilm to release the antimicrobial agents inside the biofilm. The Ag^+ ions and antibiotic gentamicin are released from the nanocomposites following a pH-responsive and enzyme-responsive mechanism, respectively, at the site of low pH and high concentration of hyaluronidase. The antibiotic gentamicin exhibits antimicrobial activity by combining with 16s rRNA resulting in the inhibition of the transcription process, thus eventually leading to cell death. The Ag^+ released from AgNPs enhances the bactericidal activity of gentamicin by increasing the bacterial membrane permeability. Moreover, Ag^+ generates ROS by interacting with the functional groups of proteins and DNA, thus resulting in the loss of membrane integrity and bacterial cell death. Thus the developed nanocomposites are a potential antimicrobial tool to eradicate biofilm infection and prevent the development of resistance mechanisms by the bacteria [72]. Similarly, comparative antimicrobial results were produced in another study conducted by Harris et al. on biocompatible polyethylene glycol dimethacrylate (PEGDMA) cross-linked chitosan microbeads encapsulating superparamagnetic Fe_3O_4 NPs and loaded with vancomycin antibiotic for musculoskeletal infection treatment. These magnetically responsive nanocarriers produce an efficient antibacterial effect by controlling the drug release rate and maintaining a therapeutic concentration of antibiotics at the site of infection [73].

4.6 Temperature-sensitive nanosystems

The temperature has been considered as an external physical stimulus that triggers the release of antimicrobial agents from NPs. To this end, Yu et al. reported and designed a temperature-sensitive antibacterial nanocarrier based on poly(N-isopropyl acrylamide) (PNIPAM) functionalized core–shell NPs with an iron oxide (Fe_3O_4) core and a mesoporous silica shell. The NPs were loaded with lysozyme enzyme or tris (bipyridine) ruthenium (II) chloride [$Ru(bipy)_3^{2+}$] small dye to compare and evaluate the efficacy of PNIPAM coating, and the loading as well as the delivery potential of the nanocarrier. The investigation revealed that both nanosystems demonstrated minimal release of cargo at 25°C due to the hydrated form of PNIPAM that efficiently seals the pores and prevents the delivery of encapsulated drugs. However, at physiological pH (37°C), the nanosystem releases the entrapped agents abruptly due to the hydrophobic collapsed

form of the polymer, which allows uncapping of the pore, thus facilitating the delivery of cargo. Moreover, the lysozyme-loaded nanocarrier exhibited better antimicrobial activity with a temperature-dependent reduction of bacterial growth, when tested against Gram-positive *Bacillus cereus* and *Micrococcus luteus* [74].

5. Conclusions and future directions

For addressing the requirements related to designing a stable and active bimolecular nanoparticle system for biological applications such as antimicrobial agents, the usage of functionalized nanoparticles is highly effective. NPs' physiochemical properties, interface/linking agents, and selective biomolecules enable them to control antimicrobial activities. Although we are starting to understand the interaction between functionalized nanoparticles and microorganisms/biosystems, the exact mechanism of action is yet to be revealed. Increased understanding of this mechanism would enable the selection of compatible biomolecules which would help in the development of future bionic nanotechnology for novel therapeutics. We hope that the research in this field will unravel and provide the foundation for the development of different shape-controlled functional nanomaterials and biosystems.

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CHAPTER 4

Biomass-based functionalized carbon dots: A promising shield with antimicrobial activities

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1. Introduction

The nano-range conversion of materials (nanomaterials) has brought about unexpected features and a paradigm shift in materials research. Nanomaterials are useful in a variety of fields, including power generation, medicines, environmental legislation, information technology, food, agriculture, and many more [1]. Nanomaterials therefore provide potential to improve responsivity and stability, fast response times, permit in situ analysis, and are very affordable. Any medical application requires all of these traits. Nanomaterials have undoubtedly changed several scientific disciplines, innovations, and enterprises, and are utilized in a wide range of groundbreaking activities, however their antimicrobial effects are of most interest. Majorly due to two primary factors, (1) lower effectiveness of antibiotics due to antimicrobial resistance and (2) distinct antibacterial activity of nanoparticles, bacteria have a lower chance of developing resistance [2]. Globally, infectious diseases caused by bacteria, fungi, viruses, and parasites are the leading cause of mortality and increasing medical expenses, as treatment becomes more complex when infections acquire multidrug resistance. Drug resistance affects almost all important diseases and all types of epidemiologic settings, such as medical centers, long-term-care institutions, communities, and so on [3].

A steady drop in the discovery and development of novel medicines has accompanied the growth of multidrug-resistant (MDR) pathogens, causing significant global difficulties. Antibiotic resistance could cause 300 million additional deaths and cost an additional US$100 trillion by 2050, therefore immediate and comprehensive action is required to solve this problem [4,5].

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Most disinfectants and antimicrobials are abrasive and poisonous, causing serious problems such as dermatitis and mucocutaneous inflammation, and they are not efficient due to bacteria's ability for adaption and resistance. This creates an urgent need to identify an alternative strategy with higher efficiency and reduced toxicity to combat multidrug resistance and the management of infections. Photodynamic activation is one of the potential, noninvasive, and harmless techniques for the inactivation of microorganisms, and there is very less chance of microbial drug resistance for photodynamic activation as the targeted molecules (lipids, proteins, and nucleic acids) are undefined. In more recent developments, nano-scale materials have emerged as excellent alternative antimicrobial agents by serving not only as vehicles to improve the selective delivery and dispersion of photosensitizers in targeted cells, but also as photosensitizers themselves to enhance the effectiveness of photodynamic inactivation (PDI). While nanoscale metal particles and semiconductors have been widely explored for such a purpose, carbon nanomaterials, due to their broad optical spectral coverage and other advantageous materials characteristics, have also attracted much recent attention in PDI-related applications [2,4].

Carbon-based nanomaterials have emerged as a dominant material in a number of applications. Carbon, among the different chemical elements, has played a unique role and also serves as the foundation for life in nature. It exhibits varied orbital hybridization, allowing it to produce various chemical connections with different orientations. It can polymerize at the atomic level and has the ability to form a long chain [6,7]. These properties are due to the special electron structure and the smaller size of carbon in comparison to the other group IV elements. It has four electrons in the outer shell and a valence of four that can be linked by single, double, or triple covalent bonds to carbon and other atoms to form different allotropic structures. Structural differences in the carbon allotropes allow it to exhibit different properties. It has the ability to arrange its valence electrons in the sp, sp^2, and sp^3 phases of hybridization, resulting in strong covalent and weak $\pi-\pi$ bonds. Strong covalent and weak bond formations assume a variety of allotropic forms and result in a wide spectrum of structures, from minuscule to large chains [6]. It can also make graphene single sheets, mono- and multiwalled carbon nanotubes, carbon fibers, fullerenes, nano-onions, and nanodiamonds, among other nanostructures. Furthermore, carbon can bond to practically all chemical elements, resulting in an infinite number of molecules and compounds [6]. Diamond and graphite are naturally occurring carbon allotropes.

In general, nanomaterials are defined as materials containing particles with at least one dimension between 1 and 100 nm in size [6]. Carbon nanomaterials, such as carbon nanotubes, nanohorns, and nanofibers, are covalently bonded by carbon atoms and have sp^2 hybridization. With a hexagonal pattern, high mechanical strength with thermal, optical, and electrical properties, these materials owe many of their attributes to graphene. Although carbon nanomaterials have traits similar to those of graphene, their individual geometries and properties can be distinguished as their own [6].

Carbon dots are the most popular of these materials, making their mark in nanotechnology. Carbon dots are the emerging 0D fluorescent carbon nanostructures discovered by Xu et al. [8]. Due to their special structural and other characteristics, carbon dots have gained the interest of researchers, showing low toxicity, good biocompatibility, better permeability, weak interactions with proteins, swelling resistance, photo-bleaching, simple clearance from the body, low cost, and easy synthesis. These extraordinary properties have opened new avenues for their advanced applications in cell labeling, bioimaging, drug delivery, sensors, and antibacterial, antimicrobial, and energy-related devices. Antimicrobial resistance is reducing the effectiveness of antibiotics for the prevention and treatment of certain diseases caused by bacteria. In order to replace traditional antibiotics, research is concentrating on antimicrobial nanomaterials that can stop bacterial development and kill the cells. The recent development of carbon dots has made them desirable candidates for a variety of applications, including the identification and management of infections. Along with having low toxicity, being simple to synthesize and functionalize, and having a high level of biocompatibility, CDs also exhibit excellent optical qualities such as multiemission, high brightness, and photostability. In many areas, including biosensing, nanomedicine, photocatalysis, and bioimaging, CDs have demonstrated considerable promise. Therefore, the aim of this chapter is to discuss the different approaches to developing biomass-based carbon dots, their characteristics, and antimicrobial activities [6].

2. Carbon dots: preparation or synthesis

Carbon dots were first discovered in 2004 during the purification of single-walled carbon nanotubes (SWCNTs) via preparative electrophoresis. CDs are a new type of fluorescent small-carbon nanomaterial with particles smaller than 10 nm. They are used widely in the disciplines of bioimaging,

drug delivery, biosensing, disease detection, synthetic chemistry, and materials research. These nanomaterials exhibit great biocompatibility, are photochemically and physicochemically stable, have tunable fluorescence emission and excitation, and are water-soluble with low toxicities and low production costs. Therefore, there has been a lot of interest in the creation, characteristics, and applications of CDs. Future research areas include the creation of carbon dots with different morphologies, sizes, and target specificities. Traditionally, carbon NPs' surfaces have been modified using organic and polymeric compounds to create CDs. CDs can be prepared using a wide variety of procedures, including laser ablation, combustion/thermal microwave-assisted (MWA) heating, electrochemical oxidation, and supported synthesis. However, several of these approaches require very sophisticated tools and processing steps. Due to their low cost and straightforward operational stages, hydrothermal, solvothermal, and MWA synthesis processes are greatly valued. Natural resources are advantageous for CD synthesis because they are practical, affordable, straightforward, and easily accessible. Carbon dots are made using top-down and bottom-up approaches, which include chemical, electrochemical, or physical processes. "Top-down" refers to breaking down larger carbon structures into smaller structures, whereas "bottom-up" refers to combining small carbon structures to form carbon dots, as shown in Fig. 4.1 [2].

Dehydration, polymerization, carbonization, and passivation are the four main steps involved in the formation of carbon dots utilizing a top-down method. In the top-down method, centrifugation and washing are employed to remove larger particles, but in a bottom-up approach, partial replacement and passivization (fictionalization) procedures are utilized to alter carbon dots [9–13], as shown in Fig. 4.2.

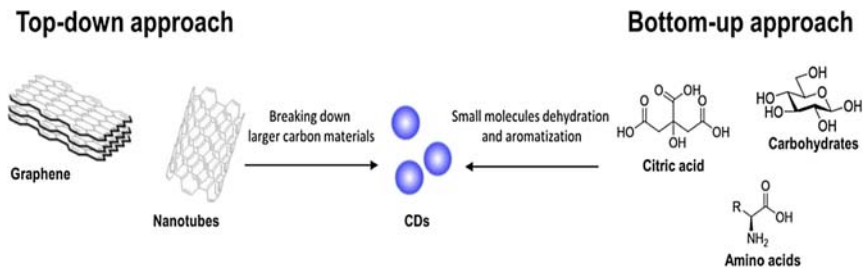

Figure 4.1 Top-down and bottom-up approaches for carbon dot preparation. *(Adapted from Ref. [2].)*

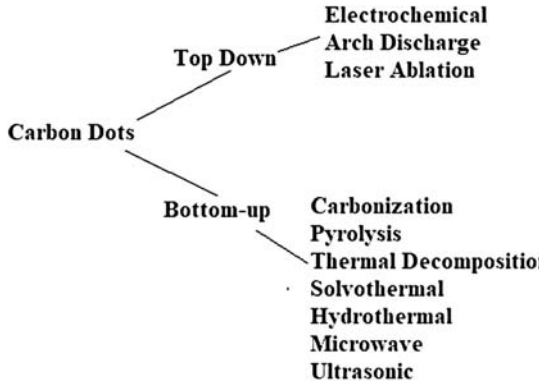

Figure 4.2 Preparation methods for carbon dots using top-down and bottom-up approaches.

2.1 Top-down approach

In the top-down approach, the synthesis of CDs is carried out using **electrochemical oxidation**, **laser ablation**, and **arc discharge** methods. Numerous methods have been proposed for the preparation of CDs. However, complex procedures and strong acid treatments are often required, and the as-prepared CDs tend to be of low quality, and in particular, have a low efficiency for photoluminescence. **Electrochemical** synthesis of CDs has attracted great interest since it was first reported by Zhou et al. It is considered one of the most prominent synthetic methods to synthesize ultrapure CDs from larger molecules. Due to the simple operation and readily available equipment, the electrochemical synthesis method is used more widely than the arc discharge and laser ablation methods. In this method, applied voltage and electrochemical reaction at the electrode usually cause the carbon electrode materials to erode and exfoliate, allowing the formation of CDs [14].

According to the study described in Ref. [15], the arc discharge method is a technique to rearrange the carbon dissolved from the bulk carbon precursors in the anodic electrode powered by the gas plasma formed in a sealed reactor. The temperature in the reactor may reach 4000 K under electric current, resulting in a high-energy plasma. Carbon quantum dots (CQDs) are formed when carbon vapor condenses in the cathode. In 2004, the arc discharge procedure was used for the first time to create CQDs of three different types [8]. By chance, single-walled carbon nanotubes (SWCNTs) with different relative molecular masses and fluorescence properties were created utilizing the arc discharge process. As prepared, the CQDs can emit

blue, green, and yellow, or orange fluorescence at 365 nm. According to further tests, CQDs possessed a hydrophilic carboxyl group attached to their surface and have a substantial particle size distribution due to the varied sizes of carbon particles released during the discharge process. The specific surface area of CQDs considerably is reduced due to their large particle size, which limits the active reaction sites during the electrocatalytic process.

Moreover, **laser ablation** is a synthetic approach that utilizes laser and carbon sources to produce carbon dots. To make luminous CDs, Sun et al. employed a process in which they combined graphite powder with cement and then heat-treated it to get a carbon source [16]. Carbon was also removed from the surface using a laser source and an argon gas vapor stream at 900°C and 75 kPa to produce carbon nanoparticles. The diameters of the produced CDs were varied, and there was no photoluminescence. After being refluxed in aqueous nitric acid for 12 h, the sample was treated with polyethylene glycol or poly(propionyl ethylene-imine-ethyleneimine). At 400 nm excitation, the photoluminescence of passivated CDs with a diameter of around 5 nm was extremely strong, with fluorescence quantum yields ranging from 4% to 10%. Table 4.1 summarizes different types of studies carried out to synthesize CDs using electrochemical oxidation/hydrothermal, laser ablation, and arch discharge methods.

2.2 Bottom-up approaches

Smaller carbon structures were turned into CDs with well-defined molecular weight and size, shape, and an easy-to-use and convenient process using bottom-up techniques. Bottom-up approaches are often low-cost, efficient, and fluorescent, all of which are necessary for practical applications of these innovative CDs [35] (Table 4.2). Hydrothermal, solvothermal, microwave-assisted, and thermal pyrolysis are the most prevalent procedures for the creation of carbon dots in bottom-up approaches [52]. Carbon dots are manufactured by hydrothermal treatment at 150−300°C from saccharides, amines, organic acids, and ionization to condensation, polymerization, and carbonization stages to form polymer-like carbonaceous carbon dots. A carbon-containing chemical was heated with organic solvents at high boiling temperatures, then extracted and concentrated using the **solvo-thermal process**. Carbon dots come in two types: hydrophilic and hydrophobic, with a diameter of 10 nm from carbohydrate. The key difficulties that may be addressed with this technology are carbonaceous aggregation, homogeneity and size control, and solubility [53].

Table 4.1 Top-down approaches for CD preparation.

S. no.	Technique used	Type of CD	Results	References
1.	Hydrothermal process	Nitrogen-doped carbon dots	Carbon dots were prepared	[17]
2.	Hydrothermal synthesis	Blue fluorescent carbon dots	Resulted in fluorescent carbon dots	[18]
3.	One-step hydrothermal synthesis method	Carbon dots	In both in vitro and in vivo microbial imaging applications, synthesized carbon dots were shown to be suitable in both live and dead cell microbiological imaging, with major properties such as biocompatibility, good penetrability, and nontoxic characteristics such as fluorescent probes	[19]
4.	Electrochemical approach	Carbon dots	CDs with a diameter of 6 −8 nm were created	[20]
5.	Electrochemical approach	Blue fluorescent CDs	The quantum yield was measured to be 8.9% for CDs with a diameter of 2−3 nm	[20]

Continued

Table 4.1 Top-down approaches for CD preparation.—cont'd

S. no.	Technique used	Type of CD	Results	References
6.	One-pot hydrothermal synthesis	Carbon dots	As a result, the dual-emission features emerged	[21—24]
7.	Electronic flash method	Carbon nanotubes	Carbon nanoparticles were generated in a very modest proportion as a result of the arc discharge. Arc Discharge (AcD) dust frequently contains a variety of difficult-to-extract elements	[6]
8.	Arc discharge	Fluorescent CDs	CDs with high fluorescence were isolated, with an average size of 18 nm	[8]
9.	Laser ablation method and chemical oxidation	Fluorescent CDs	Laser ablation approach produces effective outcomes	[25]
10.	Pulsed laser deposition and chemical oxidation	Carbon films	Diamond-like carbon films produced by pulsed laser deposition provide exceptional protective properties	[26]

11.	Laser ablation method	Carbon dot-like nanostructures	Controlling the ablation period and altering the ablation and excitation laser wavelengths allows CDs to be adjusted from near-UV to green wavelengths	[27]
12.	Laser ablation method and chemical oxidation	Carbon dots (CDs)	Carbon-based nanomaterials have unique optical properties, great biocompatibility, cheap cost, ease of modification, and functionalization, and show significant potential for a wide range of applications	[28,29]
13.	Laser ablation method and chemical oxidation	Graphene quantum dots	Liquid-phase LA is a quicker and cleaner one-step technique for manufacturing GQDs with fewer starting ingredients and by-products as compared to CO	[30]

Continued

Table 4.1 Top-down approaches for CD preparation.—cont'd

S. no.	Technique used	Type of CD	Results	References
14.	Laser ablation method and chemical oxidation	Carbon quantum dots (CDs)	These scientists found that liquid from laser ablation creates quantum dots in a considerably quicker and safer one-step approach with fewer starting chemicals and residues than chemical oxidation	[31]
15.	Laser ablation method	Luminescent carbon dots	Optical tests revealed that fluorescent particles or quasi-molecular fluorophores produced during the ablation process are the predominant source of luminescence in the resulting nanostructures	[32]
16.	Laser ablation in liquid	Fluorescent carbon and graphene oxide nanoparticles	The photoluminescence of the received nanoparticles was strong and wide in both cases, with a maximum that was dependent on the excitation wavelength	[33]

17.	Double-pulse femtosecond laser ablation	Ultrasmall carbon dots	These findings show that, in addition to single-pulse ablation, the double-pulse approach may be used to synthesize ultrasmall CDs with numerous surface functional groups, as well as other nanoparticles for catalytic and sensing applications	[34]

Table 4.2 Bottom-up approaches for CD preparation.

S. no.	Type of technique used	Type of CDs	Results	References
1.	Microwave-assisted synthesis	Carbon dots	Manufactured luminous CDs with a size of 3.7 nm, researchers employed first-time microwave irradiation	[36,37]
2.	Microwave-assisted synthesis	Carbon dots	Developed carbon source multicolor photoluminescence CDs with an average size of 5 nm	[38]
3.	Microwave	Carbon dots	Carbon dots with the size of 2.6 nm	[39]
4.	Microwave	Carbon dots	The carbon dots produced have an average diameter of 2–5 nm	[40]
5.	Microwave	Carbon dots	Carbon dots produced measured between 1 and 7 nm	[40]
6.	Thermal decomposition	Carbon dots	Carbon dots with the size of ~0.9 nm	[41]
7.	Carbonization	Carbon dots	Carbon dots between the sizes of ~2.4 ± 0.5 nm	[42]
8.	Carbonization	Carbon dots	Carbon dots between the sizes of 1 and 7 nm	[43]
9.	Pyrolysis	Carbon dots	Carbon dots with the size of 2.28 ± 0.42 nm	[12,13]
10.	Pyrolysis	Carbon dots	Carbon dots between the sizes of 5–8 nm	[44]

11.	Solvothermal method	Carbon dots	Carbon dots with the size of 3.3 nm	[45]
12.	Solvothermal method	Carbon dots	Carbon dots with the size of 7 ± 2 nm	[46]
13.	Solvothermal method	Boron-doped carbon dots	Carbon dots with the size of ~16 nm	[47]
14.	Ultrasonic	Fluorescent carbon dots	Carbon dots between the sizes of 5–10 nm	[48]
15.	Ultrasonic	Carbon dots	Developed carbon dots	[49]
16.	Ultrasonic	Carbon dots	Developed carbon dots	[50]
17.	Ultrasonic	Carbon dots	Developed carbon dots	[51]

Pyrolysis is an irreversible thermal breakdown in an inert environment that is used to synthesize carbon dots in the presence of a strong acid or alkali. Solid carbon residues originate from physical and chemical changes in organic materials. Researchers used hairs to make carbon dots by pyrolyzing them in one step at 200°C for 24 h. Pyrolysis is a three-step process that involves absorption, pyrolysis, and the release of carbon dots that have been created [15].

Carbonization is a chemical process in which organic material is pyrolyzed for a long time, resulting in a high concentration of carbon molecules [54]. **Microwave-assisted synthesis** produced CDs using electromagnetic irradiation with wavelengths ranging from 1 mm to 1 m, and is quick, low-cost, scalable, and nontoxic [55]. Thermal decomposition is an endothermic process in which substances are broken down by heat [52]. The ultrasonic method has also been recognized as an effective way for developing diverse carbon dots, and as a result, a large body of literature has been devoted to this type of carbon dosing. Carbon precursors, as well as acid, alkali, and other oxidants, are held under intense ultrasonic waves, causing carbon particles to break down into very tiny nanoparticles. The molecules are continuously cavitated. The use of high-energy ultrasonic waves eliminates the need for a complicated posttreatment process, allowing for the simple synthesis of CQDs with tiny dimensions [56].

2.3 Passivation

Several surface passivation procedures are available to brighten the synthesized carbon dots. Moreover, their size and surface chemical groups should be maintained to improve the electrical and optical properties of CDs. Heteroatom doping (nitrogen, sulfur, boron, phosphorus, and silicon) is a promising method in passivation and also improves the photoluminescence and functionality. Bourlinos et al. discovered that doping of CDs with boron significantly improved the nonlinear optical response of CDs. Gadolinium was added to the CD synthesis by Gong et al. and the resultant products could be used as fluorescent labels and magnetic resonance imaging contrast agents [57]. Aside from heterodoping, codoping CDs is a simple approach to improve their features. Li et al. employed a one-step microwave-mediated synthesis with citric acid and thiourea as precursors to produce sulfur and nitrogen codoped CDs with much higher Photoluminescence (PL)quantum yields than nitrogen-only CDs. CDs have a variety of functional groups that allow covalently bonding,

electrostatically interaction, or bonding passivation by inorganic, macromolecular, and organic molecules at reactive sites (hydroxyl, amine, and carboxyl groups) on the surface [58,59].

3. Different types of carbon dots

CDs are now classed mostly as carbon quantum dots (CQDs) or carbon dots, graphene quantum dots (GQDs), and carbonization polymer dots (CPDs) arranged in various forms [54,60]. Although the relationship between them may be established by altering the graphene layer and carbonization, the mechanism, micro/nanostructures, and characteristics (Fig. 4.3), GQDs are made by cutting larger graphitized carbon materials such as graphite powder, carbon rods, carbon fibers, carbon nanotubes, carbon black, or graphene oxide into small pieces using a top-down technique. The size of π-conjugated domains and the surface/edge architecture determine their optical characteristics. GQDs are anisotropic, having lateral dimensions greater than their height, whereas CQDs and CPDs are normally spherical, and are commonly made from tiny molecules, polymers, or biomass by "bottom-up" processes of assembly, polymerization, cross-linking, and carbonization (e.g., combustion, thermal treatment) [63–65].

CQDs have multiple-layer graphite structures in their spherical cores, and the inherent state luminescence and the quantum confinement effect of size dominate their photoluminescence emission features. CQDs are invariably spherical, with visible crystal lattices and chemical groups on the surface, demonstrating an intrinsic state of luminescence and the quantum confinement effect of their size. This has crucial significance in altering the size of CQDs to control the wavelength of photoluminescence. CDs have a

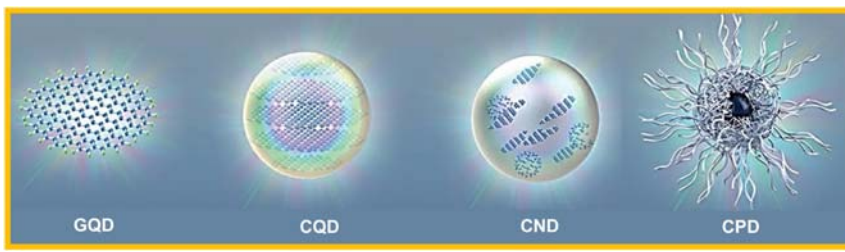

Figure 4.3 Classification of CDs. *CD*, carbon nanodot; *CPD*, carbonized polymer dot; *CQD*, carbon quantum dot; *GQD*, graphene quantum dot. *(Adapted from Refs. [54,61,62] with permission from Wiley.)*

high degree of carbonization and some chemical groups on the surface, but no obvious crystal lattice structure or polymer features, and their photoluminescence is primarily caused by defects/surface states and subdomain states within the graphitic carbon core, with no quantum confinement effect due to particle size [63–65].

CPDs are hybrid nanostructures made up of aggregated/cross-linked carbon cores and polymer chains shells, with the molecular state and cross-link structure determining the optical characteristics. CPDs have a polymer/carbon hybrid structure on the surface with many functional groups/polymer chains and a carbon core. Two types of totally carbonization cores, comparable to CDs or CQDs, a para-crystalline carbon structure formed of small carbon clusters surrounded by polymer frames and a highly dehydrated cross-linking and close-knit polymer frame structure are the four subclasses of the carbon core. The surface state, subdomain state, molecular state, and cross-link enhanced emission (CEE) effect all contribute to the photoluminescence of CPDs. The major optical characteristic is contributed by the molecular state and CEE effect, while other types of CDs lack these photoluminescence properties and mechanisms [63–65].

3.1 Biomass-based carbon dots

Natural products have always intrigued researchers because of their limitless availability and eco-friendly nature. NCDs are carbon dots made from common, unprocessed materials that are cost-effective, nonpoisonous, mostly inexhaustible, and simple to construct. These NCDs do not have to be synthesized in natural solvents; in fact, if all other factors are equal, they could be formed in watery arrangements, which increases their water dissolvability. The combination of NCDs necessitates the use of external energy. Because of the regular availability of unprocessed components and low assembly costs, carbon dots and their applications have evolved significantly, according to many studies.

By boiling an ethanol solution of pulp-free lemon juice [66], a low-cost, eco-friendly device with a high quantum yield (QY) of 28% and attractive optical characteristics was produced. Utilizing *Wedelia trilobata* biomass [67], unique rose-red fluorescence carbon dots (wCDs) were generated using a one-step microwave-solvothermal treatment. The long-wavelength emission of these nanodots was 654 nm. Effective bioimaging applications using leek as biomass for the production of dual-emission and single-emission carbon dots have also been reported [28,29].

Plum-based carbon quantum dots (PCQDs) have been generated using a simple bottom-up technique to use plum as a precursor [68]. This approach has strong antiinterference properties and has been successfully applied to the analysis of DOX in human urine and human serum samples with reasonable recoveries (92.61%−116.64%), indicating that it may be utilized as a clinical alternative for DOX detection. By hydrothermal carbonization of *Fusobacterium nucleatum*, an anaerobic bacteria [69], created *F. nucleatum*-carbon dots (Fn-CDs). Strong fluorescence, great stability, and outstanding biocompatibility were all characteristics of the *F. nucleatum*-carbon dots (Fn-CDs) that were created. Green pepper seeds were used to create blue-emitting carbon dots [70]. The suggested technology is simple, cost-effective, and environmentally friendly, and it may be used for environmental monitoring and biological imaging. By using the hydrothermal-carbonization process Atchudan et al. [71], were able to effectively convert leftover kiwi (*Actinidia deliciosa*) fruit peels into useful fluorescent carbon dots (KN-CDs). KN-CDs are also a good possibility for a selective and sensitive fluorescence sensor, according to the researchers.

Researchers have reported different approaches and methods to develop carbon dots from biomass and successfully utilized them for different biomedical applications. Fig. 4.4 [10] presents CDs prepared with watermelon peel [73], lychee seeds [72], and peanut shells using the pyrolysis method.

The attributes of the produced CDs can be adjusted by varying the pyrolysis states, such as pyrolysis temperature, pyrolysis term, and pH value [74]. Zhou et al. accomplished enormous scope in the creation of CDs by pyrolysis of waste watermelon strips under low temperature followed by filtration. The produced CDs have a strong blue brightness, excellent water solvency, and excellent stability in a wide range of pH and salinity. The as-arranged carbon dots were effectively utilized in HeLa cell imaging (Figs. 4.4A−4.8) [73].

4. Properties of carbon dots

Due to the excellent electrochemical and optical properties of CDs, they are widely used in a variety of applications. Carbon dots have superior charge transferability, increased electro-conductivity, effective surface area, and low toxicity when compared to other carbon-based nanomaterials and are therefore suitable for use in electrochemical and electrocatalysis applications.

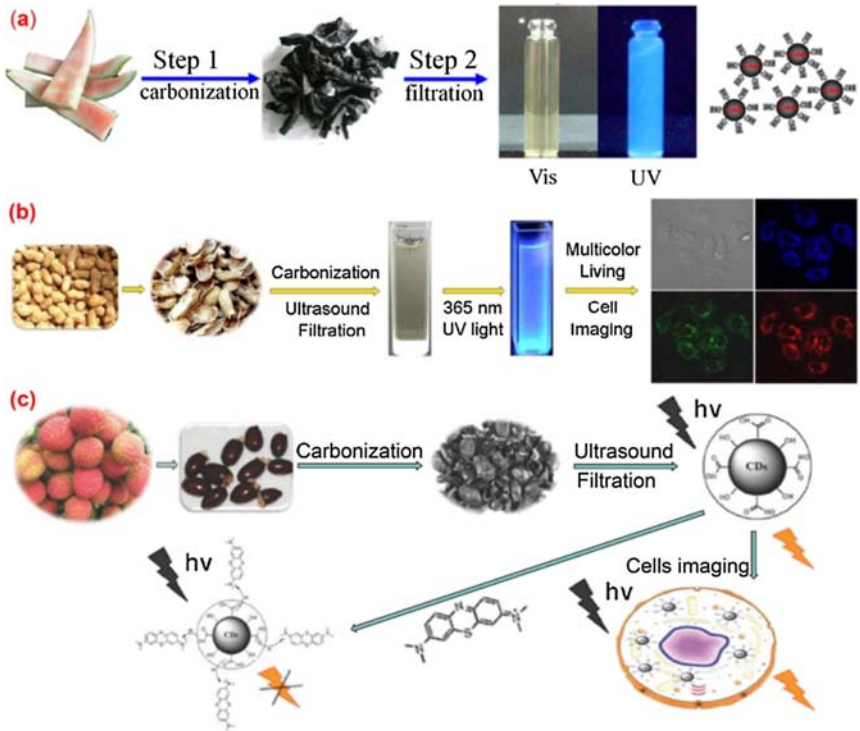

Figure 4.4 Illustrates the successful use of as-prepared carbon dots in HeLa cell imaging (A). Pyrolysis of lychee seeds produced fluorescent CDs with a quantum yield of 10.6% and little intrinsic cytotoxicity, which were used to image live HepG2 cells [72] (B). Because of the vast range of particle sizes and emissive locations, the emission spectra of the CDs created using this method were excitation-/wavelength-dependent, according to the scientists. This kind of CD has been employed in multicolor live-cell imaging with great success (C). pyrolysis process to make CDs from durian peel waste, which they used as an effective dopant in a composite electrode with a specific capacitance of 60, which is considerably greater than that for the pure activated carbon electrode. Using a simple thermal pyrolysis process, sago industrial waste was also utilized as a carbon source for the synthesis of CDs [73,74]. Furthermore, the porosity of CDs generated by pyrolysis methods makes them suitable for anticancer drug-delivery applications.

CDs create a Schottky barrier that forms an electrolyte—catalyst junction that may be easily eliminated, therefore confirming successful energy transformation. CDs may also move electrons very quickly during electrochemical processes due to their great electrical conductivity. CDs can effectively operate as active centers in electrochemical processes due to their

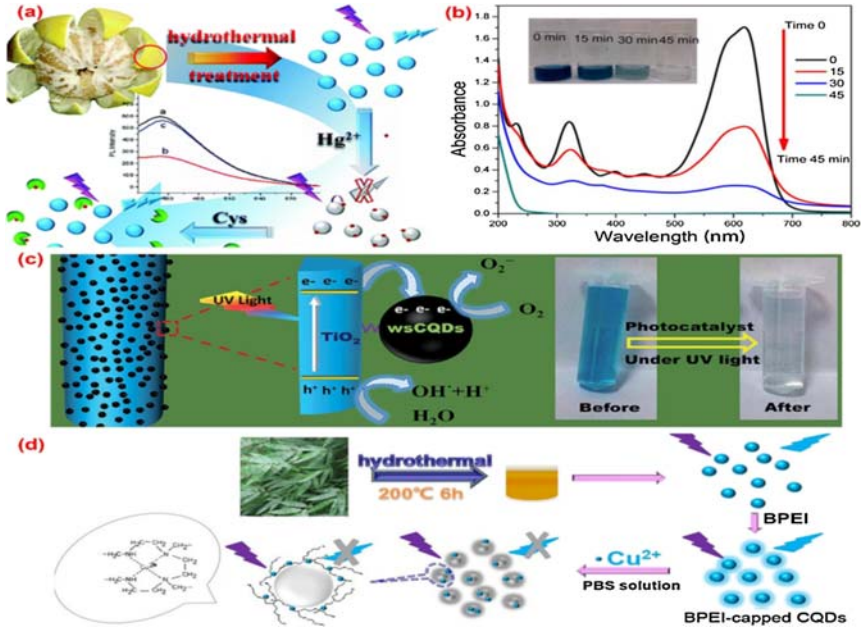

Figure 4.5 Presents the preparation of fluorescence CDs from biomass wastes through the hydrothermal method. (A) illustrates the preparation and application of CDs made from pomelo peel to make water-soluble CDs with a quantum yield of 6.9% for the selective and sensitive detection of Hg^{2+} using a hydrothermal technique [75]. (B) presents the azo dye naphthol blue-black (NBB) absorption spectra over CDs/ZnO at various irradiation intervals prepared with a simple one-pot hydrothermal carbonization process for the synthesis of fluorescent CDs from orange peel waste under moderate circumstances, and then the CDs were composited with ZnO for photocatalyzing the degradation of naphthol blue-black azo dye [76]. (C) presents UV light irradiation, photocatalytic degradation of methylene blue (MB) on a TiO_2—CDs composite. In this method, a simple hydrothermal process was utilized to obtain CDs with spherical morphology and oxygen-rich surface functionalities from lemon peel waste, which was used to determine Cr^{6+} and prepare TiO_2—CDs for the photocatalytic degradation of methylene blue dye under UV light irradiation [77]. (D) shows the production and use of CDs made from bamboo leaves [78,79]. *(Resource: [10])*

superior electro-conductivity, many defect sites and active edges, and huge surface area-to-volume ratio. When CDs are fused together with conductive materials, the electrochemical performance and properties may be greatly improved [35,61,62,88].

Several functional groups (hydroxyl, carboxyl, amine, and others) present on the surface of carbon dots, which provides a high number of sites for surface modification and increased electro-catalytic activity by accelerating intermolecular electro-conductivity. CDs have been shown to be the

Figure 4.6 Presents the development of fluorescence CDs from biomass using the microwave technique. (A) presents the preparation of CDs from eggshell membranes. Wang et al. presented a readily reusable and environmentally friendly microwave-assisted method for preparing CDs from protein-rich kitchen eggshell layers. The obtained CDs displayed excellent water solubility and fluorescence, with a quantum yield of roughly 14%, and they were used to ensure the simultaneous presence of Cu^{2+} and glutathione. (B) illustrates the synthesis and application of CDs from mango leaves using a one-pot microwave method. Their CDs displayed excitation-autonomous NIR discharge, prevalent cell take-up, high photostability, great biocompatibility, and intracellular temperature-detecting ability [80]. (C) illustrates the preparation and application of CDs from crab shell [81]. Bankoti et al. created CDs synthesized from onion peel to test their efficacy in accelerating wound healing. These were co-doped with nitrogen, sulfur, and phosphorus through straightforward microwave treatment of culinary waste onion strip (D). CDs demonstrated solid green iridescence, high dependability against pH and UV, and excellent cytocompatibility and wound healing efficiency in speeding up wound healing [82].

optimal nanomaterials for increasing the chemical stability of hybrid catalysts due to the huge number of active functional groups on their surfaces and their long-term chemical stability in a wide variety of solvents [89].

The intramolecular charge transferability of CDs doped with heteroatoms such as nitrogen, phosphorus, sulfur, boron, and others can greatly improve their electronic properties. When heteroatoms such as nitrogen,

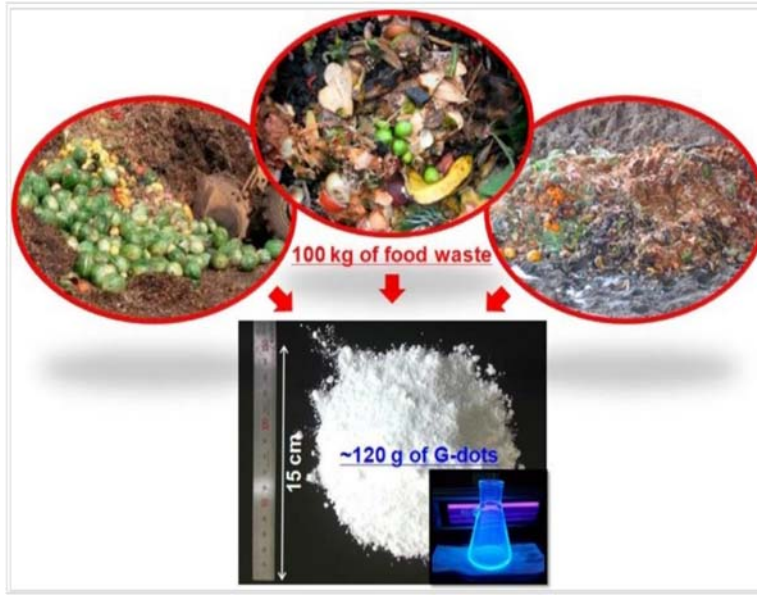

Figure 4.7 Large-scale synthesis of green CDs from food wastes. *(Adapted from Ref. [10].)*

phosphorous, sulfur, boron, and other elements are doped into CDs, the appropriate chemical structure is achieved, and the electric charge is efficiently transmitted from nearby carbon atoms [89,90].

The enhancement of intrinsic activity of surface functional sites, the distortion of their electronic configuration, tuning of local densities, as well as the acceleration of adsorption and desorption phenomena, all contribute to the exceptional electrochemical performance of heteroatom-doped CDs. Furthermore, during the fabrication of their hybrid nanocomposites with metals and metal oxides, CDs may be utilized as supporting materials, which can prevent agglomeration and therefore boost electro-catalytic activity. Furthermore, due to electrostatic stabilization, CDs can show high stability in aqueous conditions, facilitating the stability of hybrid catalysts [89,90].

Fluorescent CDs have been widely employed in a variety of healthcare applications, particularly in the fields of biosensing, bioimaging, and therapeutic development, because of their remarkable optical properties. The optical characteristics of CDs must be studied and understood in order to create a range of CDs for a variety of biomedical applications. CDs' absorbance is created in the short-wavelength region due to the transition

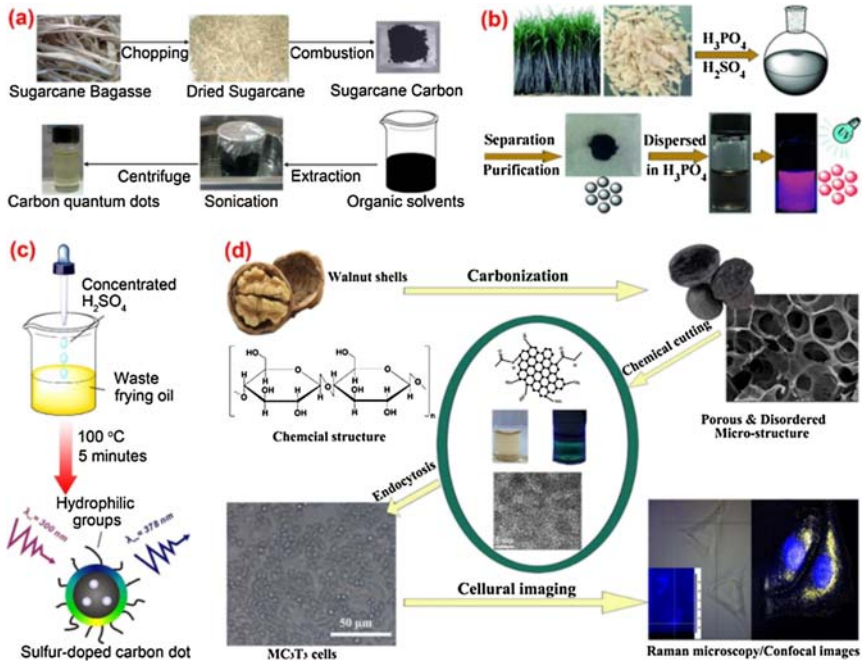

Figure 4.8 Illustrates a simple ultrasonic treatment-based technique for the large-scale synthesis of water-soluble CDs from food waste-derived carbon sources, achieving 120 g CDs from 100 kg of food waste mixes [83]. The synthetic process of CDs from sugarcane bagasse pulp including substance oxidation and a straightforward peeling process for green combination of fluorescent CDs from squander sugarcane bagasse mash is shown in (A). CDs had elements of high fluorescent quantum yield (around 18.7%), exceptional crystallinity, and excellent biocompatibility [84]. (B) illustrates the use of sugarcane bagasse as a carbon source in the planning of red-transmitting CDs for specific assurance of vaporous smelling salts by using carbonization through concentrated sulfuric and phosphoric corrosive [85]. (C) shows the preparation of sulfur-doped carbon dots obtained from waste frying oil, as described in Ref. [86]. (D) presents the outcome of another study showing the synthesis and application of CDs from walnut [87]. *(Resource: [10])*

of C═C bonds in their structure. From 260 to 320 nm (i.e., in the UV area), CDs show high optical absorption. Due to surface functional groups and surface passivation, their absorbance range varies depending on the kind of CD. Under electrical activation, CDs may generate photons in the visible range, which is crucial for studying their electrochemiluminescence (ECL) features. This results in a stable ECL due to improved electron transport due to a substantial quantity of sp^2 carbon in CDs. Chemiluminescence (CL) is a chemical process that produces light. CDs can create CL in aqueous solvents

under the right redox conditions, with the unstable products arising from intermediate radicals during CL [91].

4.1 Factors affecting the properties of carbon dots

The four primary aspects governing the fluorescence features of CDs are quantum size effects, surface imperfection states, band gap advancement, and surface passivation [92–95]. According to some studies, the surface condition is most likely the most important factor in understanding the photoluminescence features of CDs [96]. Surface defects caused-shift in the emission wavelength of CDs. Fluorescence characteristics of carbon dots are also influenced by the functional groups present on their surface. As a result, surface passivation or surface functionalization is critical in controlling CD luminous characteristics. Further, natural substances used in the union of CDs could affect their fluorescence properties. In one study, CDs obtained from pineapple peel were completely destroyed after a few weeks of storage, but the CDs obtained from cucumber peel remained stable. Furthermore, fungus developed on the surfaces of the CDs made from pineapple, but not on the CDs made from cucumber peel. Raw material sources have their own place in the characteristics of CDs [97]. A carbonization technique is used in the manufacture of fluorescent CDs using biomass wastes as carbon sources. Because carbonization is an endothermic process, temperature plays an important role in CD synthesis. In one study, a simple and low-cost pyrolysis process was studied to see the effect of pyrolysis temperature on the luminescence characteristics of CDs synthesized from various plant leaves (e.g., lotus leaves, pine needles, oriental plane leaves, and palm leaves). Their findings revealed that when different carbon sources were employed to synthesize CDs, the optimal pyrolysis temperatures were different. Proper temperature must be maintained for an effective outcome [36,37].

Further, overcarbonization will destroy the surface structure of CDs if the reaction time is too lengthy. A short response time, on the other hand, will result in insouciant carbonization of the carbon source, resulting in CDs with weak fluorescence emission. It should be mentioned that the temperature affects the effect of the reaction time on the optical characteristics of CDs. Only when the reaction is carried out at the right temperature does the optimization of reaction time make sense. Even when using an ultra-long reaction time, if the reaction temperature is not high enough, no usable end-product will be created [86].

The fluorescence emission intensities of CDs formed from certain biomass wastes changed with respect to the pH value. According to the study carried out by Chunduri et al., CDs from coconut husk had a lot of carboxyl and hydroxyl groups on their surface. The fluorescence emission intensity of the CDs steadily reduced as the pH value climbed from 4 to 12 due to protonation and deprotonation of carboxyl groups under varied pH circumstances and the associated change in electrostatic charge behavior [98]. Many studies have employed heteroatom doping to enhance the characteristics of CDs. The insertion of heteroatoms into the carbon atom framework may be used to effectively control the electrical characteristics, internal chemical properties, and surface chemical properties of CDs [99].

CDs are frequently passivated or functionalized to increase their fluorescence emission intensity and therefore their relevance to bioanalytical tests. Surface passivation of CDs can reduce surface imperfections and improve the chance of exciton–hole recombination, preventing CD aggregation and increasing fluorescence emission intensity. Surface passivation can be accomplished in two ways: capping bare CDs with long-chain agents or oxidizing CD surfaces with strong acids. Carbonization and passivation occur at the same time during the synthesis process of CDs from biomass waste due to the presence of long-chain carboxylic acids and other functional chemicals in carbon sources. As a result, CDs made from waste biomass are frequently self-passivated. Hydroxyl, amine, and carboxyl are abundant on their surfaces [100].

5. Carbon dots as potent antimicrobial agents

The number of bacteria that are developing medication resistance is increasing, and bacterial diseases become harder to cure if the pathogens continue to evolve and become MDR, which raises mortality rates and expenditures for healthcare. Additionally, the problems with resistance are no longer limited to a small number of distinct pathogenic species and a limited number of healthcare facilities, but rather affect almost all major pathogens and every type of epidemiological setting, including acute-care hospitals, long-term-care facilities, communities, etc. The serendipitous discovery of CDs sparked a deliberate effort to develop a unique nanomaterial-based technique for treating infectious diseases with great selectivity and specificity to defeat bacterial infections that are resistant to a variety of drugs. Recent studies have demonstrated that doping commonly used antibiotics, such as ciprofloxacin, on the surface of CDs significantly

increases the antibiotics' selectivity and specificity. This makes CDs an effective platform for building a novel drug-delivery system and improving the efficacy/selectivity of the currently used antibacterial agents [101].

There are several mechanisms proposed by the researchers during the study of Bing et al. showing that positively charged CDs interact electrostatically with the negatively charged cell wall of *Escherichia coli* (*E. coli*), encouraging nanoparticle uptake and bacterial death. The presence of ammonium on the surface of CDs and carboxyl and phosphate salts on the bacterial cell wall allows first stage contact as illustrated in Fig. 4.9A [102]. Physical and mechanical damage to the bacterial membrane, destruction of the bacterial cell wall with subsequent leakage of cytoplasmic material (Fig. 4.9B) [103], inactivation via PTT effects due to localized temperature increase, direct or light-promoted generation of ROS [21−24], and DNA and protein damage and fragmentation (Fig. 4.9C) [104,105] are all examples of CDs' bacteriostatic or bactericidal effects. Bacterial inactivation caused by membrane disruption is another typical effect of CD intercalation in bacterial membranes [102]. It has been discovered that not all carbon dots are created equal and that their structural characteristics, such as the type of core and surface capabilities, have a substantial impact on how these materials interact with other cells and creatures (such as Gram-negative or Gram-positive bacteria). CDs have been discovered to act as photosensitizers that can be activated with excellent spatiotemporal control upon exposure to light, resulting in the formation of ROS and membrane damage, in addition to their fluorescent features being used as a technique

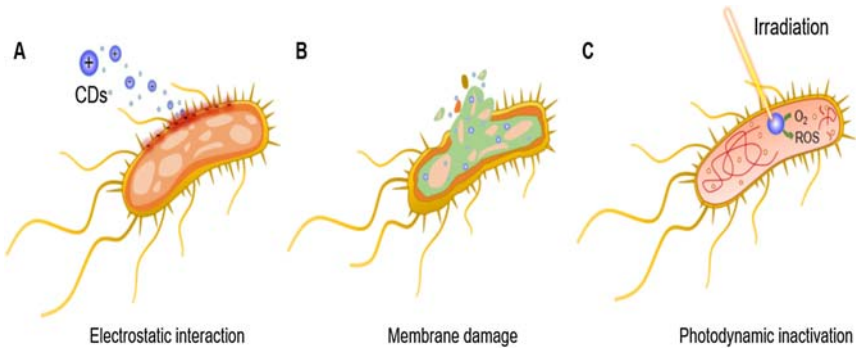

Figure 4.9 The mechanism of antimicrobial activity. (A) The initial electrostatic contact between CDs and the bacterial cell wall. (B) Irreversible rupturing of the cell membrane. (C) Cytoplasm material leakage and photodynamic inactivation induced by CDs, accompanied by the generation of reactive oxygen species (ROS) and DNA damage.

to label and photograph bacteria. Effective theranostic agents with enhanced antibacterial properties have also been demonstrated in nanocomposites of antimicrobial agents (such as antibiotics and transition metals) with CDs. CNDs with various functional groups also have the potential to serve as antibacterial agents. The core structure and functional groups revealed on the CD surface are intimately linked to the functional and biological capabilities of nanomaterials. Because the structure of a CD is largely dependent on the precursors and synthetic procedures utilized, tiny differences in precursor types, solvents, and synthesis methodologies result in structurally different nanoparticles. It is difficult to predict the potential antibacterial activity and selectivity of any novel CD without carrying out comprehensive structural characterization studies [106–108].

When exposed to visible light, the ROS produced by CDs boosts the antibacterial properties and expedites sterilization, which aids in wound healing. Additionally, minute quantities of ROS can function as crucial mediators of cell signaling, hasten wound healing, and encourage skin cells to actively participate in skin regeneration (Fig. 4.10) through the in situ development of cationic CDs on embellished black phosphorus nanosheets (BPs). When compared to conventional antibacterial medications, CDs have superior optical qualities, strong biocompatibility and solubility, and a

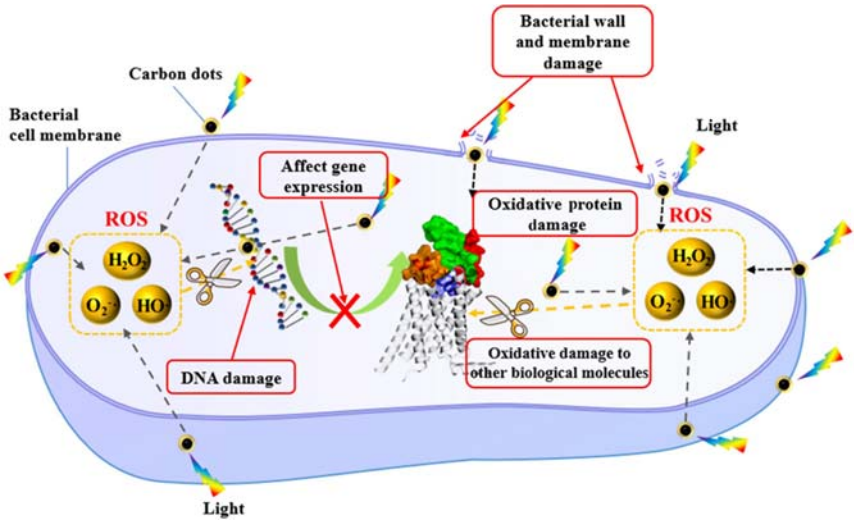

Figure 4.10 Cartoon representation of the antibacterial properties of photoactivated CDs. CD adhesion to bacterial surfaces and ROS production brought on by visible light. ROS, reactive oxygen species.

variety of rich and tunable surface-functional groups. They can effectively combat bacterial resistance with their photodynamic antibacterial mode. By adhering to bacterial cell membranes, CDs can alter the bacterial metabolism and break down the cell membrane. In order to eliminate germs, photogenerated ROS can damage bacterial membranes. The antibacterial activity of CDs is influenced by their particle size, surface functional groups, surface charges, light intensity, and precursors of the synthetic CDs. For use as wound dressings to stop bacterial infections and hasten wound healing, CDs can be manufactured for use in a variety of dressing materials and combined with various polymer composite materials. Their special qualities can also be used to create multipurpose antibacterial substances [109].

These functional groups can be attached to antibacterial medications, boosting their characteristics even further. For example, lauryl betaine (BS-12) is a quaternary ammonium molecule with a quaternary ammonium group, a lengthy hydrocarbon chain, and a carboxyl group. The hydrocarbon group has the capacity to integrate itself into the cell wall, and the ammonium group involved has antibacterial action. The hydroxyl groups aid in the binding of molecules to one another or to nanoparticles. As a result, quaternary ammonium compounds can be used to tag CDs. The fluorescent characteristic of CDs aids in the tracking of molecules, whereas BS-12 aids in the recognition of germs as well as the killing of Gram-positive bacteria [101].

Ampicillin (AMP) was used as the starting material for a one-step hydrothermal synthesis of CDs. Antibiotic AMP, a β-lactam, has the elements C, O, N, and S. Therefore, AMP can be employed as a precursor for the high quantum yield synthesis of N- and S-co-doped CDs. CDs can be made from broad-spectrum antibiotics like metronidazole, which act against obligate anaerobes like *Peptostreptococcus micros*, *Prevotella intermedia*, *P. gingvivalis*, fusobacterium, and facultative anaerobes like *Streptococcus mutans*, as well as CDs made from penicillin G (*Staphylococcus aureus*, *Escherichia coli*) [101,110]. According to the data, CDs had a bactericidal efficacy against *S. aureus* of almost 100% at a concentration of 0.7 mg/mL under visible light irradiation for 60 min. This efficiency was comparable to that of AMP at the same concentration. Furthermore, the CDs could be employed in multicolor bioimaging due to their high fluorescence stability and biocompatibility. The findings demonstrated that the synthetic CDs selectively stained *S. aureus* and *L. monocytogenes* but not *E. coli* or *Salmonella*, enabling the use of the CDs to distinguish between Gram-positive and Gram-negative bacteria. Spermidine was used as a carbon precursor in the

development of an antibacterial agent for bacterial keratitis, and it was found to be effective against a wide range of bacteria, including *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Salmonella enterica* serovar *Enteritidis*, as well as multidrug-resistant bacteria such as meticillin-resistant *Staphylococcus aureus* (Table 4.3) [116].

CDs have been shown to be effective in the treatment of bacterial keratitis (BK) in infectious diseases . Direct pyrolysis of spermidine trihydrochloride powder yielded supercationic CDs (CQDSpds). The CQDSpds have been found to kill Gram-positive and Gram-negative bacteria, as well as multidrug-resistant microorganisms like meticillin-resistant *S. aureus* (MRSA). CQDSpds' antibacterial action was due to their significantly positive charge (z-potential ca. 45 mV), which induced severe bacterial membrane rupture and death. Ocular injection of CQDSpds can cause the opening of the tight junction of corneal epithelial cells and cure *S. aureus*-induced eye infection, according to in vivo antibacterial research in rabbit eyes.

Researchers have also proven the utility of CDs in the fight against viral infection [123]. Curcumin was transformed to curcumin CDs (Cur-CQDs) using a simple dry heating technique, which had polymer-like curcumin and somewhat damaged (pyrolytic) curcumin polymers or molecules on the surfaces. In RD cells, Cur-CQDs were effective against EV71 infection (human rhabdomyosarcoma). Cur-CQDs can prevent the EV71 virus from attaching to the cell membrane of RD cells, as well as inhibiting EV71- and EV71-induced eIF4G cleavage and lowering the expression of phosphorylated p38 kinase. Cur-CQDs are an efficient antiviral drug for protecting newborn mice against EV71 infection, according to in vivo animal experiments.

The bacteriostatic activity of the CDs was shown against Gram-positive *Bacillus subtilis*, *Staphylococcus aureus*, and *Escherichia coli*, as well as Gram-negative *Bacillus* sp. WL-6 and *E. coli*. It was discovered that a concentration of 50 g/mL was sufficient for the *Bacillus* species (*B. subtilis* and *B.* sp. WL-6) to completely prevent colony development, however two times greater concentrations were required for the other two species. When ampicillin-resistant *E. coli* was treated with the CDs, the same outcomes were attained. These findings demonstrate the CDs from vitamin C's broad-spectrum antibacterial action. The use of CDs to classify and recognize bacteria kinds is another fascinating subject [101]. This allows for rapid Gram-type identification and even selective bacterial inactivation. Yang et al. successfully demonstrated that their CDs were adsorbed onto

Table 4.3 Antimicrobial activities of carbon dots (CDs).

Types of carbon dots	Antimicrobial effects	References
EDA-CDs	EDA-CDs treatment for 30 min reduced ~4 logs of *E. coli* viable cell numbers	[1,11]
EDA-CDs, PEI_{600}-CDs, and PEI_{1200}-CDs	Treatment of EDA-CDs with 0.1 mg/mL for 1 h decreased the number of viable cells by 3.26 logs Treatment with PEI600-CDs and PEI1200-CDs for 1 h (0.1 mg/mL) reduced viable cells by >7 logs and 1.82 logs, respectively	[111]
Carbon dot nanopowders combined with H_2O_2	Dots at a concentration of 10 g/mL and 8.82 mM H_2O_2 reduced the number of viable cells by 2.46 logs	[112,113]
Dot samples coupled with TiO_2	The treatment (1 μg/mL) of dot samples for 24 h inactivated 90.9% *E. coli* and 92.8% *S. aureus*	[93,94]
Dot sample combined with ZnO in hydrogel	Dot samples treatment inactivated 99.9% of the bacteria	[114]
Dot sample with $Na_2W_4O_{13}/WO_3$	Treatment for 100 min inactivated about 2×10^7 CFU/mL of *E. coli* cells	[21–24]
Dot sample from carbonization in polymer films	Light irradiation for 60 min caused up to 5 logs of inhibition effects against *S. aureus*, *E. coli*, and *K. pneumoniae*	[115]
Dot sample with penicillin	The treatment at 100 μg/mL inhibited more than 50% of MDR in *S. aureus* and *E. coli* (DH5α)	[116]

Continued

Table 4.3 Antimicrobial activities of carbon dots (CDs).—cont'd

Types of carbon dots	Antimicrobial effects	References
Dot sample coupled with ampicillin	The MIC value decreased to 14 μg/mL from free ampicillin of 25 μg/mL	[117]
Dot sample carrying ciprofloxacin hydrochloride	The MIC value was lower for *E. coli* than for *S. aureus*	[118]
Dot sample carrying metronidazole	Showed antibacterial activity against *P. gingivalis*	[110]
Dot sample from carbonization of ammonium citric coupled with spermidine	Antibacterial activities against *E. coli*, *S. aureus*, *B. subtilis*, and *P. aeruginosa*	[119]
Dot sample carrying quaternary ammonium moieties	Dot sample inhibited the growth of *S. aureus*	[101]
Dot sample from vitamin C	Treatment of *R. solani* and *P. grisea* fungi (300 μg/mL) significantly reduced the growth of the fungi	[58,59]
Dot sample synthesis doped with Au	*C. albicans* fungus showed significant antifungal activity with MIC80 ~250 μg/mL	[120]
Dot sample from PEG-diamine and ascorbic acid as precursor	Significantly inhibited the multiplication of the pseudorabies virus	[121]
EDA-CDs	EDA-CDs inhibited 100% of the binding of human norovirus-like particles (VLPs) to histo-blood group antigens receptors on human cells	[112,113]
Dot sample prepared from benzoxazine monomer	Dot sample showed potent antiviral efficacy against adenovirus-associated viruses, zika, dengue, and pig parvovirus	[122]

Gram-positive bacteria, resulting in inactivation [124]. Lin et al. give a complete account of current improvements in CDs for sensing and destroying microorganisms, including bacteria, fungi, and viruses [7, 8]. The antibacterial activity of CDs is directly linked to their nitrogen content and surface charges. To assure the creation of CDs containing cationic groups on the CD surface, several reported antimicrobial CDs employ amines or quaternary ammonium salts as starting materials for the synthesis of these carbon-based probes [125]. During CD synthesis, nitrogen (along with other heteroatoms such as P, O, and S) was also added utilizing a variety of different starting materials [126].

The ability to decay into CO_2, CO, and H_2O under a variety of situations is another advantage of the vitamin C-derived CDs, with visible light, a mild temperature (37°C), and air causing the fastest deterioration. This degradation may occur within microbes, therefore, CDs decay after killing bacteria or preventing their growth and are no longer a hazard to other microbes. Due to the CDs' ability to attach to DNA, it was discovered that when they created CDs from tamarind, they could stop the growth of *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *E. coli*, and *S. aureus* [127].

Polyamines, amino acids, biomass such as plant leaves and fungus, food, and industrial and waste byproducts, among other things, have been utilized in the creation of doped CDs [128–134]. Two independent comparison investigations from the Kang [10] and Travlou [134] research groups revealed that N- and S-doped CDs had extremely distinct antibacterial activities. These scientists found that higher S-doping concentration was associated with higher repulsive forces between fewer positively charged CDs (when compared to N-doped CDs) and negatively charged microorganisms (Fig. 4.11).

Bagheri et al. investigated the potential of CDs and the conjugates that they can produce for antifungal activity against the fungus *C. albicans* [135]. Interestingly, GQD derived from GO does not exhibit any antibacterial activity in vitro. However, the intrinsic peroxidase-like activity of GQDs mediates the decomposition of H_2O_2 to generate OH radicals with stronger antibacterial activity. This enables wound healing/disinfection using GQD bandages with a low concentration of H_2O_2. The therapy of bacterial keratitis in rabbit eyes demonstrated that spermidine CDs (CQDSpds, made by heating spermidine in one step) have in vivo antibacterial activity [136]. According to Li et al., the CDs used to kill bacteria also had broad-spectrum antifungal properties against *R. solani* and *P. grisea* [58,59]. Additionally

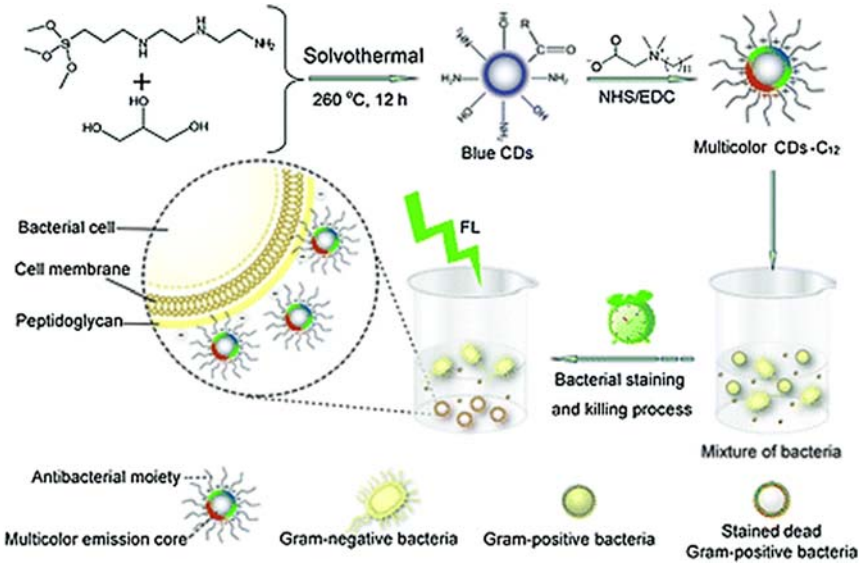

Figure 4.11 Schematic representation of the strategy for the synthesis of amine-functionalized CDs modified with lauryl betaine for selective labeling and inhibition of Gram-positive bacteria in a mixture of Gram-positive (e.g., *S. aureus*) and Gram-negative (e.g., *E. coli*) bacteria.

discovered were CDs' antifungal properties on *C. albicans*. Similar to this, ciprofloxacin-conjugated CDs were tested on *Saccharomyces cerevisiae* yeast cells[113], and the brilliant green fluorescence emissions were believed to be caused by the CDs inside the cells [137].

Over several decades, oxidizing antimicrobial substances like sodium hypochlorite (NaOCl) and hydrogen peroxide (H_2O_2) have been widely used as all-purpose disinfectants against a variety of microorganisms [112,113]. The pairing of CDs with traditional antibiotics, in which the dots also act as drug carriers, is comparable to the combination method. For instance, Jijie et al. investigated the dot-AMP "conjugates" as visible light-triggered antibacterial agents by coupling ampicillin (AMP) to CDs containing surface amino moieties. The inactivation of *E. coli* cells under visible light illumination is evidence that the conjugate arrangement conserved the antibacterial capabilities of AMP and CDs while improving the stability of AMP relative to that of free AMP. Additionally, CDs-derived conjugates have been utilized in conjunction with antibiotics for things like regulated drug release to prevent the development of microbial resistance brought on by excessive antibiotic use [117].

The construction of a multifunctional CDs-based theranostic platform for merging the therapeutic effects and diagnostic capabilities at the same time has been made possible by the growing body of research and increased understanding of the microbicidal qualities of CDs. A few studies have already been published on the use of CDs for photodynamic treatment, medication administration, and bioimaging to produce simultaneous effects. For instance, CDs were coated onto the surface of a ZnO nanorod for use in bioimaging and antimicrobial applications. The resultant nanohybrid showed brilliant green fluorescence emissions when taken up by *S. aureus* cells and also showed concentration-dependent antibacterial activity against *S. aureus* and *E. coli*.

As a result of a one-step hydrothermal process, effective CD photocatalysts with high quantum yield were created. The as-prepared CDs displayed numerous special qualities, such as strong biocompatibility and controllable brightness. Under visible light illumination, the CDs selectively interacted with *S. aureus* and demonstrated potent antibacterial activity by rupturing the bacterial membranes. According to our findings, CDs had a bactericidal effectiveness against *S. aureus* of about 100% at a concentration of 0.7 mg/mL when exposed to visible light for 60 min, which was comparable to AMP's effectiveness at the same dose. The CDs could also be employed in multicolor bioimaging because of their excellent fluorescence stability and biocompatibility. Furthermore, the creation of a distinct bandgap between the fundamental and excited states of the CDs resulted in less ROS production and, as a result, less bactericidal activity. Zhang et al. [21–24] found a link between CD photo-oxidative activity, phosphorescent quantum yield, and N content, emphasizing the need for N-doping to improve CD photosensitization. Markovi'c et al. [138] found that F- and Cl-doped CDs reduce the photodynamic antibacterial impact of nanoparticles as compared to nondoped ones due to lower ROS generation. The combined analysis of these findings illustrates the critical role of N-doping during CD synthesis as a necessary characteristic for producing CDs with strong antibacterial activity.

CDs may be a useful tool for achieving the desired maximum antibacterial activity at the lowest possible dose of individual agents, thereby minimizing the potential harm that antimicrobial chemicals may cause to the environment and the general public, as well as the emergence of microbial resistance. Therefore, based upon the above studies, extraordinary functioning, and characteristics, we can state that carbon dots are a potential source for antimicrobial activities and can easily be synthesized using

different types of biomass. Their potential for antimicrobial activities cannot be neglected.

6. Conclusions

In summary, as a result, the multifunctional CDs in their current state could be a useful tool for a variety of biomedical applications. One of the most recent developments in carbon-based nanomaterials is carbon dots. These are employed in a variety of applications because of their numerous features. Recently, their antimicrobial qualities were also investigated. In a few instances, CDs naturally possess antibacterial properties, but in many others, antibacterial features are added to CDs or their performance is improved by applying them to specified synthesis conditions or functionalization approaches. Although a lot of research has been done using this strategy, another choice is to boost the antibacterial activity of CDs after exposure to various radiation wavelengths. Antibiotic resistance is on the rise, and this poses serious health and economic problems for everyone. The slow rate of discovery of new antibacterial agents necessitates the creation of novel antimicrobial medications, but it also necessitates the improvement of repurposing tactics for already-existing agents and efficient diagnostic tools that can guide antibiotic prescription. The creation of new probes that can target bacteria for detection and elimination as efficient theranostic methods has become increasingly important in recent years. Due to their many benefits over molecular fluorophores and other fluorescent nanoparticles, such as their water solubility and ease of production, carbon dots (CDs) have gained popularity as prospective bioimaging probes. These materials have favorable physicochemical characteristics, such as chemical and photochemical stability and low toxicity, which make them perfect for biological applications, as we have seen in the examples given above. In fact, since their discovery, this class of carbon-based fluorescent nanodots has been used in a wide variety of biological and medicinal applications. It has become clear that more work is still needed to define the key parameters necessary to develop reliable and reproducible synthetic strategies that result in homogeneous materials with defined molecular functions because the CDs' functional and biological characteristics are linked to the nanomaterial's molecular structure, which depends on the choice of starting materials and synthetic strategy. Additionally, CDs have found use in the creation of novel materials such as hydrogels, nanofibrous materials, and polymers for use in wound healing and tissue regeneration as well as in

materials that can offer durable immunity against infections. Improved and tailored CD-based probes and materials will be developed as we get a deeper knowledge of the critical functional factors necessary for bacterial targeting at the molecular level. We are excited to monitor the developments in the coming years of this fast-expanding field of research, which has already made enormous strides. Despite the fact that we are most likely still some distance from realizing the full potential of CDs, our discoveries provide important information for the creation of "next-generation" antibacterial nanomaterials.

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SECTION 2

Functionalized nanoparticles-based coatings for food and packaging applications

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CHAPTER 5

Potentially effective and active antibacterial nanocomposites for the food industry

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1. Introduction

1.1 From conventional to bionanocomposites: the priority trends in food packaging

Many studies have increasingly concentrated on the development of easily degradable and biocompatible food packaging materials in response to the increased demand for sustainability and ecological safety. After usage, biopolymer-based packaging materials may be disposed of at biowaste decomposition facilities, producing organic byproducts such as carbon dioxide (CO_2) and water (H_2O). However, the use of biodegradable polymers in food packaging systems is frequently limited due to flaws such as relatively mild mechanical barrier capabilities in comparison to synthetic polymers and heat properties in comparison to standard nonbiodegradable petroleum-based plastics. Brittle nature coherence, low resistance to lengthy manufacturing methods, and a lower heat distortion temperature requirement are a few of the most unfavorable characteristics of these natural biopolymers, owing to low melting resistance and melting enthalpy, as well as limited flexibility. Nonetheless, multiple studies have been conducted to improve biopolymers for use in food packaging systems due to the numerous advantages afforded by these biodegradable polymers, including ecological safety and sustainability. Among the different ways for improving biopolymers, the utilization of nanotechnological ideas is a new discovery with many beneficial characteristics [1,2]. Thus, nanotechnology-improved food packaging solutions have an environmental benefit over their conventional equivalents that use plastic barriers, while functional

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elements such as antibacterial agents allow for longer product shelf life. It may also identify numerous spoiling signs, such as the formation of off-flavors, color, and dangerous food toxins. The development of smart and intelligent food packaging systems based on nanotechnology improves system efficiency and food security by localizing, sensing, reporting, and remote control of food items [3], as well as increasing food nutraceutical quality via nano-based delivery methods [4]. The majority of nanoparticles investigated for food packaging applications are potential antibacterial agents that may also operate as carriers of other bioactive substances and prevent microbial contamination and spoiling. These nanoparticles are used to release different bioactive chemicals such as antioxidants, enzymes, flavors, antibrowning agents, antimicrobials, and other bioactive materials in order to maintain food quality and extend product life, even after the packaging has been opened [5]. The packaging industry has paid substantial attention to antimicrobial packaging because it is a great alternative method for reducing, limiting, or inhibiting the growth of harmful and spoilage bacteria in food goods as well as extending shelf life. Antimicrobial packaging films are created by combining the antimicrobial agents in a polymer matrix to inhibit the growth of specific microorganisms whose activity would otherwise contaminate food. These antimicrobial packaging methods were created to achieve and support three key goals, namely the maintenance of quality, assurance of safety, and extension of shelf life. Under particular circumstances, nanoparticles of certain metals and metal oxides, such as iron, silver, zinc oxides, carbon, magnesium oxides, titanium oxides, and silicon dioxide nanoparticles, are widely used as antimicrobials and food additives (He et al., 2019). Bionanocomposites and nano-encapsulation have lately arisen as promising alternatives to traditional nanoparticle usage in active food packaging, among other nano-applications. Despite a long list of benefits, the toxicological concerns associated with heavy particle and nanoparticle migration cannot be overlooked. For example, the European Food Safety Authority [6] states that the top limit for silver migration in food packaging must be greater than 0.05 mg/L in water and 0.05 mg/kg in food [7]. As a result, created nanobiocomposites and their disposal should be thoroughly investigated, including in regard to the migration phenomena. Lee et al. [8] demonstrated that in vivo exposure to silver nanoparticles might produce immunotoxicity and neurotoxicity by altering the expression of genes involved in immune cells, neurodegenerative illnesses, and motor neuron disorders. For the creation of safe, biodegradable antimicrobial packaging, a

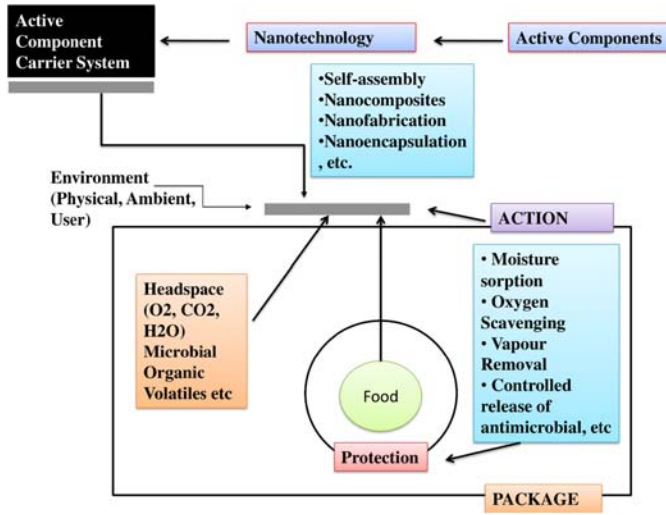

Figure 5.1 The active component carrier system.

number of methods have been found and investigated. Two key methods involve either using a natural polymer with built-in antimicrobial properties or incorporating specific antimicrobials into the biopolymer matrix. Bacteriocins, essential oils, plant extracts, enzymes, organic acids (like lauric acid), and inorganic/metallic nanoparticles are a few of the various classes of antimicrobial agents that have been identified and used in biodegradable packaging systems (Fig. 5.1) [9]. As a result, the majority of food packaging systems are made up of three main parts: the food product, the headspace packing atmosphere, and the packaging material. These three parts work together to provide the intended results.

1.2 Nano-based composite films: associated safety concerns

Controlled nanoparticle addition increases physical qualities while also imparting various functional properties such as antioxidant, antibacterial, and so on. However, the key worry is the migration of these nanoparticles from the container to the meal or onto the food surface, which restricts their widespread use. However, much more study is needed to reliably support the results against the possible hazardous effects of nano-based composite films on human health and safety. Furthermore, materials that do not migrate at all or migrate insufficiently, i.e., inadequate quantity, have been permitted for continuing use [6]; for example, the usage of silver nanoparticles has been known for a long time. However, it has been

questioned whether these nanoparticles might penetrate the human system and concentrate in key organs, resulting in increased creation of reactive oxygen species [10]. These nanoparticles have been shown in studies to produce cytotoxicity, genotoxicity, apoptosis, necrosis, and even DNA strand breaking [11–13]. As a result, rigorous risk evaluation of nanoparticle materials presents a unique food safety problem [14,15].

1.3 A multiphase material: bionanocomposites

Bionanocomposite is described as "a multiphase material composed of two or more components, one of which is a continuous phase, i.e., a matrix, especially a biopolymer, and the other is a noncontinuous nanodimensional phase, i.e., a nanofiller (100 nm)" [16] (Fig. 5.1). The preparation of an antimicrobial bionanocomposite film has two advantages: the nanocomposite matrix offers ideal structural integrity and barrier features, while the impregnated antimicrobial chemicals provide antimicrobial properties to the created film. Furthermore, because these bionanocomposite films are of natural origin, they are safe ecological materials with all of the benefits of both biopolymer and nanocomposite systems [17–19]. The nanofillers utilized in the system serve as a structural reinforcement material, enhancing the mechanical and barrier properties of the biopolymer by transmitting matrix tension to the nanofillers via the boundary between them [2,20]. The addition of various nanoparticles as nanofillers to the biopolymer matrix, such as silicate and clay nanoplatelets, titanium dioxide, SiO_2, carbon nanotubes, chitin, graphene, or chitosan nanoparticles, cellulose-based nanofibers, starch nanocrystals, and other inorganics, improves the overall performance of the resulting packaging material, such as improved thermal and gas barrier characteristics with fire-resistant and lighter matrix [18,21].

Furthermore, the incorporation of nanofillers confers other functional properties to food packaging systems, where the bionanocomposite films may interact with food and act as an antimicrobial or antioxidant agent, scavenger (oxygen or moisture), and/or a biosensor to improve product shelf life [4,20,22]. To fully appreciate the benefits of natural biopolymer–nanocomposite systems, however, complete exfoliation and homogeneous dispersion of the nanoparticles in the biopolymer matrix is required. Various processes, including as solution casting, in situ polymerization, and melt processing, have been widely used in the fabrication of

nanocomposite materials for a variety of purposes, including the manufacturing of antimicrobial packaging films [23]. Biopolymer matrices mixed with nanosized metals constitute a viable method for addressing stability issues while also providing a regulated antibacterial effect. Furthermore, the inclusion of these metals at lower levels causes morphological changes in the surface of the polymer, which aids in the altering of surface roughness and wettability of the nanocomposite [24]. Various chitosan nanocomposite films containing silver nanoparticles have been reported to exhibit high antibacterial properties [4]. Furthermore, PLA displayed increased anti-UV and antibacterial action when nanoZnO was added at a lower concentration (1−3 wt.%), and such nanocomposites do not degrade PLA during manufacture and melt processing due to the presence of surface-treated (with silane) ZnO nanoparticles [25]. Rhim et al. [26] demonstrated the antibacterial activity of these nanoparticles against *Escherichia coli* O157:H7 (Gram-negative) and *Listeria monocytogenes* (Gram-positive) pathogenic bacteria using silver-incorporated agar nanocomposite films. Similarly, Busolo, Fernandez, Ocio, and Lagaron [27] reported that PLA/silver-based nanoclay (organo-modified MMT) bionanocomposite films had a good inhibitory effect against Gram-negative *Salmonella* spp. Because of their stability during processing, a variety of metals or their oxide-derived nanoparticles have received the most attention. To name a few, silver (Ag), copper (Cu), iron (Fe), gold (Au), zinc (Zn), titanium dioxide (TiO_2), palladium (Pd), and others have been used in the development of antibacterial, oxygen scavenging, and ethylene scavenging active packaging systems during the last 2 decades. Hoseinnejad et al. [28] compiled several mechanisms involved in nanoparticle bactericidal activity, including the generation of reactive oxygen species such as hydrogen peroxide, the emergence of electron−hole pairs when exposed to light irradiation, and the binding of metal ions with microorganism membranes to extend the lag phase. Hosseinkhani et al. [29] further declared that these action mechanisms disrupt active transportation and degrade DNA, RNA, and protein synthesis, resulting in cell lysis. Meanwhile, the antibacterial mechanism of gold nanoparticles has been described by two approaches: changes in metabolism leading to a decrease in adenosine triphosphate (ATP) synthase and cellular dysfunction resulting to changes in tRNA assembly [28].

1.4 Encapsulation systems with nanocarriers: nanoencapsulation

With the development of nano-based packaging systems incorporated with natural antimicrobial substances for protecting food products against undesirable biological changes and environmental stresses during storage and distribution, nanotechnology has brought about a revolution in the food packaging industry [4,28]. Nanoencapsulation, or encapsulation systems with nanocarriers, has recently arisen as a key field of nanotechnological applications in the food sector, including the manufacture of nano-sized particles (10^{-9} m) in a two-step procedure. Carriers are first packed with antimicrobial chemicals, and then their size is decreased to a nanoscale (10^{-9} m) dimension in the second stage. Due to the greater surface area of the carriers compared to their bulk counterparts, this technique improves the functional properties of the nanosystem such as high adsorption and solubility with higher bioavailability and regulated release of the bioactive chemicals [30]. It also protects bioactive compounds from external challenges while assuring exact release due to the presence of appropriate wall materials [31]. Encapsulating nisin into a nanoliposome, for example, provided for high retention rates and regulated release of nisin from the coating materials [32]. As a result, instead of adding antimicrobials in their free form, the insertion of a nanocarrier encapsulating the bioactive agents into the packaging films or coatings is the most efficient method of developing active packaging solutions for the food sector. Such packaging technologies for antimicrobial controlled release are economically feasible and helpful strategies for improving food quality and shelf life, with the advantages including [33]:

- ➢ Increased contact with biological entities owing to increased surface area
- ➢ Protection of antimicrobial chemicals, particularly volatile molecules, against changes caused by environmental conditions [34]
- ➢ Enhanced bioactive compound solubility and absorption
- ➢ Food components are protected from unfavorable interactions with antimicrobials
- ➢ In controlled-release antimicrobial active packaging systems, bioactive chemicals are released in a controlled and targeted manner [31,35,36].

Nanoemulsions, biopolymeric nanocarriers, SLNs, electrospun nanofibers, and nanoliposomes are some of the most prevalent nano-encapsulating structures used in the development of innovative nano-based active antimicrobial packaging systems with controlled release.

- As a lipid-based system, nanoemulsions are typically composed of two immiscible liquids (e.g., water and oil) stabilized with appropriate

emulsifiers. In the food packaging industry, nanoemulsions are produced using high-energy techniques, often in two processes, in which rotor—stator homogenizers first form a coarse emulsion, which is subsequently reduced to nano-size using high-energy equipment such as high-pressure homogenizers or ultrasonicators [37,38].

- Because of the benign nature of biopolymers, as well as their functional aspects such as antimicrobial and antioxidant activities [39], emulsification, gelling, and foaming qualities, biopolymer-based nanoencapsulation systems including antimicrobials have also been created. Several nanocarriers have previously been produced employing polysaccharides and proteins, either independently or in combination [35].

Solid lipid nanoparticles (SLNs) are comparable to O/W nanoemulsions in that the oil phase is present as a solid rather than a liquid in order to limit the mobility of antimicrobial chemicals for controlled release from the nanocarrier [40]. The oil-in-water nanoemulsion is created in this approach by homogenizing the surfactant (aqueous) and lipid (solid) at temperatures above the melting point of the lipid used [41]. Because of their unique properties such as small particle size and particle shape, unique surface chemistry, and high surface area, SLNs can serve as remarkable nanocarriers in packaging, providing large loading capacity, biocompatibility, higher stability, controlled and targeted release, cost-effectiveness, higher entrapment efficiency, and lower toxicity [40,41].

The electrospinning process is a typical method for producing electrospun nanofibers as an end product from biopolymer solutions. Physical adsorption, covalent immobilization, coaxial, and mix electrospinning are the most popular types of electrospinning techniques [42]. Rezaei et al. [43], as well as Zhang et al. [44], have conducted extensive research on this issue and its use in active food packaging.

Nanoliposomes, which are spherical and made up of at least one lipid bilayer, are another form of lipid-based encapsulating structure. One of the most significant benefits is the coencapsulation of both lipophilic and hydrophilic components within a single nanocarrier. Nanoliposomes have been created using a variety of processes, including microfluidization, sonication, extrusion, and others. Bacteriocins, for example, are the most typically contained bioactive chemicals in nanoliposomes [45]. By first encapsulating nisin in nanoliposomes and then adding these nanoliposomes to the film structure, nanoliposome-based gelatin and casein active films were created. The produced edible films inhibited *Listeria monocytogenes*, *Clostridium perfringens*, and *Bacillus cereus* effectively, according to the results [46].

Despite the large number of studies done to improve the longevity and performance of bio-based packaging materials, more research is still needed to develop more practical solutions and improve on the ones that already exist to overcome these drawbacks. With the application of nanotechnological concepts to packaging, the issue in question could potentially be solved. Many researchers have thoroughly examined the benefits provided by the use of nanotechnology in the food packaging industry, particularly in edible films and coatings where the nanotechnological aspects may not only mask the off-flavors and prevent the chemical breakdown of the functional compounds but may also increase their solubility along with the controlled release.

2. The toxicological consequences: nano-toxicity and safety aspects of nano-based food packaging systems

Nano-based food packaging systems provide multiple advantages and may solve numerous disadvantages of standard packaging systems by improving material attributes such as mechanical and barrier properties, heat resistance, processability, and durability, among others [47]. Nonetheless, along with the benefits, the nanotechnological path has distinct negative impacts, hazards, and unfavorable repercussions for humanity and the environment. The toxicological impact of nanomaterials [48] is mostly related to their nondegradable and persistent nature, with the favorable elements of nanoparticles' new capabilities conferred by their tiny size and high surface area. However, they have drawbacks such as high reactivity when interacting with biological components [49]. Nanoparticles, being highly active natural components, may swiftly overcome membrane barriers and blood vessels, potentially causing a variety of toxicological consequences [4]. Furthermore, because of their tiny size and huge surface area, nanoparticles have unique biokinetic properties that may boost their migration from packaging materials to food items, as well as the likelihood of their free movement and cell penetration in the body [50].

The toxicity of nanoparticles has been found to be inversely linked to particle size, i.e., toxicity increases as particle size decreases [4]. Silver nanoparticles with a diameter of 20 nm, for example, are more hazardous to lung tissue than silver nanoparticles with a diameter of 100 nm. As a result, the migration of nanocomponents from packing material to food may result in unfavorable health effects; in addition, a few investigations have

suggested that it is carcinogenic and genotoxic [51]. In addition, Sharma et al. [52] documented the genotoxic impact of zinc-oxide nanoparticles in human epidermal cells, emphasizing the importance of particle size and diameter in comparison to its bulk analogue ZnO, which has no toxicity [53]. The toxicological impact of nano-based edible films and coatings is greater when the edible film is a component of the food product to be taken directly, and therefore its toxicity is not dependent on nanoparticle migration. Existing research into the toxicity of different nanomaterials revealed that nano-based structures have a toxicological influence not only on living creatures but also on numerous environmental ecosystems. The living species, or flora and fauna, in the ecosystem play an important role in maintaining the ecological balance, which has been found to be upset by nanomaterials due to their ecotoxicity [54].

3. Edible antimicrobial packaging: economic sustainability

Despite environmental concerns, there are numerous other impediments to the transition from fossil-based packaging products to biobased or edible antimicrobial packaging production, including but not limited to: biobased material production costs, inadequate policy support, and a lack of appropriate waste management facilities [55]. Unfortunately, no specific information on the cost comparison of fossil and biobased packaging have been compiled thus far. With a broad background of investigations being a functioning component of the economic sustainability of bio-based and antimicrobial active packaging, biopolymer nanocomposite films have a promising future for their environmental friendliness (Table 5.1). However, a few studies have found that biobased packaging created from wastes is 3–5 times more expensive than fossil-based packaging materials [56,57]. This rising cost is exacerbated by inadequate economies of scale, biomass mobilization challenges, and a lack of technological innovation [55,58]. Furthermore, FDA and EU regulations impose limitations on the implementation of standards, such as the need for support for biowaste food packaging materials, the use of standards on bio-based materials and food contacts explicitly in labels, and the lack of proper waste management facilities, all of which obstruct the commercial production of bio-based or active food packaging materials.

By integrating different additives, such as antibacterial agents, antioxidants, nutrients, and colors, etc., biopolymer-derived films have proven to

Table 5.1 The various nanocomposite antimicrobial packaging and formulations specially designed to overcome microbial contamination in various food products.

Sr. No.	Antimicrobial film formulation	Method of film preparation	Microorganism tested	Food product	Observation
1.	Hydroxypropyl high-amylose starch/ pomegranate peel (PGP)	Solution casting	*S. aureus*, *Salmonella*	Agar-disk diffusion assay	• High antibacterial activity against both Gram-positive and Gram-negative bacteria • Increased film tensile strength and stiffness • Good compatibility between starch and PGP particles
2.	Polylactic acid (PLA)/ nano-TiO_2/nano-Ag	Solvent volatilization	*E. coli*, *Listeria monocytogenes*	Mueller-Hinton broth	• Increased thermal stability • Strong antibacterial action • NP release below specified limits • Low water vapor permeability (WVP), poor transparency • Elongation at break rose as tensile strength and elastic modulus dropped

3.	Poly(3-hydroxybutyrate) (PHB)/ZnO nanoparticles	Solution casting	*Staphylococcus aureus*, *E. coli*	Nutrient broth medium	• Increased crystallization temperature and crystallinity, as well as restricted diffusion of volatiles created during the breakdown process • Improved thermal stability, Young's modulus, tensile, and impact strength of the biopolymer • Reduced water absorption and enhanced gas and vapor barrier characteristics • Strong antibacterial action against both Gram-positive and Gram-negative microorganisms
4.	Chitosan/grape seed extract/carvacrol microcapsules	Solution casting	Mesophilic and psychrophilic bacteria, *Pseudomonas* spp.	Salmon	• Higher film thickness, moisture content, color characteristics, WVP, O2P, and CO2P • Low TVB-N, pH, and bacterial count • Shelf life is extended (4–7 days)

Continued

Table 5.1 The various nanocomposite antimicrobial packaging and formulations specially designed to overcome microbial contamination in various food products.—cont'd

Sr. No.	Antimicrobial film formulation	Method of film preparation	Microorganism tested	Food product	Observation
5.	Tapioca starch/nisin(N)/ potassium sorbate (KS)	Solution casting	*Listeria innocua*, *Zygosaccharomyces bailii*	Petri dishes containing TSYE or Saboureaud agar with pH 5.2 to resemble a food product	• Strong antibacterial activity, i.e., bacteriostatic efficacy against *Listeria innocua* and yeast count decrease (*Zygosaccharomyces bailii*) • Increased elongation at break and water solubility due to the antimicrobials in the film's extensive plasticizing impact
6.	Carboxymethyl cellulose (CMC)/curcumin/zinc oxide (ZnO)	Solution casting	*Listeria monocytogenes*, *E. coli*	TSB and BHI broth	• Uniform particle dispersion • Significant improvement in UV-barrier and water vapor barrier properties • Antioxidant and antibacterial activity is high

7.	Cassava starch (CS)/ chitosan (CH)/pitanga (*Eugenia uniflora* L.) leaf extract (PE)/natamycin (NA)	Solution casting	*Aspergillus flavus*, *Aspergillus parasiticus*	PDA agar surface in petri dish	• Changes in the physicochemical and microstructural properties of films • The rheological features of the CS/CH mixes were preserved, but the chemical composition was changed • Film tensile strength and flexibility are reduced • NA-containing films have a positive antifungal effect • Films containing PE had higher antioxidant activity, however NA+PE had lower activity
8.	Cellulose/silver nanoparticles	Solution casting	*Staphylococcus aureus*, *E. coli*	Nutrient agar plate	• Uniform dispersion of silver nanoparticles • High antibacterial activity • Improved tensile strength, transparency, and thermal stability • Silver nanoparticles have a slow diffusion rate

Continued

Table 5.1 The various nanocomposite antimicrobial packaging and formulations specially designed to overcome microbial contamination in various food products.—cont'd

Sr. No.	Antimicrobial film formulation	Method of film preparation	Microorganism tested	Food product	Observation
9.	Tapioca starch/chitosan nanoparticles (CNP)	Solution casting	*Bacillus cereus*, *Staphylococcus aureus, E. coli*, *S. typhimurium*	Cherry tomatoes	• Antimicrobial activity was shown in 15% −20% w/w starch/CNP films • Inhibitory effect is concentration-dependent • Gram-positivebacteria suppressed Gram-negative bacteria more effectively • An in vivo investigation found that a 15% w/w starch/CNP film was more effective at limiting microbial development in cherry tomatoes, resulting in a longer shelf life

10.	Polylactic acid (PLA)/ aluminum-doped zinc oxide nanoparticle (AZO) coatings	Extrusion process	*E. coli*	Luria Bertani medium	• Films containing 10% PSP performed best • Elongation at break and transparency values were reduced • Increased film stiffness and resistance to water • Only *S. aureus* exhibits high heat stability and significant inhibition
11.	Chitosan/clove essential oil (CO)/nisin (NI)	Solution casting	*Staphylococcus aureus*, *S. typhimurium*, *E. coli*, *Listeria monocytogenes*	Pork patties	• Minimal changes in quality • Significant antioxidant and antibacterial activities • Possible synergistic effects of CO and NI • Sensory ratings and microbiological counts are gradually declining and increasing • CS-CO−NI films have a twofold improvement in shelf life

Continued

Table 5.1 The various nanocomposite antimicrobial packaging and formulations specially designed to overcome microbial contamination in various food products.—cont'd

Sr. No.	Antimicrobial film formulation	Method of film preparation	Microorganism tested	Food product	Observation
12.	Poly(3-hydroxybutyrate) (PHB)/silver nanoparticles (AgNPs)	Compression using hot-plate hydraulic press	*Salmonella enterica*, *Listeria monocytogenes*	Tryptic Soy broth in petri dishes	• High antibacterial activity • AgNPs had no negative effects on the thermal degradation, optical characteristics, or biodegradability of polymers
13.	Chitosan/kombucha tea (KT)	Solution casting	*E. coli*, *Staphylococcus aureus*	Minced beef	• Increased water vapor permeability, antioxidant activity, and UV protection • The shelf life of minced beef flesh was extended
14.	Sweet potato starch (SPS)/montmorillonite (MMT) nanoclay/thyme essential oil (TEO)	Solution casting	*E. coli*, *S. typhimurium*	Baby spinach leaves	• Effective *E. coli* and *S. typhimurium* suppression • Improved microbiological quality of baby spinach during refrigeration • There are no negative impacts on the sensory system

15.	Chitosan/*Herba lophatheri* extract (HLE)	Solution casting	*Staphylococcus aureus*, *E. coli*	Nutrient agar in petri dishes	• Film moisture content, water solubility, swelling degree, water vapor permeability, and oil absorption rate have all decreased • Increased opacity and deeper tones, with a more reddish and yellowish look • Water and oil resistance, antioxidant activity, and antibacterial capabilities are all improved

be a great matrix for creating functional packaging materials. By limiting microbial growth, active ingredients improve food quality as well as product shelf life.

One of these key advancements in active food packaging technology is the incorporation of antimicrobial agents into biopolymer-based edible films. To overcome these constraints, policy assistance should be carefully considered and implemented in accordance with the principles of sustainable development. It might lessen the likelihood of unpleasant flavors developing as a result of adding active ingredients directly to meals. The use of nanotechnological ideas like bionanocomposites and nanoencapsulation systems has further improved the synergism of antimicrobial bio-based packaging systems. While highlighting recent research studies on the application of nanotechnology to build novel bio-based packaging solutions, this study assesses the current situation and applications of antimicrobial biodegradable films in the food packaging business. Edible films and packaging materials have several advantages, including superior mechanical qualities, customer acceptability, nontoxicity, and reliance on renewable resources. However, the overall performance and cost of edible films have always been the most difficult obstacles to overcome [59]. Antimicrobial food packaging has also gained popularity, which has accelerated research into the creation and use of biodegradable materials such as polysaccharides, proteins, and lipids while taking environmental risks into consideration. Here, a variety of antimicrobial substances like bacteriocins, enzymes, and essential oils have been successfully included into biopolymer-based films with noteworthy effects that have been demonstrated. They can be added to the biopolymer-based packaging matrix to limit or prevent microbial development on the food surface, extending the shelf life of the product without compromising its quality or safety.

To overcome these restrictions, scientific interventions at the R&D level are necessary to develop choices that can bridge the gaps between natural and synthetic packaging materials in the coming years [60]. Researchers have moved their focus to sustainable developments in active packaging systems that preserve food quality and sensory qualities over time in response to growing consumer awareness of and expectations for high-quality meals in eco-friendly packaging. The incorporation of antimicrobial agents into biopolymer-based edible films has significantly improved the technology of active food packaging. It is incredibly effective in preventing or eradicating the pathogenic/spoilage bacteria that contaminate food. Determination is needed of the necessary concentrations of the right

active agent to be applied for effective inhibition because antimicrobial drugs have specific inhibitory effects against different bacteria. Additionally, the inclusion of antimicrobial compounds in packaging materials may result in a complete discrepancy in their antibacterial action. It is crucial to choose the appropriate antimicrobial agent that is tailored specifically for food and to package it in a manner that takes into account the minimum inhibitory concentration of the target organisms.

3.1 Potential applications of edible antimicrobial films in food

The use of active antimicrobial packaging solutions based on biopolymers infused with various bioactive agents has enormous promise for enhancing food quality and safety, as well as potentially increasing shelf life. As described said, a wide range of bioactive compounds, both synthetic and natural, such as essential oils, antimicrobial peptides, enzymes, and so on, have been studied and used in antimicrobial packaging systems. Several studies on this issue have shown that antimicrobial packaging methods have the ability to successfully suppress the targeted spoilage bacteria by applying an appropriate mix of biopolymer and a bioactive chemical for the development of an antimicrobial film [9]. Fruits and vegetables are recognized for their high nutritional quality due to their high fiber, mineral, and vitamin contents, but they are prone to quick degradation due to high moisture content and hence increased water activity. Furthermore, because they are made up of living tissues, they are susceptible to microbial contamination, the formation of off-flavors, enzymatic browning, and textural deterioration. To address the issues raised by these undesirable properties of fruits and vegetables, as well as to meet ever-increasing consumer demands, the food packaging industry has invested in a variety of alternatives that can protect fresh fruits and vegetables from microbiological contamination and spoilage, thereby increasing their shelf life [61]. Sánchez-González et al. [62] created an edible coating activated with bergamot EO (essential oil) for cold-stored grapes using hydroxypropyl methylcellulose (HPMC) and chitosan. They proposed a chitosan and HPMC coating containing bergamot EO as the most effective formulation in terms of displaying the most potent inhibitory action and maximum control over respiration rates with minimal weight losses during postharvest cold storage, when compared to chitosan alone with bergamot EO. Salvia-Trujillo et al. [63] and Raybaudi-Massilia et al. [64] achieved similar findings in research based on apples and melons, respectively.

Saucedo-Pompa et al. [65] also created a candelilla wax-based edible film with ellagic acid (a phenolic component) as the active agent to increase the microbiological quality and shelf life of avocados. The 6-week storage trial of the produced active films yielded good results in terms of product quality, indicating that these edible films might be used to preserve the quality and prolong the shelf life of avocados. Meat provides the bulk of the animal protein needed for the human diet, including both fresh and cured meat products. However, it deteriorates rapidly owing to microbial contamination, particularly by pathogens such as *Listeria monocytogenes*, posing a huge challenge for the packaging sector to address the problem of microbial recontamination in various ready-to-eat meat products [61]. Protein quality is extremely important in meat from a nutritional standpoint, and this may also be accomplished through correct packing. Among the numerous options available, the use of ecological biopolymer packaging materials that assure high quality and safety maintenance in meat products is frequently used [66].

Zinoviadou et al. [67] demonstrated antimicrobial activity of whey protein edible films with oregano EO as the active agent in refrigerated beef samples, whereas Emirolu et al. [68] reported reduced microbial counts in fresh ground beef patties at refrigeration temperature when coated with soy-based edible films embedded with oregano and thyme EOs. Furthermore, Seol et al. [69] found that β-carrageenan edible films combined with ethylenediaminetetraacetic acid (EDTA) and ovotransferrin had a substantial inhibitory impact on *E. coli* as well as total aerobic bacterial counts in fresh chicken breasts stored at 5°C. Juck et al. [70] applied different active packaging coatings developed using various biopolymers such as starch, alginate, xanthan gum, pectin, and β-carrageenan, and activated with various bioactive compounds such as nisin, sodium lactate, Novagard CB1, potassium sorbate, sodium diacetate, and others to turkey products to prevent contamination caused by *Listeria monocytogenes*. Alginate coatings were shown to be the most efficient against *L. monocytogenes* contamination among the various biopolymers, whereas different combinations of nisin, sodium acetate, and sodium diacetate were found to be the best formulations for the preservation of various turkey products. For poached turkey, for example, a combination of sodium lactate and either nisin or sodium diacetate worked best, but for processed deli turkey, a combination of nisin and either sodium lactate or sodium diacetate was indicated as the most convenient. Furthermore, cellulose-based active films containing lysozyme or a mix of lysozyme and lactoferrin were revealed to be the best packing

medium for preserving thin raw beef slices. Another study found that packaging chicken fillets with gelatin-based bionanocomposite films integrated with chitosan nanofibers and ZnO nanoparticles resulted in lower overall bacterial counts as well as reduced growth of other pathogens such as *Staphylococcus aureus* and *E. coli* after 12 days of storage compared to control samples [71]. Similar results were found using ginger EO nanoemulsions, which increased the shelf life of chicken breast [72]. Furthermore, covering pork chops with active chitosan films containing free or nanoencapsulated *Paulownia tomentosa* EO resulted in a considerable decrease of chemical and microbiological deterioration during storage [73]. Lin et al. [74] electrospun a gelatin nanofibrous matrix packed with thyme EO/-cyclodextrin-polylysine nanoparticles to inhibit *Campylobacter jejuni* surface contamination in chicken. The results indicated that the antimicrobial nanofiber coating effectively inhibited *C. jejuni* without impairing the beef product's quality and sensory attributes. Siripatrawan and Noipha [75] developed active chitosan films containing green tea extract for the packaging of pork sausages, which resulted in the successful inhibition of microbial growth in sausages stored at 4°C, as well as improvements in the film's antimicrobial and antioxidant properties, ensuring improved food safety and quality. Dairy goods broadly comprise milk and many other milk products such as fermented milk, cheese, cream, and so on, all of which have high nutritional content and are essential components of the human diet. Extrinsic variables such as moisture, oxygen, microbes, and light are driving forces toward spoiling and other undesired changes such as oxidation, microbial contamination, discoloration, and off-flavor production, leading to fast degradation of dairy products [66]. Implementing innovative active packaging techniques in the dairy industry, such as biopolymer- or nanomaterial-based antimicrobial packaging systems, may help to overcome the shortcomings of traditional systems by preserving product quality while improving shelf life in an environmentally friendly manner [76]. Furthermore, these innovative elements may increase the functional qualities of the packaging matrix, such as improved barrier and mechanical properties [77]. Among the numerous dairy products, cheese has received the greatest attention in terms of shelf life extension through the use of edible antimicrobial coatings [78].

The use of nisin-supplemented sodium caseinate films in cheese held at refrigerator temperature showed substantial antibacterial action against *L. monocytogenes* [79]. Cui et al. [80] found that the presence of chitosan coatings embedded with nisin—silica liposomes on cheese samples

effectively inhibited *L. monocytogenes* development at various storage conditions (25°C for 7 days and 4°C for 15 days). The findings demonstrated that coatings were "better" than noncoated samples at protecting the cheese quality of both fresh and stored samples while retaining sensory qualities, resulting in coated goods having a longer shelf life. Ollé Resa et al. [81] investigated the efficacy of produced nisin and natamycin-enriched tapioca starch films against surface contamination (*Listeria innocua* and *Saccharomyces cerevisiae*) in Port Salut cheese. The coatings inhibited surface growth of *S. cerevisiae* even after 5 days of storage at 25°C, but *L. innocua* growth was not significantly delayed. Furthermore, an oregano EO nanoemulsion was combined with sodium alginate, mandarin fibers, and tween 80 to create a packaging material for low-fat cut cheese, where the incorporated EO not only reduced *S. aureus* counts but also restricted the growth of psychrophilic bacteria, yeast, and molds in cheese during refrigerated storage [82].

Refrigerated milk products that are commonly contaminated by *L. monocytogenes* and *S. aureus* may be protected by adding nisin to the packing system [83]. Coating skim milk packaging with nisin-supplemented polylactic acid was proposed as an effective method for preventing the development and contamination of *L. monocytogenes* in skim milk [84]. A research in which sliced Prato cheese was packaged in a starch-based biodegradable film supplemented with bactericidal levels of cell-free supernatant of *Lactobacillus curvatus* P99 high in bacteriocin-like active chemicals yielded comparable results. The storage investigation revealed that the active films were effective in limiting the development and multiplication of *L. monocytogenes* in cheese held at refrigeration temperature for 10 days [85]. Gelatin-based edible films were treated with cinnamon bark EO to boost their antibacterial activity and were then tested for their influence on the quality and sustainability of mozzarella cheese during 3 weeks of refrigerated storage [86]. The active films had considerable antibacterial activity and significantly inhibited the development of *L. monocytogenes* in wrapped cheese samples compared to the unwrapped control.

Furthermore, Göksen et al. [87] investigated the inhibitory impact of EO-loaded zein nanofibers films against *S. aureus* and *L. monocytogenes* in cheese. The findings showed a significant decrease in *S. aureus* and *L. monocytogenes* populations, as well as robust suppression of mesophilic bacteria in cheese samples wrapped with active films even after 28 days of storage, showing that the created films had outstanding antibacterial properties. High lipid content is the primary cause of fast breakdown in fish

and shellfish products, resulting in significant moisture loss and influencing chemical degradation and sensory qualities. As a result, using active antimicrobial packaging methods such as biopolymer-based antimicrobial films to prolong the shelf life of fish products by preserving them and protecting them from surface microbial contamination is a realistic alternative [61]. In research into the preservation of cold-smoked salmon fillets and slices, Neetoo et al. [88] found that alginate coatings embedded with sodium diacetate and sodium lactate significantly delayed and decreased the development of *L. monocytogenes* in salmon held for 30 days at 4°C. Similarly, oregano/rosemary EOs-based gelatin films with and without chitosan were created and studied for their involvement in maintaining the quality of cold-smoked sardine [89]. The findings suggested that sardine wrapped with EOs-activated gelatin films had higher product stability and decreased lipid oxidation rates. Furthermore, as compared to control films, lemon EO-supplemented carrageenan films considerably increased the shelf life of trout fillets [90].

For the preservation of fish megrim (*Lepidorhombus whiffiagonis*) during storage at 4°C, a biodegradable polylactic acid (PLA) film containing sorbic acid and lyophilized alga (*Ficus spiralis*) as bioactive agents was created. Activated PLA films were able to keep the sensory quality of the fish for 11 days longer than control samples, which had lost their sensory and quality features by that time [91]. Hake and sole fillets wrapped in edible gelatin films supplemented with chitosan, pepper, or clove essential oils showed reduced microbial growth due to the films' strong inhibitory action against *L. monocytogenes*, *Aeromonas hydrophila*, and *Staphylococcus aureus* [92,93].

The effectiveness of biodegradable methylcellulose coatings containing *Pimpinella affinis* EO (1.5%) in inhibiting microbial growth and contamination until 12 days of refrigerated storage while maintaining the product's quality and sensory attributes was demonstrated in a study on fresh silver carp fillets. Furthermore, coatings of sodium alginate embedded with horsemint EO at 1% on bighead carp fillets resulted in significantly lower rates of microbiological degradation and lipid oxidation in the product [94], while a similar decline in psychotropic bacterial populations as well as volatile base formations was reported in rainbow trout wrapped in oregano EO-enriched fish gelatin-based coatings during 16 days of storage at [95].

Kakaei and Shahbazi [96] also found that minced trout fillets covered in gelatin- and chitosan-based films containing *Ziziphora clinopodioides* EO and grape seed extract as active agents had a longer shelf life than unwrapped fillets.

During an 11-day storage period, active films not only decreased the microbial population (total viable counts, Enterobacteriaceae counts, psychrotrophic bacteria counts), but also the total volatile base nitrogen and peroxide values.

4. Conclusion

With the increase in demand for the bio-packaging of food material to ensure protection and quality of food, nanobiopolymers have been used as an alternative to conventional and toxic ones. Various techniques and aspects such as nanoencapsulation and bionanocomposites are being utilized to ensure safety and quality and to retain good flavors in food items. Keeping in view the need of the hour and the current trends, research is needed to identify the combinatorial effects of different bioactive agents, and finally working out a suitable composition and processing techniques for bionanocomposites, so that a detailed methodology and outcomes can be obtained for safety trends, and antimicrobial packaging and toxicological aspects can be easily explored. The utilization of effective antimicrobial coatings and formulations not only helps in preserving the quality of the food product by preventing some of the usual undesirable changes like color and flavor changes, but also ensures a quality product in terms of economics and consumer perception. Keeping in view the high interest in these safe bionanocomposites, further future prospective should be aimed at understanding and screening of some synergistic combinations for examining specific antimicrobial nanocarriers to be tagged with specific food components. In addition, aspects like toxicology and safety studies can be undertaken to provide an environment related to safe application of nanocomponents in food packaging. Although bionanocomposites have very high potential for future packaging applications, their widespread use is limited by high process costs and slow manufacturing rates. Further studies could be directed at identifying and understanding the synergistic interactions among various bioactive agents, developing the best formulations and compositions for each individual polymer and processing methods for various bionanocomposites, examining the interactions between food components and antimicrobial nanocarriers, and determining the appropriate conanoencapsulation systems for various bionanocomposites, all while bearing in mind the current trends in the food and packaging industries. Before using nanoparticles in food products, rigorous toxicity studies, safety precautions, and in-depth research into nano-based antimicrobial packaging techniques must be conducted.

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CHAPTER 6

Nanosilver in the food sector: Prospects and challenges

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1. Introduction

In recent decades, nanotechnology has opened up a new era in the field of nanoscience [1–4]. The unique features of NPs have been used in a variety of fields, including medicine, cosmetics, renewable energy, environmental clean-up, biomedical devices, and the food industry [5–13]. Silver nanoparticles (AgNPs) have grabbed researchers' interest due to their different physical, chemical, and biological properties compared to their macro-scaled counterparts [14,15]. Due to their high electrical and thermal conductivity, chemical stability, catalytic activity, and nonlinear optical behavior they can be applied in inks, microelectronics, and medical imaging [16–19]. Furthermore, AgNPs have a broad spectrum of bactericidal and fungicidal activities [20,21], which has led to their extensive use in a variety of consumer products such as plastics, pastes, food, soaps, and textiles, boosting their market value [22,23]. The demand for "ready to eat," "ready to cook," and "ready to use" food has risen considerably in recent decades, creating a greater need for manufacturers to provide minimally processed food appealingly and hygienically [24]. One of the most important concerns in food processing is the prevention of foodborne infections, which remain a major public health concern worldwide [25]. The development of antimicrobial food packaging is very important for preventing foodborne infections. Antimicrobial materials present in food packaging release active biocide compounds which improve food quality and increase **shelf** life [26,27]. In comparison to inorganic antimicrobial compounds, organic antimicrobial materials are less stable at high temperature, whereas metal

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and metal oxide nanoparticles (NPs) can survive even in harsh processing conditions [28].

Unfortunately, due to the widespread use of antibiotics, drug-resistant bacteria have emerged, posing a serious threat to human health [29,30]. As a result, new bacterial treatment strategies must be discovered. It has been already established that different metal (gold, silver, copper titanium, iron) nanoparticles have antibacterial and antifungal properties [31–36]. Out of these, AgNPs, was found to be the most effective bactericidal agent against a variety of pathogenic microorganisms, including bacteria, yeasts, and fungi [37–39]. The size and shape of AgNPs play a crucial role in determining the antimicrobial efficacy, viz. AgNPs with triangle-shaped nanoplates have stronger antibacterial properties than other shapes [40]. AgNPs have little volatility and are stable at high temperatures [41]. AgNPs can be coated, absorbed, or directly included in the synthesis processes, and they can be placed in diverse matrices such as polymers and stabilizing agents [26,42]. Although the use of AgNPs as antimicrobial agents in food packaging is a well-established practice, there remain concerns about the hazards of ingesting Ag ions that have migrated into food and beverages. As a result, food safety regulators adopt a cautious stance [43]. AgNPs can suppress bacterial development by altering the bacterial cell surface, penetrating bacterial cells, and causing reactive oxygen species (ROS), destroying DNA and proteins, or decreasing enzyme activities [44–47]. In a resistant *E. coli* strain (DH5a) and a *Staphylococcus aureus* strain (BB255), alloy nanoparticles including silver and other metals exhibit greater antibacterial powers than pure AgNPs or CuNPs [48,49]. In an experiment indicating the benefit of mixing Ag, Pt, and Au with the support of an Au core, the strong NIR SPR response could be transferred to the Ag–Pt alloy shell, and the alloy material bestowed extra light-enhanced effects in its properties, including overcoming bacterial resistance [50]. In addition, Ag was added to a Co–Cr alloy composition in an implant to improve the antibacterial characteristics of the material [51]. Due to the strong antibacterial efficacy of AgNPs, the application of AgNPs is increasing in a variety of industries [52], including food packaging, which has seen major growth during the last decade [53]. Improved packaging, in which AgNPs are mixed into the polymer matrix to improve gas barrier properties, includes polymer/clay nanocomposites. In active packaging, AgNPs interact directly with the food or the environment to allow for better food protection [54–56].

Various types of simple, green, cost-effective methods are already established for the synthesis of AgNPs and, for this reason, different food

packaging industries are very interested in applying it as a food packaging material. In this study we have made a comprehensive analysis of the antimicrobial activities of AgNPs with a special emphasis on food packaging and food processing techniques along with challenges and future perspectives.

2. Different methods to synthesize AgNPs

Top-down and bottom-up methods are primarily involved in the synthesis of AgNPs [57]. In the top-down method, bulk materials are converted into powder forms of AgNPs by different methods such as lithography or laser ablation method. Some of the physical parameters (e.g., size, shape) are less controlled when a top-down method is followed [58]. In contrast, the bottom-up method follows the assembly of molecules, atoms, or ions from silver materials to produce AgNPs through the addition of a reducing agent such as $NaBH_4$ [12,59]. In this technique, stabilizing agents are added which prevent aggregation by capping AgNPs. The size and surface characteristics of AgNPs are also very dependent on the reducing and capping process [58,60]. The bottom-up approach can be classified into three categories as discussed in the following.

2.1 Chemical methods

Chemical synthesis of AgNPs is one of the most popular methods due to its simplicity. Generally, $AgNO_3$ is used as a precursor of AgNPs [61,62]. Several reducing agents have been reported for the reduction of $AgNO_3$ solution to produce Ag(0) particles which assemble to produce AgNPs. Sun et al. reported the polyol process to produce silver nanocubes by reducing $AgNO_3$ with ethylene glycol in the presence of polyvinylpyrrolidone (PVP) [63]. Spherical AgNPs ($\sim$17 nm) were also produced by this polyol process with a modified precursor injection technique [64]. Monodisperse AgNPs were also synthesized in an oleylamine-liquid paraffin system [17]. Due to the high boiling point of paraffin, it can maintain the reaction temperature which controls the size of the AgNPs. The concentration of oleylamine also maintains the size and shape of AgNPs. Three main constituent components are required for the chemical synthesis of AgNPs: (1) metal precursors, (2) reducing agents, and (3) stabilizing/capping agents. Generally, an aqueous or organic-based medium is used for AgNP synthesis in this method. Silver ions (Ag^+) are reduced to atomic silver (Ag^0) and then agglomeration occurs to form oligomeric clusters which further form

AgNPs [65]. The reaction parameters like precursors, pH, temperature, reducing agents (i.e., $NaBH_4$, glucose, ethylene glycol), and stabilizing agents (i.e., PVA, PVP, sodium oleate) control the initial nucleation followed by the growth of nuclei [22,66]. Bioorganic molecules like glutathione [67] and L-valine-based oligopeptides [68] are also used as capping agents for the synthesis of AgNPs. AgNPs can be synthesized using Tollen's reagent [69]. The dimethylformamide (DMF)-reduced pathway produces different shapes of AgNPs when the stabilizing agent changes from aminopropyltriethoxysilane (APS) to polyvinylpyrrolidone (PVP) [70]. Long alkyl chain ligands can serve both purposes, i.e., solvent and stabilizer, at high temperature for the synthesis of AgNPs. In a thermolytic process, AgNPs were synthesized from $[Ag(Mes)]_4$ (Mes: mesityl or 2,4,6-trimethylphenyl) in hexadecylamine solution at 300°C [71]. Some researchers have followed the decomposition of organometallic precursors like $[Ag(C_6F_5)]$, in hexadecylamine to synthesize AgNPs [70]. Different chemical synthetic routes for AgNP preparation are shown in Table 6.1.

2.2 Physical methods

Evaporation and condensation are two common steps involved in the synthesis of AgNPs, as per the physical approach Lee et al. reported the thermal-decomposition method for the synthesis of AgNPs in powder form [78]. In this case, $AgNO_3$ and sodium oleate were mixed in water at 290°C to form an Ag^{1+}—oleate complex and it was further decomposed to form AgNPs [79]. "Laser ablation" is another common method for the synthesis of AgNPs [80]. In the laser ablation process, materials are removed from the solid surface with the irradiation of a laser beam. Material is evaporated by the absorption of laser energy and at higher laser flux it is converted to plasma [65]. The particle size was close to 9.5 nm with a very narrow size distribution. Jung et al. developed a new physical approach for the synthesis of AgNPs with a ceramic heater, that was used to evaporate the starting materials. The concentration and geometric diameter of AgNPs increase with an increase in the temperature of the heater surface. Since the temperature of the heater surface was distributed equally, the produced AgNPs were very stable. The arc discharge method was developed by Tien et al. to produce AgNPs without the addition of any surfactants in deionized water. Silver wires act as both precursors and electrodes. The consumption rate of Ag wire was 100 mg min^{-1} and the size of AgNPs was 10 nm [81]. Siegel et al. reported the synthesis of spherical AgNPs with 3.5 nm diameter with direct metal sputtering into liquid medium [82]. Other scientists established

Table 6.1 Different chemical synthesis routes for AgNPs.

Methods	Silver precursor	Reducing agents	Stabilizer	NPs shape and size (nm)	References
Chemical synthesis	$AgNO_3$	Trisodium citrate	Trisodium citrate	Nanospheres 30–60	[72]
	$AgNO_3$	Ethylene glycol	Polyvinylpyrrolidone (PVP)	Nanocubes ~50–115	[73]
	$AgNO_3$	$NaBH_4$	Dodecanoic acid (DDA)	Nanospheres ~7	[74]
	$AgNO_3$	Ethylene glycol	PVP	Nanospheres 17	[75]
	$AgNO_3$	Paraffin	Oleylamine	Nanospheres 10–14	[76]
	$AgNO_3$	Hydrazine hydrate	Dioctyl sodium sulfosuccinate (AOT)	Spherical 2–5	[77]
	$AgNO_3$	Hydrazine hydrate	PVP	Nanowires 30–40	[77]
	$AgNO_3$	Glucose	Gluconic acid	40–80	[77]

that AgNPs can be synthesized by direct sputtering in the liquid medium [60]. Round-shaped AgNPs were obtained in this process. In sputtering, only the target material is heated and the sputtered material composition becomes the same as the target [83]. Therefore, the physical methods are a single-step easy method for the formation of a huge amount of powdered form of AgNPs. However, primary costs for the investment in equipment should be considered. Table 6.2 illustrates different physical synthetic routes for the preparation of AgNPs.

2.3 Biological methods

The biological method is the green approach for AgNP synthesis as it uses different extracts from plants and microorganisms which are nontoxic and cost-effective. Fungi like *Phoma glomerata* and *Fusarium* species [87], photosynthetic plants [88], and microorganisms such as proteobacteria, cyanobacteria, and microalgae [89,90] have been already reported for AgNP synthesis. Vijayan et al. reported that seaweed can be used for the production of AgNPs [91]. The brown and green seaweeds *Enteromorpha compressa*, *Sargassum plagiophyllum*, and *Ulva reticulata* were extracted from and have been reported for the reduction of $AgNO_3$ solution at 60°C in the dark phase to produce AgNPs with 20 nm diameter [92]. Kannan et al. also reported that *Codium capitatum* can be used for the green synthesis of AgNPs at room temperature, with an average diameter of 30 nm. Kannan et al. also reported that *Codium capitatum* can be used for the green synthesis of AgNPs [93]. Kumar et al. reported that AgNPs are produced by the reduction of $AgNO_3$ using *Gracilaria corticata* at 60°C with diameters ranging from 18 to 46 nm and showing antifungal activities. The extract from the red seaweed *Gracilaria birdiae* was also used for the synthesis of AgNPs which has antibacterial activity selectively for Gram-negative *E. coli* [94]. In most cases, plant-based AgNPs synthesis methods were followed in an aqueous medium. There are also a few reports in which nonaqueous medium was used such as acetone, ethyl acetate [95] ethanol [96], petroleum ether [97], and methanol [98]. Spherical and triangular AgNPs with a size range of 5−25 nm were also synthesized by another group of researchers using marine algae *Caulerpa racemosa* [99]. *Gelidiella acerosa* algae are very useful to synthesize spherical AgNPs with an average size of 22 nm [100]. Aqueous extract of cyanobacteria can be used to synthesize AgNPs at 30°C [101]. *Bacillus licheniformis* secretes nitrate reductase and was used to synthesize AgNPs [102]. Table 6.3 summarizes different biological synthetic routes for the preparation of AgNPs.

Table 6.2 Different physical synthetic routes for AgNPs.

Methods	Silver precursor	Physical process/ energy source involved	NPs shape and size (nm)	References
Physical synthesis	$AgNO_3$	Thermal decomposition	Nanosilver powder 9.5	[79]
	Ag target	AC power	Nanospheres 6.2–21.5	[73]
	Ag foil	Ion beam	Nanospheres 2.2–5.2	[84]
	Ag wire	Electric arc discharge, water	Nanospheres ~10	[75]
	$AgNO_3$	Electric arc discharge	Nanospheres 14–27	[85]
	Ag target	Sputtering current, glycerol and water	Nanospheres 3.5	[86]

Table 6.3 Different biological synthesis routes for AgNPs.

Methods	Silver precursor	Used biological materials	NPs shape and size (nm)	References
Biological synthesis	$AgNO_3$	Peptides	Hexagonal, spheres, and triangular, 60−150	[103]
	$AgNO_3$	*Bacillus* sp.	Nanospheres, 5−15	[104]
	$AgNO_3$	*Lactobacillus*	Nanospheres, 6−15.7	[105]
	$AgNO_3$	*Shewanella oneidensis*	Nanospheres, 2−11	[106]
	$AgNO_3$	Fungus *T. viride*	Nanospheres, rod 5−40	[107]
	$AgNO_3$	*Cassia angustifolia*	Nanospheres, rod 9−31	[108]
	$AgNO_3$	*Daucus carota*	Nanospheres, 20	[109]
	$AgNO_3$	*Aspergillus niger*	Spherical, 1−20	[77]
	$AgNO_3$	*Arbutus unedo* leaf extract	Spherical, 3−20	[77]
	$AgNO_3$	Leaf extracts from *Eucalyptus macrocarpa*	Cubic, 36−40	[77]
	$AgNO_3$	*Humicola* sp.	Spherical, 5−25	[110]
	$AgNO_3$	*Fusarium semitectum*	Spherical, 10−60	[111]
	$AgNO_3$	*Phoma glomerata*	Spherical, 60−80	[112]
	$AgNO_3$	Leaf of *Ficus religiosa*	Spherical, 5−35	[113]
	$AgNO_3$	Root of *Potentilla fulgens*	Spherical, 10−15	[114]
	$AgNO_3$	Stem of *Breynia rhamnoides*	Spherical, 64	[115]
	$AgNO_3$	Fruit of *Drypetes roxburghii*	Quasi-spherical, 10−14	[116]

3. Applications of AgNPs in the food industry

3.1 AgNPs used in food processing

Food processing can be defined as a practice of preserving food with the help of methods and techniques in order to transform food to a consumable state. These techniques are designed as such that the flavor and quality of the food are kept intact but they are also protected from infestation by microorganisms that leads to food spoilage. Irradiation, ohmic heating, and high hydrostatic pressure are some of the conventional methods of food processing [117,118]. Food processing methods that involve nanomaterials include the incorporation of nutraceuticals, gelation, and viscosifying agents, nutrient delivery, mineral and vitamin fortification, and nano-encapsulation of flavors [119]. Processing of food is mainly carried out in order to keep the food intact and also to increase its shelf life. Processed foods help the producer to transfer them over very large distances without running the risk of the food being spoiled. The yearly availability of different kinds of food, especially seasonal ones such as peas or corns, is also one of the advantages of processed food. Fresh foods are not the only target of the food processing industry. Producing healthier food is also part of the aim, and therefore, currently processed food contains micronutrients, which is a huge benefit for consumers. The involvement of different nanomaterials and their techniques that find their use in the food processing industry are summarized in Table 6.4.

3.2 AgNPs used as food packaging

Packaging is usually done as a last step, after which the packed goods/products are placed in larger boxes, courier bags, bubble envelopes, cardboard, cartons, or other containers. The terms packing and packaging, on the other hand, are frequently used interchangeably. The art of presenting a product is known as packaging. This is more about the final product's appearance, color, design, or presentation wrapped in a material to entice customers. Packaging plays a vital function in luring clients in and influencing their purchasing decisions.

Food packaging methods are used to ensure that the food's quality is preserved, but they are packaged in such a way that it is safe to consume [27,136]. Packaging primarily serves to protect food from external shocks and vibrations, as well as microbial infestation and temperature in providing barrier protection by scavenging oxygen and other spoilage-causing gases [27,119]. To prevent pollution, packaging materials should preferably be

Table 6.4 Applications of AgNPs as preservative in the food industry.

Nanomaterial for admixture/ coating	Types of food	Tested microorganism	References
Polyethylene, AgNPs	Nuts	Bacteria, fungi	[120]
LDPE, Ag, ZnO NPs	Orange juice	Yeast, molds, total aerobic bacteria	[121]
LDPE, AgNPs	Barberry	Bacteria	[122]
LDPE, AgNPs, TiO_2 kaolin	Strawberry	—	[123]
LDPE, AgNPs, TiO_2	Rice	*A. flavus*	[124]
Polyvinylpyrrolidone, AgNPs	Fresh asparagus	Psychotropic bacteria, yeasts, and molds	[125]
PVC, AgNPs	Ground beef	*E. coli*, *S. aureus*	[126]
Cellulose, AgNPs	Beef meat	Lactic acid bacteria, Enterobacteriaceae, *Pseudomonas* sp.	[127]
Polyethelene, Ag, TiO_2 AgNPs	Fresh apples, white sliced bread, fresh carrots, soft cheese, fresh orange juice	*Penicillium*, *Lactobacillus*	[128]
Cellulose, AgNPs	Fresh-cut melon	Bacteria, yeasts	[129]
Hydroxypropyl methyl cellulose, AgNPs	—	*E. coli*, *S. aureus*	[125]
Cellulose nanofibril, AgNPs	—	*S. aureus*, *E. coli* O157:H7	[130]
EVOH, AgNPs	Chicken, pork, cheese, lettuce, apples, peels, egg shells	*Salmonella* spp., *L. monocytogenes*	[131]
Pullulan, AgNPs	Turkey meat	*L. monocytogenes*, *S. aureus*	[26]
Starch, AgNPs	—	*S. aureus*, *E. coli*, *C. albicans*	[26]
Chitosan, gelatin, AgNPs	Red grapes	Fungi	[132]
Chitosan, cellulose, AgNPs	—	*E. coli*, *S. aureus*	[133]
Agar, AgNPs	—	*E. coli* O157:H7, *L. monocytogenes*	[134]
Agar, banana powder, AgNPs	—	*E. coli*, *L. monocytogenes*	[135]

comprised of biodegradable materials. This vision has become a reality due to the introduction of nanotechnology into the food packaging industry. High-barrier polymers, antimicrobials, and contamination detection procedures are just a few of the ways that must be considered while food is being packaged. Table 6.5 provides a summary of the many types of nanotechniques utilized for food preservation and packaging.

Petroleum-based plastics make up a large portion of the packaging used in the food sector. Plastic packages have physical-mechanic benefits over other materials (paper, glass, wood, metals, and ceramic) in terms of weight, flexibility, mechanical resistance, and physical-chemical and biological properties connected to quality, health protection, and safety [145]. These characteristics make it possible for plastic materials to generate active packages with antibacterial capabilities by adding nanocompounds. Packages with nanotechnological applications, according to Almeida et al. [146], have improved the physical-chemical properties, reduced hydrophilic features, improved biodegradability, and higher value-added [147]. Active packages are a novel type of food packaging created by combining metallic nanoparticles with polymer films [148]. Silver antimicrobial agents have the advantage of being easily incorporated into a variety of materials, such as plastics and textiles, allowing them to be used in a wide range of applications while maintaining antimicrobial activity in situ, whereas traditional antimicrobial agents would be unstable [149]. AgNPs can be inserted into nondegradable (polyethylene, polyvinyl chloride, vinyl alcohol) and biodegradable (cellulose, starch, chitosan, agarose) polymers to manufacture food packages, according to Carbone et al. [26]. AgNPs may be incorporated into nondegradable (polyethylene, polyvinyl chloride, vinyl alcohol) and biodegradable polymers (cellulose, starch, chitosan, agarose) to produce food packages, as presented in Table 6.5.

Emamifar et al. [143] evaluated the inhibitory effect of packages impregnated with Ag and ZnO nanoparticles on *Lactobacillus plantarum* in orange juice, and observed that the bacterium was inhibited in the product stored at 4°C. However, the silver nanoparticles presented the greatest antimicrobial activity, compared with the ZnO nanoparticles, in juices stored for up to 112 days. Panea et al. demonstrated the antimicrobial effect of nanocomposite packages of chicken breast containing different ZnO and Ag ratios [137]. However, the authors observed that the meat sensory attributes were slightly affected by the package, with increased cereal odor and tenderness after 10 days of storage, although no differences were found in the color and appearance of the product after 21 days of storage.

Table 6.5 Antimicrobial effects of silver nanoparticles (AgNPs) incorporated into food packages.

Nanoparticles	Shape and size (nm)	Food product	Packaging materials	Storage condition	Antimicrobial effect	References
AgNPs	Spherical [40–50]	Minced beef	Polyvinyl chloride	3 ± 1°C for 14 days	Inhibitory effect on microbial growth of total bacteria including *S. aureus* and *E. coli*	[137]
Bergamot essential oils + TiO_2 + AgNPs	Not defined	Mangoes	Polylactic acid	Room temperature, 15 days	Effectiveness against total bacteria count	[138]
CuO + ZnO	Spherical [35–50]	Ultra-filtrated cheese	Low-density polyethylene	4 ± 0.5°C for 28 days	Decrease in the most probable number of coliforms	[139]
TiO_2+Ag	Spherical [10]	Yunnan cottage cheese	Polylactic acid	5 ± 1°C for 25 days	Inhibitory effect against total bacteria count, and yeast and mold growth	[140]
Zinc oxide + AgNP	–	Chicken breast, cooked	Low-density polyethylene	4°C for 21 days	Inhibitory effect on entero bacteriaceae and mesophilic bacteria	[141]

Pullulan	Spherical [40–50,51–60,61–70,71–80,81–90,91–100]	Raw turkey breast, raw beef, and ready-to-eat turkey breast	NI	4°C for 21 days	Effectiveness against *S. aureus*, *L. monocytogenes*, *E. coli* O157:H7	[142]
AgNPs	Spherical [3–20]	Fresh pork sirloin	Low-density polyethylene	6°C for 28 days	Decrease in viable counts of *L. piscium*, *B. thermosphacta*, *H. alvei*, *L. sakei*, and *C. divergens*	[143]
AgNPs	Spherical (10.10 + 0.60)	Chicken breast fillet	Low-density polyethylene	4°C for 12 days	Changes in viable counts of psychrotrophic bacteria, *Pseudomonas* spp., lactic acid bacteria, *B. thermosphacta*, *E. coli*, and total coliforms	[144]

4. Toxicological properties of AgNPs

AgNPs have a cytotoxic impact on mammalian cells, and scientists investigated the cytotoxicity of AgNPs that were not coated and AgNPs that were coated with chemical or biological components. The shape, size, surface charge, or coating of AgNPs, as well as the release of the ionic form of silver, all contribute to their cytotoxicity [61].

AgNPs can break a cell's membrane, impact ATP synthesis and DNA replication, alter gene expression, and oxidize the cell's biological compartments by releasing reactive oxygen species (ROS) [150,151]. The silver ions generated by AgNPs may block the cytochrome oxidase and NADH-succinate dehydrogenase regions of the bacterial respiratory chains [152,153]. Increased quantities of reactive oxygen species, decreased levels of intracellular glutathione, and a decrease in the potential of the mitochondria membrane produce cytotoxicity responses. AgNPs can trigger lung epithelial cell inflammation as well as macrophage inflammation [154]. According to studies, AgNP cytotoxicity is dependent on the size of the nanoparticles, as well as the coating substances, because the size of nanoparticles, including silver, is related to their uptake by cells.

AgNP toxicity is based on their chemical attraction to cell surfaces and the dissolution of silver ions from the nanoparticles; the AgNP coating has an impact on their cytotoxic mechanism. Surface area and size are also important elements in determining cytotoxicity levels; hence, the coating material can influence the cytotoxicity mechanism by influencing the surface area, shape, and physical qualities [155]. When coated with different coating substances (PVP, CTAB, and citrate), the cytotoxicities of silver nitrate and the other three types of AgNPs were tested when disseminated on *Allium cepa* roots. Their findings verified that all of the AgNPs studied generated oxidative stress and that uncoated silver is far more toxic than coated silver, indicating that cytotoxicity is dependent on nanoparticle concentration. Another study found that employing biological production, silver nanoparticles coated with zinc oxide reduced the cytotoxicity of AgNPs against the human cancer cell line A431 [156]. In a dose-dependent manner, A549 cells exposed to increasing concentrations of AgNPs over 24 h showed morphological alterations such as cell shrinkage, few cellular extensions, a confined spreading pattern, and cell death. Treatment with 20 nm AgNPs caused DNA damage and overexpression of metallothioneins at a dose of 0.6 nM for up to 48 h in another investigation using the same type of cells [157]. AgNPs are taken up by cells through diffusion

(translocation), endocytosis, or phagocytosis [158]. When AgNPs or Ag^+ ions penetrate the cytoplasm, they produce ROS, which cause DNA damage, protein denaturation, and apoptosis. AgNPs of various sizes and shapes tend to collect in the mitochondria, causing mitochondrial dysfunction, such as a drop in mitochondrial membrane potential (MMP), and encouraging the production of ROS. These causes intracellular proteins and nucleic acids to be damaged (Fig. 6.1A). The disruption of the mitochondrial respiratory chain by AgNPs, as reported by Grzelak et al. and Asha Rani et al., increases ROS formation and interrupts ATP synthesis, resulting in DNA damage [158]. The release of lactate dehydrogenase from ROS production can potentially harm cell membranes [159]. AgNPs can also bind with membrane proteins and activate signaling pathways, resulting in cell proliferation inhibition. On the other hand, Ag^+ ions released from AgNPs can cause the production of ROS [37,160], which is important for cellular uptake via endocytosis [161]. AgNPs contained in an acidic lysosomal environment dissociate into Ag^+ ions in this situation. The "lysosome-enhanced Trojan horse effect" [162] is the result of these ions initiating cascades or series of events that lead to intracellular toxicity. Furthermore, cytoplasmic enzymes oxidize some AgNPs that translocate into the cytoplasm via diffusion or channel proteins, releasing Ag^+ ions [163]. These ions interact with the thiol groups of mitochondrial membrane proteins, resulting in mitochondrial malfunction and the production of ROS (Fig. 6.1B).

Cytotoxicity in mammalian cells is influenced by several parameters, including nanoparticle size, shape, surface area, surface charge, surface functionalization, and particle dispersion state [166,167]. By causing ROS,

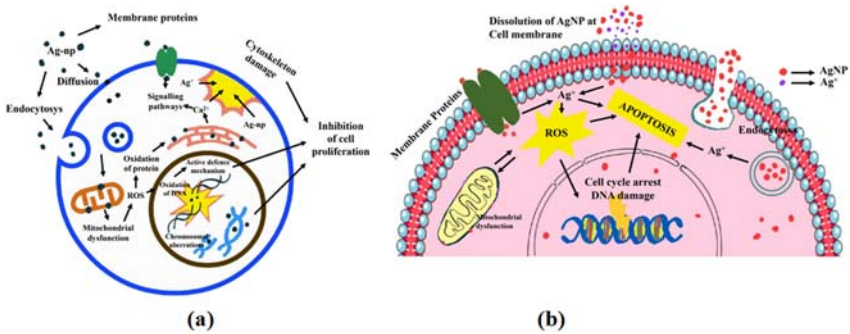

Figure 6.1 Proposed mechanisms of (A) AgNPs- and (B) silver ion-induced cytotoxicity Reprinted with permission from BMC cell biology and Elsevier respectively [164,165].

oxidative stress, and DNA damage, AgNPs tend to cause size-, dose-, and time-dependent toxicity [158,168]. The processes of AgNPs- or Ag^{+}-induced toxicity in mammalian cells are summarized in Fig. 6.1A and B.

4.1 The mechanism of AgNPs antimicrobial activity

The mechanism of antibacterial action caused by AgNPs is still not fully understood. Many scientific theories do not rule out a variety of mutually beneficial relationships. The natural properties of AgNPs for interacting with a thiol group found in cysteine, a building block of the protein bacterial cell wall, is one of the most common mechanisms of antibacterial activity. As a result, protein enzymatic action is disrupted, and the cycle of cellular respiration is disrupted. Other enzymes, such as NADH and succinate dehydrogenase, are also damaged at the same time [169]. The biocidal effects of AgNPs against Gram-negative and Gram-positive bacteria have been studied. *E. coli*, *S. aureus*, and *S. typhi* were used in the experiment. AgNPs are thought to be more efficient against Gram-negative bacteria due to differences in cell wall architecture between the two types of bacteria [44]. Gram-negative bacteria contain a lipopolysaccharide layer on the exterior of the cell wall, which is surrounded by a thin layer of peptidoglycan. The lack of stiffness and strength in the lipopolysaccharide layer structure is notable. The positively charged particles of AgNPs are attracted by a negative charge on lipopolysaccharides, which is explained by silver ions accumulating on the particle surface [170]. Gram-positive bacteria's cell walls, on the other hand, are made up primarily of a thin layer of peptidoglycan that forms a solid three-dimensional structure. Polysaccharide cross-linked short chains of protein molecules make up its structure. The rigidity and structure of these layers make it difficult for AgNPs to penetrate Gram-positive bacteria's cell wall. AgNPs, on the other hand, have been shown to permeate both types of cell walls and enter the cell, resulting in uncontrolled tyrosine phosphorylation [171]. Phosphorylation occurs when a phosphate residue binds to a nucleophilic atom (in this case, the oxygen atom of the tyrosine OH group), rendering the bacteria unable to survive [172]. The presence of AgNPs alters the control of gene expression in genes that encode proteins for all phosphorylation pathway complexes [173].

Cho et al. studied the antibacterial activity of AgNPs against Gram-positive bacteria like *S. aureus* and *E. coli* (Gram-negative bacteria) [174,175]. These researchers utilized a suspension of AgNPs with an average size of 10 nm. Both *S. aureus* and *E. coli* were shown to be strongly

inhibited by the solution. The effects of stabilizing chemicals such as poly(N-vinyl-2-pyrrolidone) (PVP) and sodium dodecyl sulfate (SDS) were investigated. The antibacterial activity of AgNPs stabilized by poly(N-vinyl-2-pyrrolidone) was shown to be greater against both strains. For *S. aureus*, the lowest effective concentration of AgNPs in the suspension was 50 mg dm^{-3}, while for *E. coli*, it was 100 mg dm^{-3} [170].

The step-by-step antiviral action of AgNPs is illustrated in Figs. 6.2 and 6.3. Elechiguerra et al. proposed a mechanism for AgNPs antiviral action against HIV-1 [176,177]. To understand the mechanism of AgNPs eliminating viruses, a detailed insight into the structure of HIV-1 is required. The HIV-1 virus's outer layer is covered with a lipid shell with glycoprotein tabs. They are made up of two subunits: the glycoprotein subunit (gp120) and the transmembrane subunit (TM) (gp41) [178,179]. Because the glycoprotein component is the most prominent element of the virus, prospective attacking agents have easy access to it. The structure of gp120 subunits was discovered to feature nine disulfide bridges. These SS links can be shattered and repurposed to form new connections. AgNPs are most likely to combine with sulfur contained in gp120 subunits, according to Elechiguerra et al. and Lara et al. silver attaches to HIV-1 by interacting with sulfur in disulfide bridges. It should be emphasized that the shape of the HIV-1 virus inhibits the ability of AgNPs to adhere to it. Bonded AgNPs should be 14 nm in size. The binding strength is much lower when the size of AgNPs differs greatly from the model size. The crux of the virus deactivation mechanism is the injection of AgNPs that specifically bind the gp120 component, resulting in virus communication with the "host" cell being blocked. There have also been studies on the action of AgNPs against

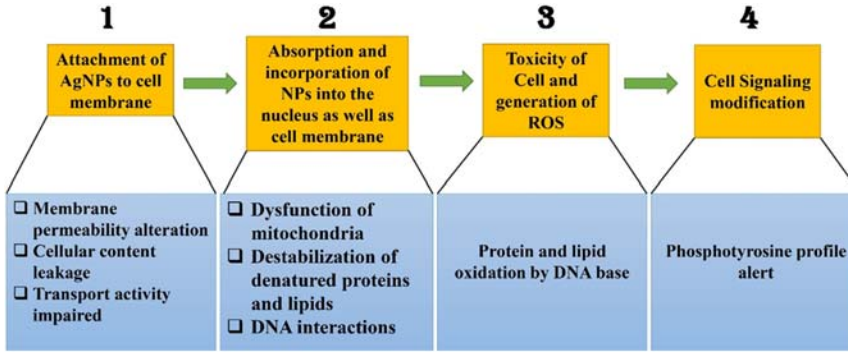

Figure 6.2 Stepwise antimicrobial action of AgNPs in a cell. *(Reproduced from Ref. [182].)*

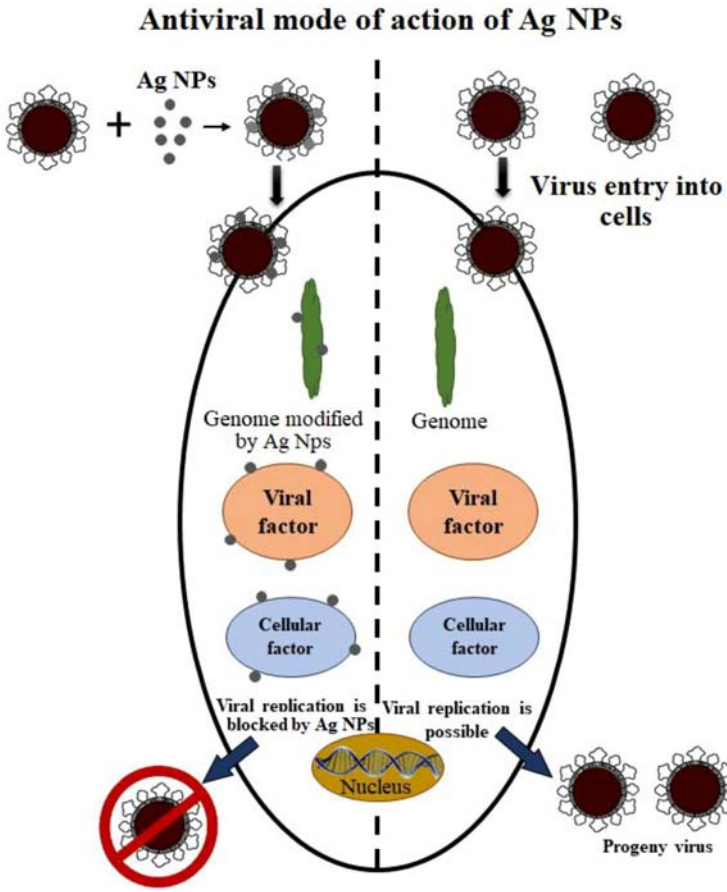

Figure 6.3 Mechanism of antiviral action of AgNPs [14].

the influenza virus [180]. The mechanism is similar in this scenario. The influenza virus coat is made up of two lipid layers from which glycoprotein subunits (HA, hemagglutinin, and NA, neuraminidase) emerge [181]. Hemagglutinin is the protein that binds the virus to the "host" cell. Disulfide bridges are also present in the structure of HA. Because silver has a natural affinity for sulfur, AgNPs may be able to inhibit the point of attachment to healthy cells by binding to the HA component.

Although it is known that AgNPs have biocidal action against *Candida albicans*, *C. tropicalis*, *Saccharomyces cerevisiae*, and *A. fumigatus*, the mechanism of AgNP activity against fungi is still unknown. Lee et al. compared the antifungal activity of AgNPs at a concentration of 60 mg dm^{-3} to that of other antimicrobial agents in a study [170]. The treatment was targeted at a

number of different fungus strains. However, the mechanism of AgNP's activity against fungi is still unknown.

5. Conclusions

Recently, the rapid growth of demand of the garden-fresh fruit industry has led to a need for the improvement of packaging to maintain the shelf life of the food. For this reason the advancement of nanotechnology is very much needed in the near future not only to improve the shelf life of the food but also to maintain the quality and nutritional value of garden-fresh products. The application of AgNPs in the food industry is still in an early stage of development. Therefore, detailed studies for the investigation of the potential toxicity and risk factors associated with AgNPs to the food industry should be considered in the future. Again, the most concerning part of food packaging is the migration of AgNPs from food, related to their toxicity. Another challenge is cost-effectiveness related to the development of food packaging with AgNPs, as the inclusion of AgNPs in the food packaging system may increase the packaging cost. It should also be remembered that the total packaging cost can be 10% of the product cost. Hence, for the inclusion AgNPs in food packaging system, a proper cost–benefit analysis is required. In addition, public acceptance of new nanotechnologies is somewhat poor as this is highly dependent on the demographic and marketplace. Most countries produce nanoparticles but few of them maintain standard regulatory rules for the application of nanoparticles in food products. It is very difficult to make any definite conclusions regarding their efficacy on nanosystems due to the insufficient scientific research in the area. The application of AgNPs in food packaging is comparatively less harmful than the usage of AgNPs as a food ingredient. There will be always a risk factor with nanoparticles entering the food chain through water, soil, and air during their manufacture and utilization, which leads to DNA damage, disruption of the cell membrane, and cell death. To date, very few in vivo studies have been performed on the effects of nanofoods on animal and human health. To increase consumer acceptability there must be proper labeling and marketing of nanofoods. Therefore, the usage of these nanoparticles, if managed and regulated properly, could play a huge role in improving food processing and maintaining product quality, which could benefit human health and well-being.

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SECTION 3

Functionalized nanoparticles-based antimicrobial coatings for environmental applications

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CHAPTER 7

Wastewater purification using advanced functionalized nanoparticles

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1. Introduction

Clean water is an essential substance for all living organisms and is the most important natural resource, with a basic impact on human life [1–3]. The supply of clean water has great environmental, social, and economic impacts, especially for developing countries that constantly face freshwater supply issues [2–4]. For instance, about 74% of the world's population had access to clean and drinking water in 2020 [5]. The main routes driving the widespread contamination of surface and groundwater are population growth, urbanization, and industrialization [6]. Water reservoirs worldwide are facing pressure and constantly being depleted and polluted due to multiple problems of inadequate sanitation, soil erosion, and contamination of surface/groundwaters by pathogens, fertilizers, detergents, chemicals, heavy metals, and pharmaceuticals [7,8]. Pollutants can be classified into three main groups: organic/inorganic pollutants, heavy metals, and microorganisms and pathogens.

Domestic wastewater contains suspended solids, organic matter, and pathogens. Wastewater treatment processes currently used aim to remove organic and inorganic pollutants and pathogens from wastewater to decrease health risks associated with the spread of diseases. In fact, given the current pandemic caused by coronavirus SARS-Cov-2, wastewater

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treatment for pathogen removal is gaining more attention. Due to the increased investment in this area, the expectation is that innovative and effective technologies to ensure safe wastewater disposal and reuse will emerge [20,21]. The matrix of pathogens in wastewaters is rather complicated through individual or combined processes, which remains a problem of public concern still to be tackled [22]. Recently, treatments for water disinfection have been widely explored, often combining chemical and biological degradation procedures [23,24]. There is also a significant number of works exploring the good antibacterial and/or antiviral properties of inorganic NPs to find a suitable solution [25]. Pollution with organic and inorganic contaminants has also been discussed due to widespread detection of their presence in surface and ground waters. Their presence in water threatens human development directly since conventional wastewater treatment plants (WWTPs) are not effective in removing these pollutants [26]. Conventional materials and technologies from these sites like nanofiltration, reverse osmosis, and adsorption are ineffective in treating complex contaminants (e.g., industrial additives, pharmaceuticals, personal care products) from urban wastewaters [27]. Several studies are already presenting alternatives for removing organic pollutants, most of them using advanced oxidation processes for this purpose [28,29]. Heavy metals are substances with densities five times higher than that of water, which can have adverse effects on plants and animals if ingested (or absorbed). Some metals (i.e., copper and zinc) are even necessary in limited amounts to maintain normal functions in organisms, but nonbiodegradable heavy metals are harmful. As, Cd, Cr, Fe, Hg, Ni, Pb, and Se are examples of metals that could lead to health and environmental problems in high concentrations. The important sources of heavy metal which could discharge into the environment include municipal sewage, weathering, erosion by water and wind, and pesticides [9–11]. Water is the major route for the entrance of heavy metals into living organisms, which has led to increasing concern regarding water pollution with heavy metals [12]. Among various treatments used to tackle heavy metals' presence in water, adsorption has been recognized as the most cost-effective approach [13–19].

Public authorities have also noticed the importance of water treatment for sustainable development with one specific Sustainable Development Goal (SDG) for clean water and sanitation (SDG 6). Target 6.3 states that "By 2030, improve water quality by reducing pollution, eliminating dumping and minimizing release of hazardous chemicals and materials,

halving the proportion of untreated wastewater and substantially increasing recycling and safe reuse globally." Despite public awareness of the relevance of this theme, indicators demonstrate that the current situation is critical and concerns are only increasing. According to a UN report on progress on Wastewater Treatment (SDG target 6.3), only 56% of the world's domestic wastewater was safely treated in 2020 (extrapolated from 128 countries representing 80% of the global population). It has also been noticed there are disparities of household wastewater that is safely treated among regions, as shown in Fig. 7.1 with data from some areas [30]. Lack of data also represents another problem when trying to understand wastewater treatment worldwide, since data are rather scarce or nonstandardized. For instance, the time series available is 2015–20, with contributions from 128 countries, covering 81% of the global population. Percentages might seem high, but UN reports on wastewater treatment progress frequently mention that no clear conclusions could be achieved due to low country coverage and lack of information. It is not even possible to weight data based on population because data are not representative of the entire population in the country, with some countries reporting data regarding only one city.

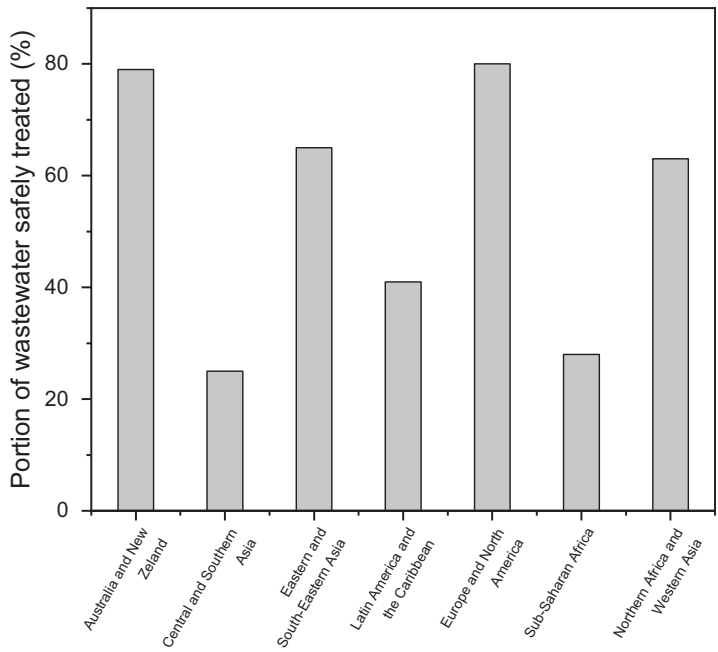

Figure 7.1 Indicator 6.3.1: Proportion of wastewater flows safely treated in 2020.

Nanomaterials could contribute to water availability, viability of water resources, and long-term water quality for the remediation category. In this category, studies dealing with water purification often focus on applying nanomaterials to treat water contaminated by bacteria and viruses, organic and inorganic pollutants, and toxic metals through different technologies [38,39]. In 2010, Ambashta et al. classified water treatment technologies into six categories: adsorption, biotechnology, ionizing radiation processes, magnetically assisted processes, catalysis, and membrane processes [40]. In this chapter, literature regarding the utilization of (1) nanotechnology, NPs and their classifications, synthesis, characterization, and applications, (2) surface functionalization, (3) functionalized inorganic NPs and (4) metal-doped NPs, (5) polymer-functionalized NPs for wastewater treatment, and (6) multifunctional silica nanomaterials for wastewater treatment are briefly discussed.

2. Nanotechnology, nanoparticles, and their classifications, synthesis, and applications

During the few last decades, nanotechnology has become a well-known and interesting field of research in the scientific community since the famous "*There's plenty of room at the bottom*" lecture by Nobel laureate Richard P. Feynman in 1959. Nanotechnology, or nanotech in its shortened form, can be defined as the manipulation of the structure of materials on a near-atomic scale to yield new materials with different structures and devices in the nanoscale level. Currently, nanotechnology promises scientific achievements in different sectors of science including medicine, food security, energy, textiles, cosmetics, and environmental applications. In the field of nanotechnology, there have been several basic developments and smart (nano) materials generated of different types at the nanosize level. Nanoparticles (NPs) are defined as various types of materials with at least one dimension less than 100 nm, and according to this definition, these (nano)materials can be classified as 0D (zero-dimensional), 1D (one-dimensional), 2D (two-dimensional), or 3D (three-dimensional) nanomaterials based on their overall shape. The zero-dimensional (0D) nanomaterials are NPs. NPs exhibit extraordinary chemical and physical properties, high surface area to volume ratio, high reactivity, and toughness properties that depend on their structure, size and shape, and high adsorption capacity, among others [1]. NPs can be classified in different types according to their size, morphology, and physical and

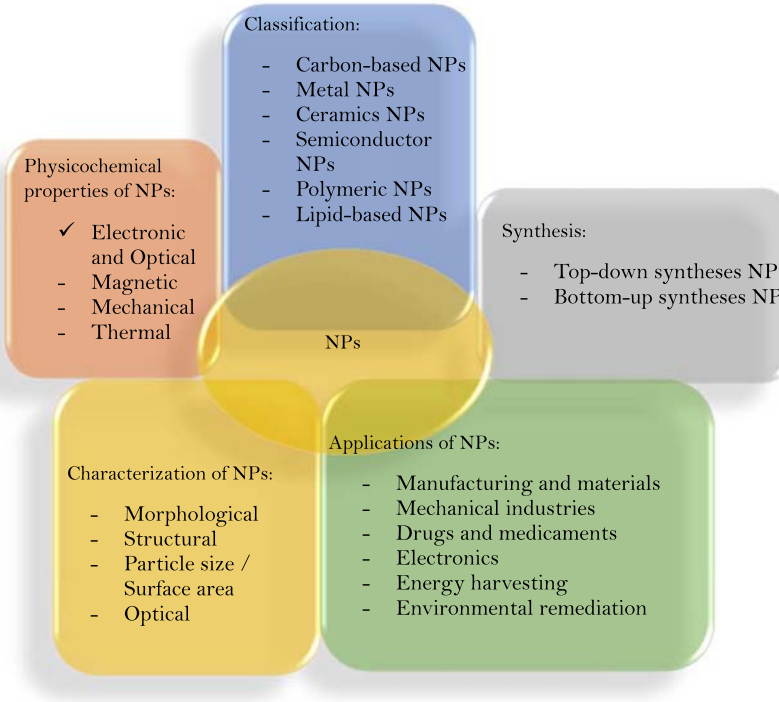

Figure 7.2 Classification, synthesis methods, characterizations, physicochemical properties, and applications of NPs.

chemical properties, as depicted in Fig. 7.2 [2]. The methods for the synthesis of NPs are based on the top-down and bottom-up approaches, where the former converts a material of regular size into an NP, and in the latter, the atoms join to form NPs [2,3]. The bottom-up approach produces better nanostructures with fewer defects and a more homogeneous chemical composition than the top-down approach. Typical NP synthesis methods include physical and chemical vapor-phase deposition, molecular self-assembly, atomic layer deposition, sol–gel nanofabrication, solvothermal, matrix-mediated (template-assisted) processing, among others [3]. The features of NPs are known through various characterizations, such as morphological characterization, structural characterization, particle size/surface area characterization, and optical characterization. NPs have been applied in several areas including wastewater treatment and water purification. Fig. 7.2 summarizes the classification, synthesis methods, characterizations, physicochemical properties, and applications of NPs.

Considering the importance of potable water for the development of all countries and the concerns regarding the viability of meeting environmental standards of water quality, there is a clear need to develop innovative solutions. More advanced and cost-efficient methods and materials are required despite the increasing reports of new methodologies and strategies to tackle this problem [31]. Given this perspective, nanotechnology could play an important role with new nanomaterials for water purification. Materials in this category have dimensions ranging from 1 to 100 nm and, for this reason, often present different and novel physical, biological, and chemical properties. Inorganic (metal oxides, metal alloys, ceramics, etc.), organic (nanostructured carbon material and polymeric micelles), organometallic, and composite NPs have been developed for a wide range of wastewater treatments [32–36]. Environmental applications of nanomaterials often fall into one of the following three main categories: (1) sensors and detectors for environmental protection, (2) environmental remediation and purification (soil, air, water, and wastewater, etc.), and (3) environmental-friendly products [37].

3. Functionalized inorganic nanoparticles for environmental applications

Inorganic NPs are more hydrophilic and highly stable in water compared to organic materials [41]. Reduced metal NPs have received more attention (silver and gold NPs), but metal oxides (copper oxide, iron oxide, zinc oxide, and titanium oxide) also have been widely explored in recent years for several applications [42]. For instance, a quick research in the search engine Web of Science for "inorganic NPs" returned 21,741 results for documents published from 2015 to 2021. Annual production in the period studied is presented in Fig. 7.3, along with the evolution in the percentage of works dealing with environmental applications of inorganic NPs (determined in the same search engine using "inorganic NPs" and "environmental application" as keywords).

As observed, the number of documents related to inorganic NPs and the percentage regarding environmental sciences in the Web of Science database increased from 2339 to 3645 and from 2.73% to 5.814%, respectively, during 2015–21. A decrease of about 5.2% in annual scientific production observed in 2021 can be associated with the pandemic of the SARS-Cov-2 virus once lockdown around the world made it impossible for scientists to run experiments in the laboratory. Despite the decrease in annual

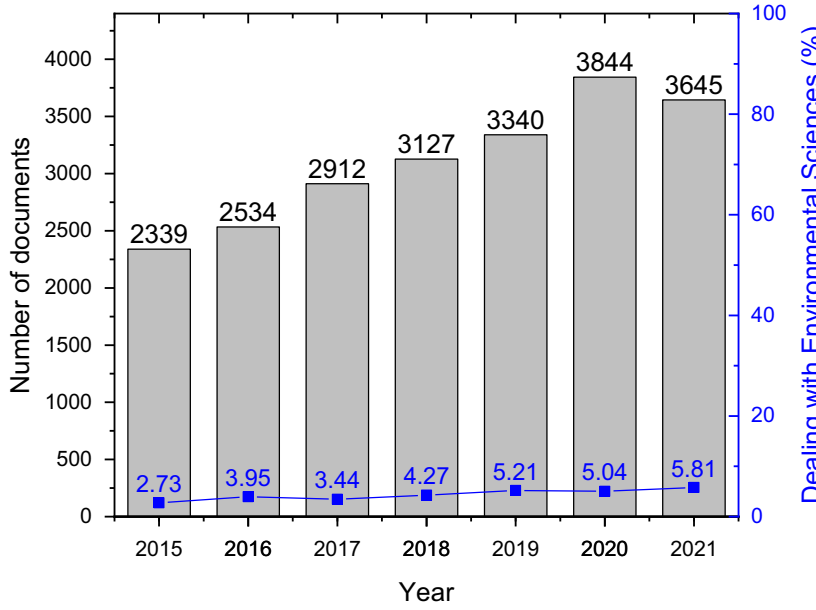

Figure 7.3 Scientific production related to inorganic NPs.

production related to inorganic NPs in 2021 (from 3844 to 3645 documents), the percentage of works dealing with environmental sciences increased from 2020 (5.043% to 5.814%). This simple systematic literature review on inorganic NPs demonstrates that inorganic NP utilization in environmental sciences is increasing, reinforcing the topic's relevance. Additionally, only publications within "Environmental Sciences" were considered for the plot, but more topics probably deal with environmental applications of inorganic NPs (i.e., "Environmental Engineering" subcluster inside "Inorganic NPs").

Documents inside the final cluster obtained deal with the application of inorganic NPs for environmental engineering. Using biblioshiny, a free tool from bibliometric R package, it is possible to analyze tendencies inside this cluster and see the main environmental applications. The 50 most common author's keywords and keywords plus are shown in Fig. 7.4. A word's size in the word cloud representation is proportional to the word's frequency in this database. It is clear with this analysis that most works inside the environmental subcluster of inorganic NPs application cluster deals with wastewater treatments.

The environment around the nanoparticle can significantly impact their efficiency and sometimes even structure. Unprotected inorganic NPs are

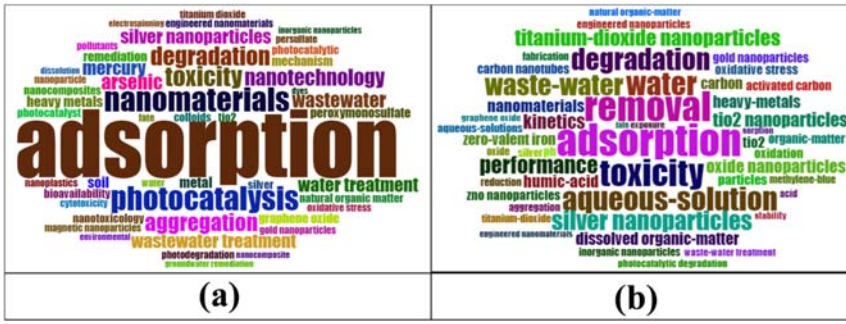

Figure 7.4 50 most used author (A) keywords and (B) keywords plus.

thermodynamically unstable and can aggregate in liquid media. Additionally, materials in this class of NPs can interact with air and fluids and suffer corrosion [43]. To overcome this problem, one good solution is functionalization of the inorganic NPs to protect their surface against corrosion and prevent them from aggregating. Functionalization can also improve inorganic NPs' efficiency in a given application, leading to an ideal scenario of the synergistic effect of the nanoparticle's protection and performance [44].

Functionalization increases the properties and characteristics of NPs through surface modification. Functionalization of NPs typically involves the addition of organic molecules on the surface of the inorganic NPs (Fig. 7.5). The success of this functionalization depends on the high surface to volume ratio and the conjugation of organic molecule—NPs of various functionalization approaches, such as: (1) noncovalent binding, (2) covalent conjugation, (3) amorphous nanoparticle coating, or (4) surface epitaxial growth [45]. The most relevant utilization of functionalized NPs for water treatment will be presented in this work. The focus herein is the discussion of how the structure of the materials is suitable for the applications, with mechanisms and brief discussions regarding how functionalization can

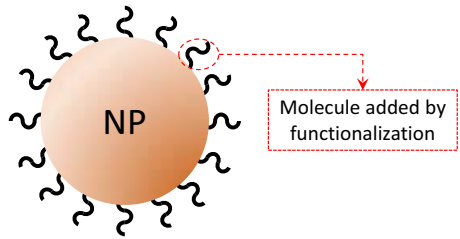

Figure 7.5 NPs linked to a molecule by functionalization.

improve inorganic NPs' efficiency for water remediation. Detailed discussion regarding NPs' synthesis is not provided here, as it is beyond the chapter's scope. However, some images of materials will be shown to enable the reader to see functionalized NPs as a matter of scientific curiosity. Next, functionalized inorganic NPs for heavy metals removal, water disinfection, and organic pollutants mitigation are presented.

3.1 Functionalized inorganic nanoparticles for heavy metals removal

The class of functionalized magnetic NPs (FMNPs) has been extensively explored for environmental applications due to their diverse advantages such as low toxicity, large-scale production, and tunable properties [39,46,47]. FMNPs can potentially remove heavy metals from wastewaters through adsorption using the linker (the molecule used to functionalize the inorganic NPs). In addition, the magnetic properties of the NPs allow them to separate from the solution before its regeneration for reuse [48]. In the case of surface-modified NPs, chelation or chemisorption usually represents the bonding mechanism between pollutants and NPs. External and intrinsic parameters can affect the performance of FMNPs in the adsorption process. External parameters could be temperature, pH, sorbent concentration, and contact time. Intrinsic characteristics influencing the adsorption process are size, shape, Fe^{2+}/Fe^{3+} ratio, surface charge, and availability of active sites [49]. Kinetic modeling is frequently used as a tool to design better adsorption systems, and models are already well-reviewed in the literature by several works [50–52].

The adsorption capacity of FMNPs is strongly influenced by their pH of zero charge (pH_{pzc}) [53]. By functionalizing NPs' surfaces, one can design better materials to achieve higher performances considering the pollutant of interest. Singh et al. explored using nanomaterials with carboxyl, amine, and thiol functional groups on the surface to remove some toxic metal ions (Cr^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Cd^{2+}, Pb^{2+}, and As^{3+}). For instance, pH_{pzc} of bare Fe_3O_4 decreases upon surface functionalization with $-COOH$, $-NH_2$, and $-SH$ groups. Amino- and carboxyl-functionalized surfaces have similar surface charge behavior, with a positive charge at $pH > pH_{pzc}$ and a negative charge otherwise. On the other hand, thiol-functionalized surfaces have a negative charge in the pH range 2–12 [54]. Carboxyl-functionalized surfaces have better adsorption results for heavy metals at $pH > pH_{pzc}$. Adsorption of heavy metals by thiol-functionalized surfaces is enabled by the strong metal–sulfur complexation combined with weak

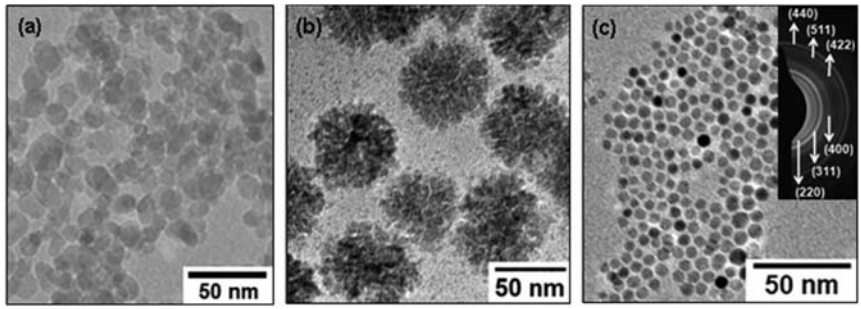

Figure 7.6 TEM images of (A) carboxyl, (B) amine, and (C) thiol FMNPs. A typical electron diffraction pattern of thiol MNP is shown in (C) (inset). *(This image has been modified from Ref. [21], an Elsevier-authorized publication.)*

electrostatic interactions. For amino-functionalized surfaces, complexation with heavy metals is favored at $pH < pH_{pzc}$. A detailed explanation of the mechanisms is presented in Reference [39] for readers wishing to learn more about it. TEM images of nanomaterials are shown in Fig. 7.6 as a matter of curiosity, but they are not discussed herein as this is not the focus of this chapter.

Other functionalized metal-derivate NPs can be used to remove heavy metals from water, such as alumina (Al_2O_3) [55], iron sulfide (FeS) [56], magnesium oxide (MgO) [57], and copper oxide (CuO) [58]. Furthermore, modified oxides have also demonstrated potential application in removing heavy metals. For instance, aluminum-silicate mixed oxides functionalized with diethylenetriamine, triazine, and L-cysteine (heterogeneous nano-dendrimer) showed promising results for removing Hg (II) ions from aqueous media. The mechanism enabling ions adsorption onto the nano-dendrimer could happen through paths such as toxic metal chelation, ionic exchange, or electrostatic interaction [59].

Natural sulfides such as pyrrhotite ($Fe_{1-x}S$), pyrite (FeS_2), and mackinawite (FeS) have been recognized to possess a strong scavenging effect with mercury ions [60]. This occurs due to the chemical interaction of mercury, a soft Lewis acid, with sulfur, a soft Lewis base. The removal of mercury from polluted waters by utilizing FeS derivative materials happens through the precipitation of mercury sulfide, which is insoluble in water. The immobilization mechanism can be ion exchange, surface complexation, or chemical precipitation, and chemical reactions in each case are represented in systems (i), (ii), and (iii) below [61].

(i) Ion exchange:

$$FeS(s) + xHg^{2+} \leftrightarrow [Fe_{1-x}, Hg_x]S(s) + xFe^{2+},\ x < 1$$

(ii) Surface complexation of Hg^{2+} with active sites on FeS:

$$\equiv FeS(s) + Hg^{2+} \leftrightarrow \equiv FeS - Hg^{2+}$$

(iii) Chemical precipitation of HgS(s):

$$FeS(S) + H^{+} \leftrightarrow Fe^{2+} + HS^{-}$$

$$Hg^{2+} + HS^{-} \leftrightarrow HgS(s) + H^{+}$$

$$FeS(s) + Hg^{2+} \leftrightarrow HgS(s) + Fe^{2+}$$

Nanoscale synthetic FeS NPs are expected to have better efficiencies in removing Hg than natural ones due to their larger surface area and potentially higher reactivity. However, pure NPs can face problems associated with stability in water and aggregation, which could lead to less efficient processes. Proper functionalization on the nanoparticle's surface could circumvent NPs from lumping and increase stability in water. In the work developed by Gong et al., FeS NPs were functionalized with carboxymethyl cellulose (CMC) and subsequently used to remove mercury from contaminated waters. Different CMC-to-FeS molar ratios were explored to assess which would return the best result for mercury removal. The test revealed that increasing the molar ratio from 0 to 0.0006 improved mercury adsorption capacity by 20%. Other analytical methods results (XRD and FTIR) suggested that ion exchange, surface complexation, and precipitation were all relevant for mercury removal. In the same study, the authors proposed an isothermal model that can be used to estimate the contributions of adsorption and precipitation to optimize nanoparticle dosage [56]. Fig. 7.7 demonstrates the effect caused by CMC

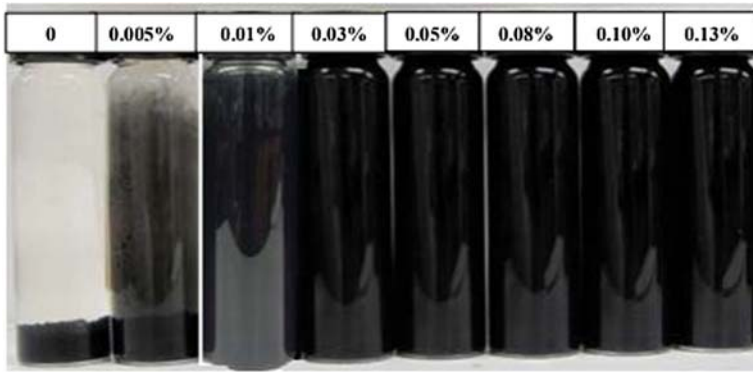

Figure 7.7 Aqueous suspensions of CMC-FeS NPs prepared with molar ratios of CMC to FeS of 0, 0.0001, 0.0002, 0.0006, 0.0010, 0.0016, 0.002, and 0.0025. *(This image was taken from Ref. [56] with permission from ACS Publications.)*

functionalization in FeS NPs, in which it is possible to observe increased stability for molar ratios above 0.0006.

3.2 Functionalized inorganic nanoparticles for water and wastewater disinfection

The widespread utilization of antibiotics directly impacts the environment, increasing the emergence of resistant bacterial strains [62]. Searching for new materials to deal with these problems has led to utilizing amine-modified inorganic materials that often display an interesting behavior. Studies dealing with wastewater disinfection approaches often consider the antimicrobial assessment of these materials using two bacterial strains, one Gram-positive (*Staphylococcus epidermidis*) and another Gram-negative (*Escherichia coli*). In the study done by Bouazizi et al., amine-based DEA functionalization in CuO was able to restrict NPs from releasing copper cations, improving the antibacterial capacity. Moreover, protonation of amino groups increased the antibacterial property by strong electrostatic interactions with negatively charged bacterial membranes. In other words, this study showed improved antibacterial properties achieved by amino functionalization in CuO NPs [63].

FMNPs can also be used to remove bacteria from wastewater [64,65]. In this case, the interaction of the magnetic NPs with the polar head of bacterial membrane lipids is directly responsible for depolarization of the membrane. Within this strategy, bacteria die due to the disruption of structural integrity. Due to more complex Gram-negative walls composed of the outer lipopolysaccharide membrane, the efficiency of FMNPs is lower. On the other hand, FMNPs present high efficiency for removing Gram-positive bacterial strains. Functionalization of magnetic NPs' surfaces with molecules such as bioproteins, carbohydrates, polymers, and dendrimers results in higher efficiencies since the surface would have more active sites due to free functional groups and increased water stability. In the study by Singh et al., the authors also studied the capture efficiency of *E. coli* by FMNPs. They observed that efficiency was also highly dependent on the concentration of FMNPs on media and inoculation time [21]. TEM images of *E. coli* (control) and *E. coli* treated with carboxyl-functionalized MNPs were analyzed to determine the mechanisms related to antibacterial activity from functionalized materials. The images (see Fig. 7.8) prove that magnetic NPs interact with the polar head of membrane lipids, as mentioned above, killing the microorganism by disrupting its structural integrity.

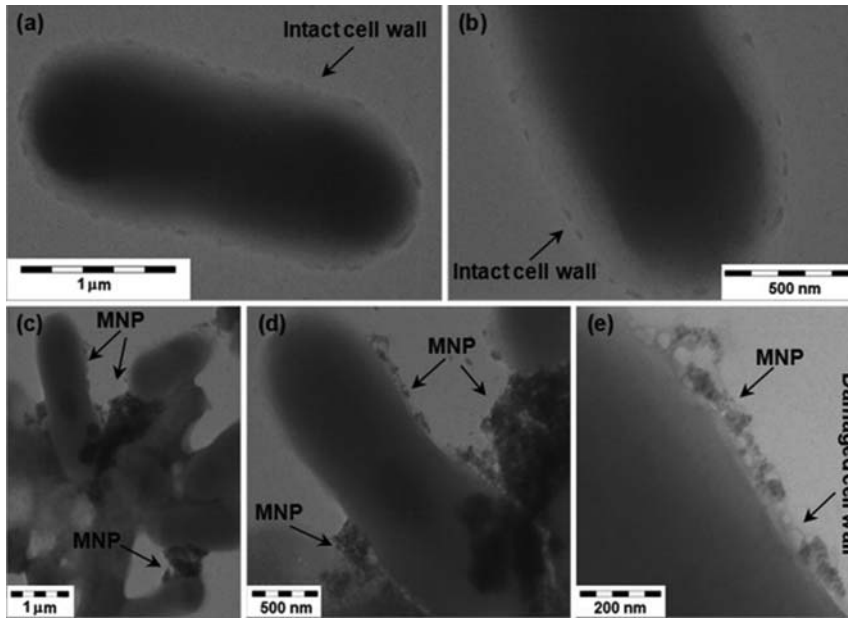

Figure 7.8 TEM images of *E. coli* control samples (A and B) and *E. coli* treated with carboxyl-functionalized MNPs (C—E). *(This image was taken from Ref. [21] with permission from Elsevier.)*

3.3 Functionalized inorganic nanoparticles for organic pollutants degradation

Heavy metals and pathogens have already been briefly discussed, but another class of contaminants that represents a threat to aquatic and human health is the organic contaminants [27,66,67]. Organic pollutants include herbicides, pesticides, food additives, surfactants, hormones, sterols, and self-care and pharmaceutical products. In recent years, the concentration of these pollutants has been increasing, representing a threat of public concern. Rising levels of organic carbon in water are the current challenge addressed to wastewater treatment plants worldwide, which currently lacks cost-effective options to deal with the issue [68]. Consequently, most organic contaminants are not properly removed from wastewater and accumulate in the environment [69].

Solutions to the presence of organic contaminants on wastewaters have been studied in recent years. Within the search for these solutions new classes of advanced materials arise that provide the support that innovative solutions require. Nanoscale zero-valent iron (NZVI) is one example of a material that can deal with organic pollutants in wastewaters [70].

Nevertheless, NZVI alone has low stability and consequently efficiency in further applications once their surface can endure corrosion. On the other hand, NZVI functionalized with sulfide (SNZVI) has been used as a good alternative to overcome NZVI limitations. Numerous works explore other NZVI surface functionalizations to increase antibacterial activity and performance for water remediation [71–73]. For instance, Piang et al. used SNZVI to remove 2,4-dichlorophenol (DCP) through Fenton-like reactions. Studying reaction mechanisms allowed the authors to observe the dominance of the Fenton-like reaction during the degradation of DCP into harmless alkanes and inorganic matters [74]. TEM and SEM images for NZVI and SNZVI NPs are shown in Fig. 7.9.

TiO_2 NPs are among the most explored photocatalysts, showing interesting results for removing organic contaminants from wastewaters. Several works have been developed using this material for water treatments considering different organic pollutants using photocatalytic technology, mainly UV-light [75,76]. Despite good results for removing a wide spectrum of contaminants, transference of this technology to the real scale is rather complicated due to the operational costs associated with UV-light. In this regard, the sun could be a good solution for the light source in

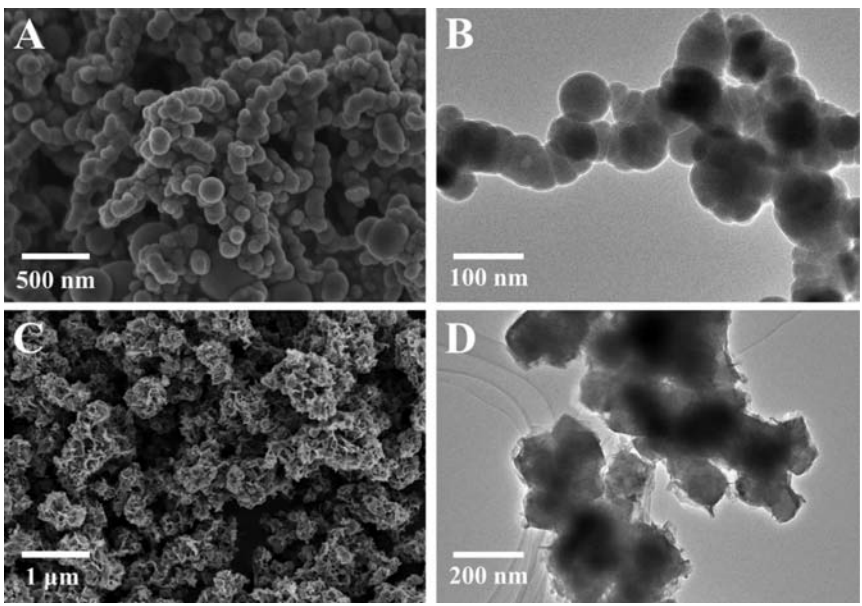

Figure 7.9 NZVI images of SEM (A) and TEM (B); SNZVI images of SEM (C) and TEM (D). *(This image was taken from Ref. [74] with permission from Elsevier.)*

photocatalytic reactions [77]. However, efficiencies within this approach are still lower than what would be considered acceptable or applicable. TiO_2 loses significant activity when the sun is used as a light source once the material has a large bandgap (3.2 eV for anatase phase), limiting photocatalytic capacity [78].

Beyond photocatalysts, TiO_2 NPs can also be used as nanoadsorbents for removing pollutants, benefitting from functionalization treatments to improve adsorption capacities. Some works inserted in this thematic have demonstrated the capability of some TiO_2-based NPs even for real wastewaters [79,80]. Mousavi et al., for example, used cyclodextrin/glycine-functionalized TiO_2 (TiO_2/Gly/β-CD) to remove dyes from real textile wastewater. Testing adsorption with pure TiO_2, TiO_2/Gly (TiO_2 functionalized with glycine), and TiO_2/Gly/β-CD showed an improvement of at least 40% in removing dyes for all modeled tests (MB, MO, AB113, and DR1 dyes were considered for this evaluation). The good result obtained with this nanoparticle for dye adsorption lies in the several hydroxyl and amino groups on the NPs' surfaces, providing effective adsorption sites. A TEM image of functionalized NPs is shown in Fig. 7.10 [81].

MNPs also have applicability in organic pollutants degradation through a heterogeneous Fenton reaction, also known as catalytic wet peroxide oxidation (CWPO). The presence of octahedral sites containing Fe^{2+} ions

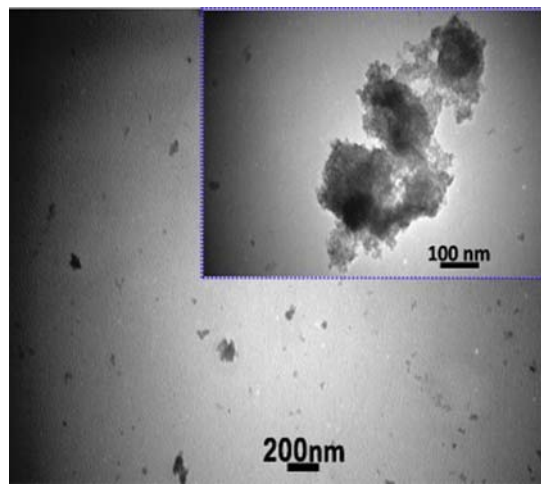

Figure 7.10 TEM image of TiO_2/Gly/β-CD NPs. *(This image was taken from Ref. [81] with permission from Elsevier.)*

on the material is the factor responsible for enhancing the production of hydroxyl radicals (HO). Beyond high efficiencies achieved in CWPO, MNPs are easy to prepare, separate from reaction media, and present high stability in water [82]. As mentioned in another section, MNPs have problems with the surrounding environment during application experiments and can suffer corrosion. In this context, the synthesis of hybrid materials by functionalizing magnetic NPs could lead to increased stability of MNPs. For instance, carbon-coated magnetic NPs show promising results to degrade organic pollutants [83–86].

Magnetic NPs also are capable of locally converting magnetic induction into heat, which can be interesting for wastewater treatments via advanced oxidation processes (AOPs), as reported by Ribeiro et al. [84]. In this work, the utilization of carbon-based magnetic NPs to remove organic pollutants is explored in a different reaction setup, this time exploring the advantage of local heating on the nanoparticle's surface. This work reported a new nomenclature for a heterogeneous Fenton reaction using magnetic fields: magnetically activated catalytic wet peroxide oxidation (MA-CWPO). The removal performance of the model organic pollutant (4-nitrophenol) was enhanced in this new experimental setup due to local temperature increase in the NPs' surface due to an AC magnetic field, which accelerated decomposition of H_2O_2 into hydroxyl radicals [84].

4. Metal-doped nanoparticles for environmental applications

Doping represents one strategy used to change the properties of a determined material by introducing compounds into the substrate [87]. Doping can enhance the biological, optical, and electrical activity of NPs. In this context, doping represents an excellent strategy to design advanced materials for a wide range of applications [88–90]. The main difference between doping and functionalization treatments mentioned in the "functionalized inorganic NPs" topic is that doping introduces impurities into NP surfaces to achieve better electronic, biological, and optical properties. On the other hand, functionalization is the surface modification with functional molecules or groups [91].

Searching for documents related to the term "doped NPs" in the Web of Science search engine in the last 5 years returned 53,270 files. A total of 74,630 documents were obtained without filtering years of interest, which shows that scientific production in 6 years corresponds to 71.4% of the total since the first record (1992). Fig. 7.11 illustrates the annual production

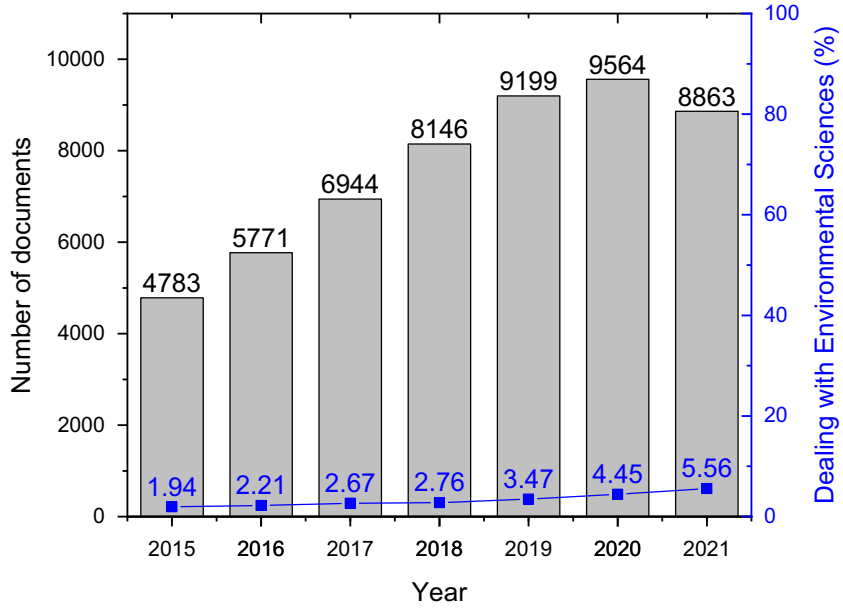

Figure 7.11 Scientific production related to doped NPs.

related to the term and percentage of works dealing with doped NPs for environmental applications (determined in the same engine searcher using "inorganic NPs" and "environmental application" as keywords).

As observed, the published documents doubled in the last 5 years (4783 documents in 2015 and 9564 in 2020). The interest in the environmental application of doped NPs in environmental science has strongly increased (from 1.94% to 5.56% for 2015–21). Although a decrease of 7.3% in annual production was observed in 2021, a growing number of scientific documents dealing with doped NPs demonstrates that this material has potential applications still to be studied. The percentage of works approaching the use of doped NPs for environmental applications increased in the period studied, reinforcing the relevance of this niche. Once again, this simple analysis of the literature was performed considering only documents inside the cluster "Environmental Sciences." For instance, other topics probably use doped NPs for environmental applications but might not be in this database (i.e., those listed in the "Environmental Engineering" field). The analysis here was used to prove the point: increasing interest in this field.

Documents inside the final cluster obtained deal with applying doped NPs for environmental engineering. Using biblioshiny, a free tool from bibliometric R package, it is possible to analyze tendencies inside this cluster and see the main environmental applications. The 50 most common author

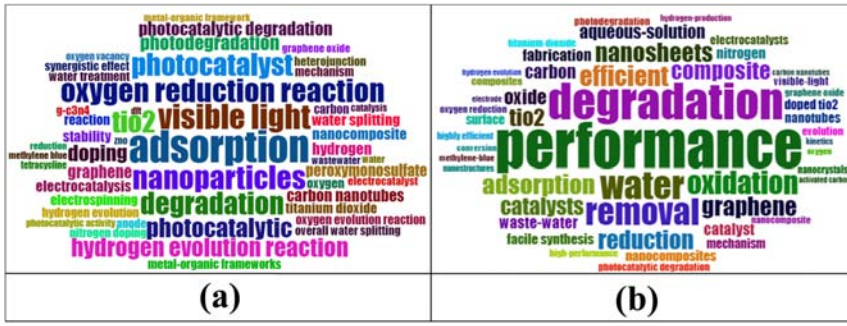

Figure 7.12 50 most used author (A) keywords and (B) keywords plus.

keywords and keywords plus are shown in Fig. 7.12, with the word size being proportional to the word's frequency in this database. It is clear with this analysis that most works inside the environmental subcluster of the doped NPs application cluster deal with wastewater treatments.

Doped NPs used for wastewater treatment purposes include several types of nanomaterials ranging from a single component to hybrid materials such as core–shell, yolk–shell, among others. With the advanced know-how in synthesis, advanced materials merge each day with sophisticated materials designed for increased performance for specific applications. In this context, doping has been widely explored to achieve particular features in materials, enabling them to improve the performance of known (and sometimes new) applications. Fig. 7.13 brings one representation of a typical metal-doped NP that will be discussed in this topic. Methods for preparing these NPs will not be discussed herein, as this is not the focus of this chapter. Next, metal-doped NPs for heavy metals removal, water disinfection, and organic pollutants mitigation will be presented.

4.1 Metal-doped nanoparticles for heavy metals removal

The most studied treatment for removing heavy metals from wastewater is adsorption, which has the highest cost-efficiency [92–94]. In this regard,

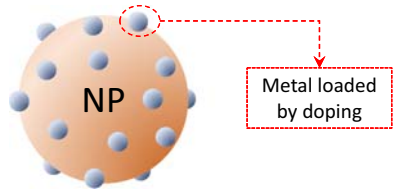

Figure 7.13 Metal-doped NPs.

magnetic NPs have advantages compared to other materials since their recovery is fast, simple, and easy to be performed with an external magnetic field. Another important characteristic for a material to present successful application for removal of heavy metals through adsorption is the affinity with target heavy metals [95]. In the work developed by Buccolieri et al., for example, the authors studied the utilization of Mn-doped iron oxides to remove Ni^{2+} from a simulated matrix. The presence of manganese on the superparamagnetic NP surface enhanced the interaction of the material with Ni^{2+} without altering the magnetic characteristics. The materials doped with a determined amount of Mn were labeled as Mn0, Mn12, Mn25, and Mn50 (according to the amount of manganese used for doping) and subsequently used for removal of Ni^{2+}. The authors concluded that the best result obtained with Mn12 compared to the others was due to increased pore diameter (12 nm in Mn12, while it was 3 nm with bare iron oxide). The results obtained with Mn25 and Mn50 were excluded because materials lost magnetism [96]. TEM images shown in Fig. 7.14 of the functionalized NPs show the morphology changes due to functionalization.

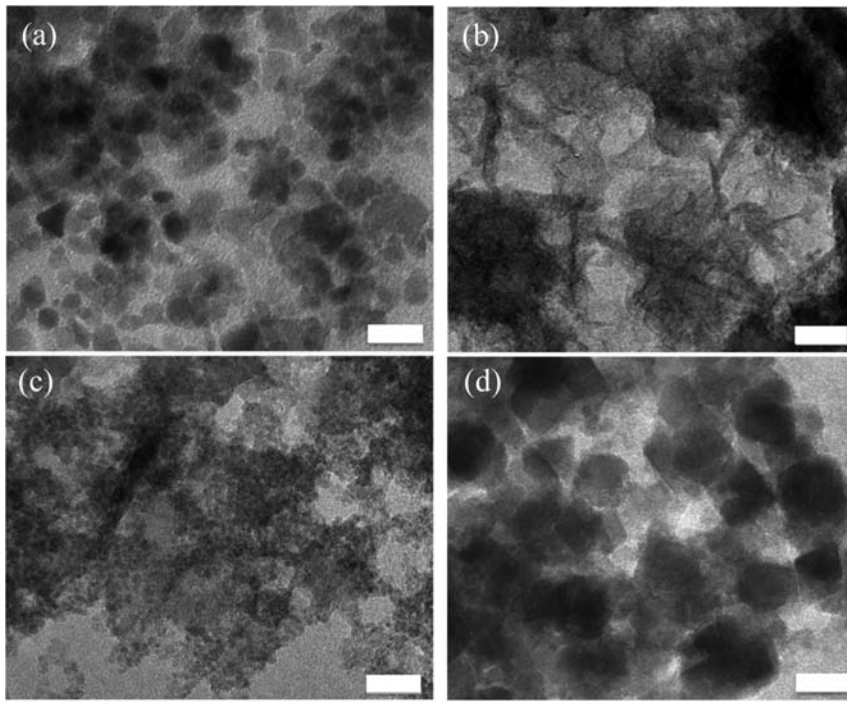

Figure 7.14 TEM images for NPs with stoichiometry ratio Fe:Mn of (A) 100:0, (B) 88:12, (C) 75:25, and (D) 50:50. Scale bar = 20 nm. *(Images were taken from Ref. [96] with permission from Hindawi.)*

Researchers have explored other doping strategies to achieve better performance on heavy metal removal, each specifically designed to target specific heavy metals [97–102].

Zinc oxide is another nanomaterial extensively used due to its high chemical stability, nontoxicity, and low-cost nature. Numerous works have used ZnO NPs for heavy metals removal, using different methodologies to design specific materials [103]. Among the strategies used, doping has been demonstrated to be effective for improving heavy metal removal from water. Doping ZnO can lead to the suspension of charge carriers, reducing their recombination and enhancing heavy metal removal from wastewaters [104]. In the study developed by Mozzamel et al., ZnO NPs were doped with Ti (Ti-doped-ZnO) and La (La-doped-ZnO) to evaluate whether the performance on the removal of Cd (II) could be improved. The authors observed increased Cd(II) adsorption with an increasing dopant in ZnO, reaching the best result with maximum dopant for both doped ZnO NPs (i.e., 8 at%). The adsorption capacity of Ti-doped-ZnO is higher compared to La-doped-ZnO for Cd (II) removal. As explained by the authors, increased adsorption for La- and Ti-doped-ZnO is due to the formation of active absorption sites. Ti and La atoms allocate in O^{2-} atomic sites in ZnO lattice, acting as donors and forming active absorption sites. The adsorption mechanism is associated with the strong bond established between the ZnO surface and heavy metals [105].

4.2 Metal-doped nanoparticles for water/wastewater disinfection

Doped NPs can also be used for water disinfection. Several works consider doped metal NPs for water disinfection, obtaining promising results. Copper, palladium, silver, gold, NPs, metal oxides, titanium oxide, and zinc oxide display antibacterial properties. The biological activity of these NPs is directly related to their capacity to generate reactive oxygen species (ROS). Furthermore, these NPs can bind with the pathogen surface and disrupt the integrity of the cell wall, leading to disintegration of microbial bodies and damage to the pathogen's DNA/RNA [106]. The efficiency of NPs in water disinfection can be dramatically improved by increasing the contact time between NPs and pathogens by surface modification of NPs. In this context, doping represents a good strategy for designing NPs with specific characteristics that could increase the affinity between NPs and pathogens, thus increasing the contact time and efficiency.

Silver NPs (Ag-NPs) were long ago discovered to have strong toxicity against several microorganisms, which led to the widespread study on their

antimicrobial effect. Ag-NPs have been demonstrated to be highly effective against both Gram-negative and Gram-positive bacteria, with lower production of residues in the process. On the other hand, the utilization of Ag-NPs still brings concerns related to their toxicity in water, which is higher than for other Ag-derivate materials. To overcome problems connected to postcontamination of water after disinfection with Ag-NPs, a good alternative could be the utilization of these NPs as dopants. Within this strategy, it is possible to explore the antimicrobial characteristic of Ag-NPs without the need to worry about posttreatment consequences. For instance, this approach is already reported for Ag-NPs doped into other vehicles such as titanium dioxide [107–109], aluminum oxide [110], carbon nanotubes [111], zinc oxide [112], and other metal oxides [113,114].

In some cases, authors have explored the degradation of organic contaminants and mitigation of pathogens, taking advantage of the high photocatalytic activity of TiO_2 and the antibacterial property of Ag [108]. Ali et al., for example, prepared Ag-doped TiO_2 (4.0 mol%) and used the material as a photocatalyst for the degradation of methylene blue under visible light and studied its antibacterial activity against bacterial strains *Pseudomonas aeruginosa*, *Escherichia coli*, *Enterobacter cloacae*, and *Klebsiella pneumonia*. Degradation of MB was higher for doped TiO_2 (96%) compared to TiO_2 NPs (30%) due to the extension of the optical response of TiO_2 with Ag incorporation, explained in more detail by the authors along with the reaction mechanisms. Experiments of reusability conducted to assess the practical use of the catalyst in real applications demonstrated the stability of the catalyst, with almost no change in conversions after five cycles. The antibacterial capacity of NPs was assessed with pure TiO_2, Ag–TiO_2 (2 mol%), Ag–TiO_2 (4 mol%), Ag–TiO_2 (6 mol%), Ag–TiO_2 (8 mol%), and P25 TiO_2 commercially available. The results demonstrated clear

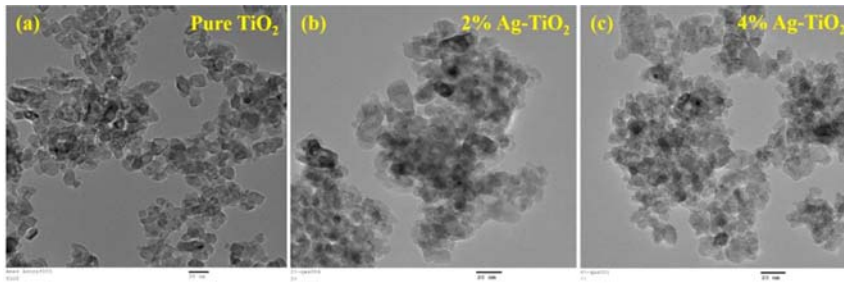

Figure 7.15 TEM images of (A) pure TiO_2 (B) 2% Ag-doped TiO_2 NPs, and (C) 4% Ag-doped TiO_2 NPs. *(Images were taken from Ref. [108] with permission from Elsevier.)*

dependence of performance on the amount of silver on NPs, with Ag—TiO_2 (8 mol%) presenting better performance. In Fig. 7.15, TEM images of Ag—TiO_2 NPs are shown.

Various studies have been conducted evaluating the performance of doped NPs for water disinfection. However, most of these consider *Escherichia coli* as a model microorganism. Frequent utilization of only one bacteria strain in the literature has shown one weakness in this area: the lack of information regarding the behavior of other bacteria. In the study performed by Venieri et al., the authors prepared Mn, Co, Co/Mn, and Mn/Co-doped TiO_2 NPs to be used in the inactivation of *Escherichia coli* and *Klebsiella pneumoniae* bacteria strains by photocatalysis using solar light. Metal-doped NPs were prepared with a molar ratio in the range of 0.02—1 wt.%. Scholars observed that doping successfully shifted the optical properties in the NPs, enabling the absorption of light in the visible region. For this reason, all NPs were effective against *Klebsiella pneumoniae*, which demonstrates potential practical application since this bacteria strain is highly resistant to several water treatments. High activity of both doped NPs was ascribed to optical absorption shifts mentioned above and to recombination delay of the electron—hole pair. In Fig. 7.16, SEM images for selected materials are exhibited. A detailed explanation of how the authors arrived at the conclusions mentioned above is given in Ref. [115].

Carbon nanotubes (CNTs) have been recognized as promising nanomaterials for stabilizing Ag-NPs due to their bactericidal properties and unique structure. Despite good results obtained by authors with the utilization of these materials for their antibacterial properties, discussions regarding mechanisms are still lacking. On the other hand, Su et al. published their study on the mechanism behind the antibacterial properties of an Ag-CNT-based material. Their study used Ag-doped multiwalled carbon nanotubes (MWCNTs) to understand the antibacterial mechanism against bacteria strain *Escherichia coli* DH5α under fluorescent irradiation. These authors observed that the antibacterial efficiency of Ag^0/MWCNTs was higher than for silver NPs, which indicates that Ag^+ ions were not the main factor related to the antimicrobial activity in Ag^0/MWCNTs. Experiments with bacterial exposure to Ag^+ demonstrated that the contribution of the silver ion in Ag^0/MWCNT bacterial mitigation was negligible. In these experiments, microbes were exposed to the maximum concentration of Ag^+ dissolved from Ag^0/MWCNTs during experiments. Further investigations proved that reactive oxygen species OH_b, OH_s, and

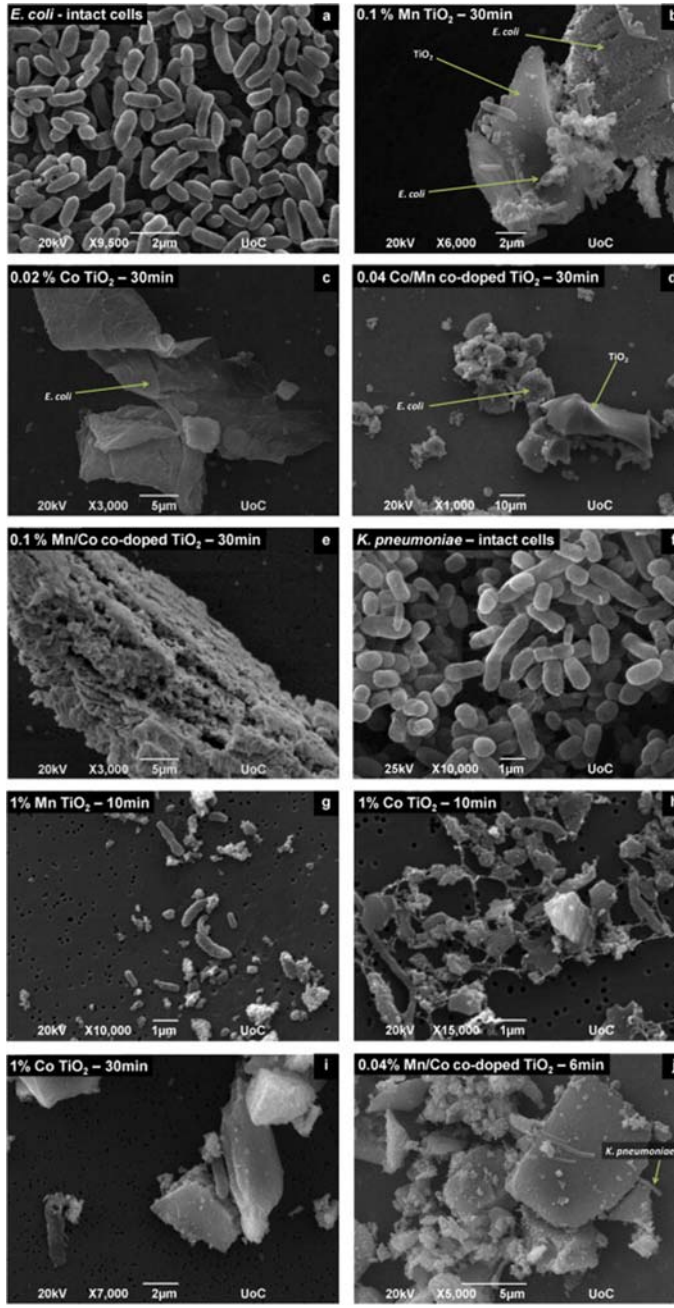

Figure 7.16 SEM images of *E. coli* (A—E) and *K. pneumoniae* (F—J) without treatment and after photocatalytic treatment in the presence of selected metal-doped TiO_2. *(These images were taken from Ref. [115] with permission from Elsevier.)*

h^+ formed during experiments are mainly responsible for the nanomaterials' bactericidal actions [111].

4.3 Metal-doped nanoparticles for organic pollutants degradation in water/wastewater

Organic pollutants have also been focused on intense investigation beyond removing pathogens from wastewaters (water disinfection) and removing heavy metals. Doped NPs also have applicability in this context, with several materials developed to enhance degradation efficiencies through different methodologies. Zinc oxide (ZnO) NPs have excellent electrical, photochemical, and photocatalytic properties at room temperature, with the ability to resist harsh conditions increasing industrial usage viability. Nevertheless, ZnO NPs' wide bandgap limits their photocatalytic performance since they can only absorb wavelengths in the UV region above 380 nm (only 5% of solar spectrum). Rapid photo-excited recombination of charge carriers is another factor that can represent a drawback for using this material as a photocatalyst. Scholars have studied strategies to increase ZnO efficiencies for light absorption and charge carrier separation within this scenario. Methods currently explored to achieve this goal include (but are not limited to) cationic/anionic surface modification, synthesis of hybrid structures, and doping. Other oxides have a similar limitation in photocatalytic reactions, requiring additional treatments to enhance the viability of practical applications.

One approach to solve this problem is doping with transition metals, generating defects in the host lattices and creating new energy levels within the bandgaps. For this reason, doping transition metals into ZnO can be an alternative to improve optical properties and enable higher efficiencies in photocatalytic water treatments. Substitutions of metal ions in host lattice also influence the properties of lattice dynamics due to changes in native lattice force and active mass. For instance, Cu-doped NPs have been developed and used as catalysts to remove organic pollutants by the Fenton reaction [116–118]. Karthik et al., for example, prepared Cu-doped ZnO NPs changing the dopant percentage from 1% to 9% and explored the performance of the doped NPs for degradation of three pollutants by photocatalytic reaction under UV-light illumination. Organic pollutants used in this work were methylene blue (MB), rhodamine (RhB), and indigo carmine (IC). The best results for degradation of dyes were observed for 3% and 5% Cu-doped samples. Reusability tests demonstrated the

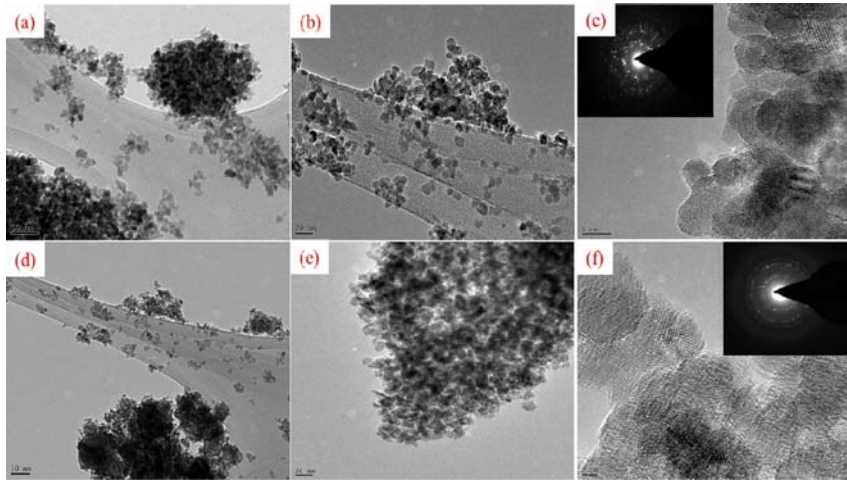

Figure 7.17 TEM images of pure and 3% Cu-doped ZnO NPs (insets in C and F: SAED patterns). *(Images were taken from Ref. [117] with permission from Elsevier.)*

stability of the photocatalyst, with almost no loss in their activity [117]. TEM images of Cu-doped NPs are shown in Fig. 7.17.

5. Polymer-functionalized nanoparticles for wastewater purification

5.1 Introduction

NPs can limit their application in wastewater treatment and water purification because they can form aggregates, which affects their stability and recyclability, which impacts the recovery cost [119]. This limitation can be overcome by combining them with polymers to generate polymer-functionalized NPs (PFNPs) with improved physical and chemical properties (chemical resistance, mechanical properties, thermal stability, flame retardancy, improved surface properties, high adsorption capacity, among others) [120–123] compared to their individual properties. The polymers stabilize inorganic NPs by weakly binding to the NP surface through polymeric ligands and polymeric steric backbone [124]. Furthermore, the structural and interfacial stabilization of NPs are preserved through polymer coating that prevents NP leaching under acid conditions, NP oxidation, and NP aggregation [125]. PFNPs exhibit properties that depend not only on the properties of the polymer matrix and the nanoscale particles, but also on the interfacial reactions between them [121], as depicted in Fig. 7.18.

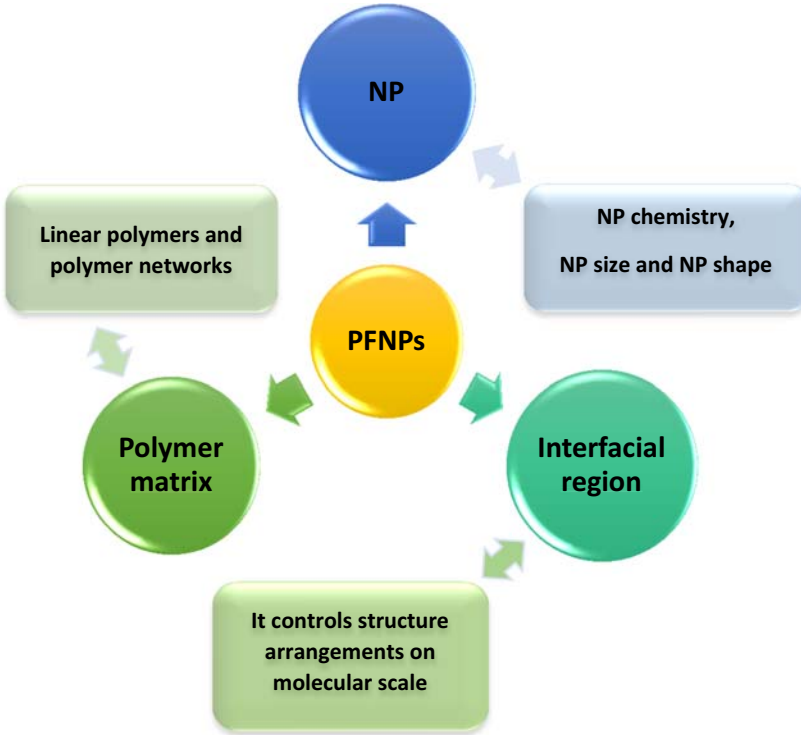

Figure 7.18 Primary components in polymer-functionalized NPs.

Furthermore, the desirable characteristics of the PFNPs are influenced by the preparation methods [126].

Various polymers have been used to functionalize NPs for wastewater treatment and water purification, such as polyethylenimine, acrylic acid, 2-acrylamido-2-methyl-1-propanesulfonic acid, poly (m-aminothiophenol), chitosan, polypyrrole, etc., as summarized in Table 7.1. The properties of polymers depend on their chemistry, molecular architecture, and processing history, such factors influence the final properties of the PFNPs [121]. Fig. 7.19 shows the classification of polymers based on source, monomer chain structure, polymer structure, and molecular forces [121,127,128].

5.2 Polymer-functionalized nanoparticles wastewater treatment

The PFNPs can be synthetized with desirable properties (catalytic, adsorption, and mechanical properties) that make them suitable for wastewater treatment and water purification with low environmental impact since PFNPs can be regenerated and reused, avoiding the difficulties

Table 7.1 Polymer-functionalized nanoparticles for wastewater treatment.

Synthesis method	Polymer-functionalized nanoparticles	Pollutant	Findings	References
One-pot free radical polymerization	Acrylic acid (AA) and 2-acrylamido-2-methyl-1-propanesulfonic acid (AMPS) on the surface of vinyl-modified Fe_3O_4@SiO_2 named FSMAA	Methylene blue	- The maximum adsorption capacity of FSMAA was 421.9 mg/g calculated from the Langmuir model - FSMAA showed good stability, regeneration ability with an adsorption capacity over 60% after eight adsorption −regeneration cycles	[132]
In situ polymerization −ultrasound	Novel magnetic network polymer composite (MCTP) was constructed by introducing the poly(m-aminothiophenol) and	Hg(II)	- The removal rate and adsorption capacity of MCTP were 98.16% and 245.49 mg/g within 15 min, respectively	[134]

Continued

Table 7.1 Polymer-functionalized nanoparticles for wastewater treatment.—cont'd

Synthesis method	Polymer-functionalized nanoparticles	Pollutant	Findings	References
	chitosan onto the magnetic-mesoporous nanoparticle under tannic acid as a cross-linking agent		- MCTP showed good recyclability after 5 cycles with excellent selectivity for Hg (II)	
Hydrothermal synthesis	Polyethylenimine (PEI)-functionalized pyroxene aegirine NPs (based on iron-silicate minerals)	Commercial red dye	Adsorption capacity of 340 and fast adsorption kinetics (<15 min)	[133]
Sono-electro-crystallization method	Iron oxide polypyrrole NPs	Copper, nickel, and cobalt heavy metal ions	Removal efficiencies of copper, nickel, and cobalt were 99.61%, 96.05%, and 94.07%, respectively	[135]
Coprecipitation, emulsification, and in situ polymerization	Fe_3O_4 @SiO_2 @MPS@poly(4-vinyl pyridine) core−shell −shell	Nitrate ions	Adsorption capacity of 80.6 (mg nitrate/g sorbent) at pH 6	[136]

In situ preparation and sonication	Entrapped silica nanopowders within calcium alginate	Pb(II)	- pH = 5 was optimum for Pb(II) adsorption [36.51 mg/g at 180 min contact time from an initial Pb(II) concentration of 50 mg/L] - Pb(II) maximum adsorption capacity on confined silica nanopowders was 83.33 mg/g	[137]
Hydrolysis, sulfation, silanization, and phosphorylation	SYFZr-Tis/PVDF and PZSA/PVDF	Oil	- COD retention ratios of 87% and 85%, respectively, and a stable permeate flux in the treated oily wastewater	[138]

Continued

Table 7.1 Polymer-functionalized nanoparticles for wastewater treatment.—cont'd

Synthesis method	Polymer-functionalized nanoparticles	Pollutant	Findings	References
Phase inversion induced by immersion precipitation method	Se/PES and Cu/PES (polyethersulfone)	Protein and activated sludge	- The morphology and permeation properties of the synthetized membranes depended on the amount of Se and Cu NPs - Compared to neat PES membrane, the 0.05 ratio of Cu/PES membrane exhibited the highest protein rejection (86.3%). However, the Se/PES membranes showed better antifouling performance	[139]

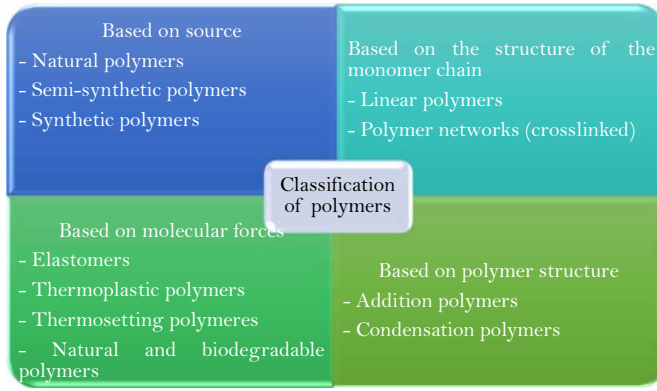

Figure 7.19 Classification of polymers.

of mass transport, separation, and reuse of NPs [126,129,130]. Comprehensive reviews on wastewater treatment and water purification by polymer nanocomposites have been reported [126,131]. The removal of diverse pollutants from wastewater has been carried out using different polymer-functionalized NPs, as evidenced by the studies included in this section and described in Table 7.1.

Several workers have synthetized PFNPs on the bases of polymer-functionalized magnetic NPs and used them to remove cations, anions, and textile dyes from wastewater. For instance, Zheng et al. [132] studied the removal of methylene blue (MB) from aqueous solutions using polymer-functionalized magnetic NPs (MNPs). The MNPs were synthesized by grafting acrylic acid (AA) and 2-acrylamido-2-methyl-1-propanesulfonic acid (AMPS) on the surface of vinyl-modified $Fe_3O_4@SiO_2$ called FSMAA. FSMAA showed a good magnetic property and had a core–shell structure with several functional groups on its structure. These authors observed that the adsorption capacity of FSMAA increased with increasing concentration of the grafted monomer and solution pH. The adsorption was attributed to: (1) electrostatic interaction that occurred between deprotonated groups ($-COO^-$, $-SO_3^-$) on the surface of FSMAA and positively charged quaternary groups in MB, (2) hydrogen bonding due to interaction between $-OH$, $-NH$ on the surface of FSMAA and amine in MB [16], and (3) hydrophobic interaction associated with nonpolar groups because of the aliphatic branches and the hydrophobic character of AMPS that reacted with benzene rings in MB [17]. Finally, FSMAA showed good stability and regeneration ability; the adsorption followed a pseudo-second-order kinetic model and MB removal

was best described by the Langmuir model. Meanwhile, Hethnawi and collaborators [133] prepared polyethylenimine-functionalized pyroxene aegirine NPs (based on iron-silicate minerals) to remove a commercial red dye (CRD) from industrial wastewater. The results revealed that the Sips model described well the adsorption isotherms with high adsorption capacity shown by the MNPC. Furthermore, rapid adsorption was observed and the experimental data were successfully modeled by the kinetic external mass transfer model that described the rate of adsorption. Moreover, Fu and coworkers [134] synthesized a magnetic network polymer composite (MCTP) for Hg(II) removal. The MCTP was prepared by introducing the poly(m-aminothiophenol) and chitosan onto the magnetic-mesoporous silica nanoparticle (Fe_3O_4@SiO_2@SiO_2) under tannic acid as a cross-linking agent. These authors, based on the intraparticle diffusion model, reported that the removal process took place in three stages, such as film diffusion (determinant adsorption step), pore diffusion, and equilibrium. The Hg(II) adsorption followed a pseudo-second-order kinetic and the isotherm adsorption was well-described by the Langmuir model. Moreover, results of Hg(II) adsorption kinetics and adsorption isotherms revealed that the adsorption of Hg(II) onto MCTP was governed by a chemical process by functional groups; thus, the adsorption mechanism was assigned to the formation of a coordination bond with Hg(II) or Hg(II)—chelate complex by multiple interactions including coordination reaction, chelation reaction, and electrostatic attraction [135].

Mosivand and Kazeminezhad [135] synthetized a core—shell structure of iron oxide/polypyrrole NPs by pulsed sono-electrocrystallization for copper, nickel, and cobalt metal ion removal. The results showed that (1) the particle size and morphology were controlled by adjusting the ultrasound amplitude and cycle, (2) the thermal study showed that the stability of the polypyrrole, a component in the shell layer of the iron oxide/polypyrrole NPs, decreased above 200°C, and (3) the magnetite NPs functionalized by polypyrrole were effective for copper, nickel, and cobalt metal ion removal from water due to their strong adsorption capacity [135]. Meanwhile, Javaheri and Hassanajili [136] studied the synthesis of a Fe_3O_4@-SiO_2@MPS@poly(4-vinylpyridine) core—shell—shell structure to remove nitrate ions from aqueous solutions. Fe_3O_4 NPs were coprecipitated and coated with SiO_2, followed by surface modification by 3-(trimethoxysilyl) propyl methacrylate emulsified by polymerization of 4-vinylpyridine. Nitrate ion removal was studied as a function of pH, contact time, and the amount of sorbent loading. The maximum adsorption capacity was 80.6

(mg nitrate/g sorbent) under optimal conditions. Also, polymer-functionalized NPs were regenerated with NaOH solution.

A silica nanopowder/alginate composite was synthetized for Pb(II) adsorption in aqueous solutions [137]. Pb(II) adsorption was enhanced with optimal initial pH = 5, removing 36.51 mg/g Pb (II) in a contact time of 180 min from an initial aqueous Pb(II) concentration of 50 mg/L. The pseudo-second-order kinetic model and the Langmuir isotherm best fit ($R^2 > 0.999$) the adsorption behavior of lead. The Pb^{2+} removal in the silica nanopowder/alginate composite was a spontaneous and exothermic adsorption process. Lead(II) adsorption was enhanced by the hydrophilicity and high adsorption capacity of algine (polymer produced from brown algae).

Polymeric membranes have also been synthesized using NPs that can form microreaction locations (MRLs) inside the membranes to enhance the integrated performance of the membranes in wastewater treatment [138]. The MRLs in the polymeric membranes enhanced the hydrophilic and antifouling properties through photocatalytic TiO_2 degradation of organic contaminants and microorganisms, as well as contributing to the decomposition of inorganic contaminants through the solid acid ZrO_2. According to this work, hybrid membranes with MRLs degrade contaminants to prevent the formation of a gel layer on the membrane surface, which suppresses contaminant deposition within membrane channels. The MRLs were formed in polyvinylidene fluoride membrane (PVDF) through $Y_xFe_yZr_{1-x-y}O_2$-coated TiO_2 solid superacid (SYFZr-Tis) and phosphorylated $Zr_xSi_{1-x}O_2/Al_2O_3$ (PZSA) functional NPs. According to these authors, the hybrid membranes showed favorable oil and COD retention ratios of 87% and 85%, respectively, and a stable permeate flux in the treatment of oily wastewater [138]. Another work reported the effect of NPs of selenium and copper on the antifouling property of polyethersulfone (PES) membrane in activated sludge filtration for wastewater treatment [139]. These authors stated that the morphology and permeation properties of PES membranes with Se and Cu NPs depended on the amounts of NPs. Cu (0.05 wt.%)/PES membrane exhibited the highest protein rejection ratio (86.3%) compared to neat PES membrane. Nevertheless, the Se/PES membranes exhibited better antifouling performance. This antifouling performance of Se/PES and Cu/PES membranes was attributed to (1) the antimicrobial properties of selenium that prevented the development of bacterial biofilms on the membrane surface by acting as a catalyst for redox reactions involving reactive oxygen species [140], and (2) the high toxicity of copper that inactivated the cell membrane of bacteria

by mechanisms such as membrane rupture, biochemical pathway blockade, protein complex formation, and DNA damage [141].

5.3 Polymer-functionalized nanoparticles for water purification

Water purification is carried out by nanofiltration and reverse osmosis processes developed through membrane technology, considered as the most profitable and widely applied for water purification. The most widely used polymeric materials in industrial filtration are polycarbonates, polyacrylonitrile, polyamide, polyvinylidene fluoride, cross-linked polyether, polypropylene, polyethersulfones, polyetherimides, and cellulose acetates, among others [142].

The polymeric membrane materials are closely related to the membrane performance for water purification. Thus, the inclusion of NPs to polymeric membranes improves the mechanical and thermal stability, fouling resistance, permeate flux, salt rejection, membrane surface hydrophilicity, and membrane permeability [143–147]. Several nanoparticle materials have been employed to improve the polymeric membrane performance in water purification, such as oxide species (TiO_2, Al_2O_3, ZnO, hydrated iron (III) oxide), metal (Ag) and activated carbon NPs, as shown in Table 7.2. These NPs increase water permeability and fouling resistance by enhancing the membrane hydrophilicity in addition to improved salt rejection capacity because of their high surface porosity, making them suitable for adsorption and catalytical applications.

TiO_2, a photocatalyst with intrinsic antimicrobial activity, has been incorporated in several polymeric membranes for water treatment and water disinfection [144,148,149]. TiO_2 has been extensively studied for water disinfection to inactivate pathogenic microorganisms (bacteria, fungi, and viruses). The possible mechanisms of the TiO_2 NPs-membrane to inactivate such microorganisms include (1) cell damage and lipid peroxidation due to NP attachments by electrostatic interaction on cell wall, (2) breaking of cytoplasmic flow due to NP obstruction of nutrient carriers, and (3) photocatalytic degradation of biological macromolecular and intracellular organelles [148]. For instance, Kwak et al. [144] fabricated TiO_2/aromatic polyamide membranes by self-assembling TiO_2 NPs on polymer chains with carboxyl groups (−COOH) on the surface. These hybrid membranes were used to study the survival of *E. coli* bacteria in the reverse osmosis (RO) process in the presence and absence of UV illumination. Complete *E. coli* sterilization was reached in 4 h with the TiO_2 self-assembled hybrid membrane under UV illumination compared to the

Table 7.2 Polymer-functionalized NPs for water purification.

Synthesis method	Polymer-functionalized nanoparticles	Pollutants	Findings	References
Via dry jet wet spinning technique	Silver NPs/cellulose acetate (CA) hollow-fiber membrane	*Escherichia coli* and *Staphylococcus aureus*	- Silver content in the CA membrane was important to maintain the antimicrobial activity in the membrane - The preservation of long-term antibacterial activity depended on a suitable range of Ag NPs (0.01 −0.1 wt.%)	[143]
Sol-gel/self-assembly methods	TiO_2/aromatic polyamide membranes	*Escherichia coli* (*E. coli*)	- The photocatalytic bactericidal efficiency of the membrane was notably higher under UV illumination compared to darkness	[144]

Continued

Table 7.2 Polymer-functionalized NPs for water purification.—cont'd

Synthesis method	Polymer-functionalized nanoparticles	Pollutants	Findings	References
Melt intercalation process	TiO_2/polypropylene polymeric membrane	*Pseudomonas aeruginosa* and *Enterococcus faecalis*	- TiO_2/membrane showed higher antimicrobial activity compared to that of the TiO_2 alone - Almost complete cell inactivation of both bacteria was obtained at 30 min	[150]
Melt blending/ sonication processes	TiO_2/EVOH membrane	*Pseudomonas aeruginosa*	Mechanism of bacteria death induced by the TiO_2/EVOH matrix	[149]
In situ polymerization	AgNPs/polyvinylidene fluoride membrane	Gram-positive and Gram-negative bacteria	- Antimicrobial AgNPs-functionalized membranes through bio-derived gallic acid	[147]
In situ impregnation	HFO-NPs/styrene-divinylbenzene (cation and anion exchanger)	As(III) and As(V)	- HFO-NPs/anion exchanger showed higher arsenate removal capacity as compared to the cation exchanger	[155]

In situ impregnation	HFO-NPs/ polypropylene and polyacrylic fibers (anion exchanger)	As(III) and As(V)	- HFO-NPs/PAN exhibited higher selectivity for As(III) and As(V) species with a high sorption capacity (∼2.9 g As/kg) due to the presence of ternary amino groups	[156]
Evaporation (solvent casting)/precipitation method	Cellulose triacetate (CTA)/activated carbon (AC) NPs	As(V)	- AC increased the fraction of pores with bigger size - 45% of As(V) was removed from a 500 μg/L arsenic solution	[155]

~58% for the plain membrane at the same time. Poor *E. coli* sterilization was reported for the hybrid membrane (42%) and plain membrane (40%) under dark conditions. These authors also reported improved RO performance upon integrating TiO_2 NPs on the membrane. A slight increase in water flux was observed during the 7-day RO test, which was attributed to (1) exposure of the TiO_2 NPs, during self-assembly on the membrane, to acidic conditions (nitric acid); the acid caused a partial hydrolysis at the membrane surface and the hydrophilicity increased and thus the water flux increased, and (2) the water absorption characteristics of the TiO_2 particles could have been involved. According to these results, TiO_2 self-assembled hybrid membrane photocatalytic bactericide shows a promising potential use of antifouling RO membrane [144]. Furthermore, the TiO_2/industrial polypropylene polymeric membrane showed higher antimicrobial activity against *Pseudomonas aeruginosa* and *Enterococcus faecalis* than the pure photocatalyst under UV illumination, as reported by Kubacka and co-workers [150]. According to these authors, enhanced photoinactivation was achieved with TiO_2/membrane charge-handling properties that increased biocidal effects and modified oxide charge carrier behavior, leading to a noncontact antimicrobial agent; therefore, almost complete cell inactivation of both bacteria was obtained at 30 min. Kubacka et al. [149] also studied the mechanism of inactivation of *Pseudomonas aeruginosa* by TiO_2 NPs incorporated on a commercial polymeric membrane (EVOH, with 71 mol%, vinyl alcohol polymeric matrix). These authors reported that the photocatalytic action of the TiO_2/EVOH matrix triggered the down-regulation of a wide variety of genes/proteins specific for growth, signaling, and regulatory functions in parallel with subsequent selective effects on ion homeostasis, independent respiration of coenzymes, and the structure of the cell wall.

Loading Ag NPs into polymeric membranes has been shown to enhance antimicrobial activity, resistance to membrane fouling, water flux, and surface hydrophilicity [146,147]. Ag NPs, modified with gallic acid (GA) from pomegranate peel extracts, were incorporated to polyvinylidene fluoride membrane to study the antimicrobial activity against Gram-positive and Gram-negative bacteria [147]. Improved antifouling ability and 3.5 times higher pure water flux compared to neat membrane were reported. In addition, the inhibition of bacterial diffusion and proliferation was observed because Ag NPs confer antimicrobial activity to the membrane against Gram-positive and Gram-negative bacteria. These authors

emphasized that GA-rich pomegranate peel extracts were effective in the membrane functionalization approach used [147].

There are several possible mechanisms of silver inhibition of bacteria that have been proposed, including (1) interference with electron transport, (2) binding to the DNA, and (3) interaction with the cell membrane [151]. The antimicrobial activity of Ag NPs has also been linked to: (1) the gradual release of Ag^+ ions that disrupt ATP production and DNA replication, (2) silver binds cellular protein (DNA and RNA) and respiratory enzymes, (3) Ag NPs and Ag^+ ions promote the production of reactive oxygen species, and (4) Ag NPs cause structural changes in the membrane cells that deactivate the structure of cell life [152–154].

The release of silver ions from the membrane is important to be controlled to maintain the antimicrobial activity of the membrane. Chou and co-workers [143] prepared Ag NPs/cellulose acetate (CA) hollow-fiber membrane to inactivate *Escherichia coli* and *Staphylococcus aureus* bacteria. These authors observed that the silver content in the CA membrane was important to maintain the antimicrobial activity in the membrane. Thus, the preservation of long-term antibacterial activity depended on a suitable range of Ag NPs (0.01–0.1 wt.%).

Polymer-supported hydrated iron (III) oxide NPs (HFO-NPs) were used to remove dissolved arsenic from naturally contaminated groundwater and drinking water [155,156]. Cumbal and Sengupta [155] loaded HFO-NPs into anion and cation exchangers to study the role of the Donnan membrane effect during arsenic removal. These authors reported that the HFO-NPs/cation exchanger did not allow the penetration of arsenate into the polymeric phase because of the Donnan membrane effect, which arose from nondiffusible, negatively charged sulfonic acid groups on the cation exchanger. However, the HFO-NPs/anion exchanger exhibited a very high arsenic removal capacity. These authors also stated that the HFO-NPs/anion exchanger was the first hybrid sorbent to use the Donnan membrane effect of the host material to enhance sorption. Another study reported the use of two fibrous ion exchangers FIBAN for HFO dispersion: HFO-NPs/PP (polypropylene) and HFO-NPs/PAN (polyacrylic) fibers anion exchanger [41]. HFO-NPs/PAN exhibited higher selectivity for As(III) and As(V) species with a high sorption capacity ($\sim$2.9 g As/kg). This was attributed to the weak base functional groups of the fibrous ion exchanger with ternary amino groups. In addition, the speed of the process was controlled by the diffusion of the arsenic species in HFO particles evenly distributed in the fiber. The presence of anions such as Cl^-, SO_4^{2-}, and $H_2PO_4^-/HPO_4^{2-}$ did not affect As(III) sorption in drinking water, but As(V) sorption decreased as phosphate concentration increased. Moreover,

the filter allowed 200 L of water to be purified per hour and 2.5–5 tons (5000–10,000 bed volumes) of purified water to be obtained from water contaminated with As(III) and As(V) (with 50–100 μg/L) without correcting the pH or pre-oxidizing As(III) [156].

Hybrid polymeric membranes was prepared with cellulose triacetate (CTA) and activated carbon (AC) NPs to be used for the removal of As(V) from water [145]. AC and CTA have an important role for rejection; however, arsenic cannot be removed mainly by size exclusion. Thus, according to the authors of this work, two additional removal mechanisms should be considered: Donnan exclusion and dielectric exclusion mechanisms. The former is promoted by the charged nature of the membrane and the charged solutes (creation of an uneven electrical charge) that cause differential rejection, while the latter mechanism is promoted by the molecule water polarization inside the pore; such polarization decreases the dielectric constant of water resulting in it being unfavorable for charged solutes to go through the pores. Thus, this results in charged solute exclusion. Furthermore, according to Terrazas-Bandala and collaborators [145], carbon NPs should confer an adsorption capacity to membrane, and also modify the net charge of the interface exposed to the liquid phases. These authors revealed that AC increased the fraction of pores with bigger size and 45% of As(V) was removed from a 500 mg/L arsenic solution at pH 6. According to the pHpzc of CA (5.5). the AC was negatively charged at the pH of the solution (pH = 6) [145].

5.4 Concluding remarks on polymer-functionalized nanoparticles for water/wastewater purification

Polymer-functionalized NPs enabled wastewater treatment and water purification due to (1) improved physical and chemical properties of the individual components and (2) antimicrobial and photocatalytic activity, in addition to improved adsorption capacity, as evidenced by the studies included in this section. The combination of NPs and polymers has resulted in the development of highly efficient materials to eliminate hazardous pollutants from aqueous environments. The synthesis method and the type of combination of NPs with polymers influence the final properties of these polymer nanocomposites with great capacity for water treatment. A diverse number of pollutants can be removed from water efficiently by these polymer nanocomposites.

6. Multifunctional silica nanomaterials for wastewater treatment

6.1 Introduction

Silica (SiO_2) is a versatile material that has been widely used in environmental remediation to remove heavy metal ions from wastewater. Silica has a high surface area and a porous surface with silanol (Si—OH) functional groups capable of immobilizing organic and inorganic contaminants from wastewater [157]. Several studies have functionalized the silica surface with different nanomaterials to enhance its adsorption capacity to remove simultaneously a diverse number of aqueous pollutants. The improved capacity of the modified materials is due to an enhancement in their surface properties, increased porosity and surface area, as well as additional functional groups in their surface. Therefore, the modified silica adsorbents or multifunctional silica nanomaterials have shown additional functions such as oil/water separation, photocatalysis, and antibacterial features for water treatment and purification [158—160].

The adsorption mechanisms, shown in Fig. 7.20, depend on the functional groups present in the contaminants (adsorbates) and the adsorbent surfaces (adsorbents), and also on the operating conditions (ionic strength, pH of the solution, etc.) of the removal process.

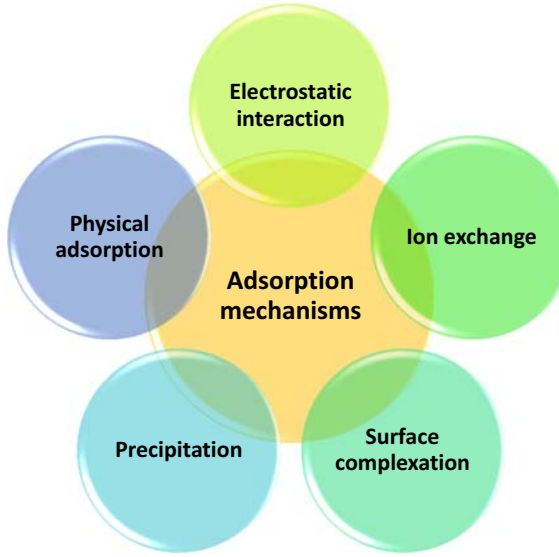

Figure 7.20 Adsorption mechanisms.

6.2 Multifunctional silica nanomaterials for water and wastewater purification

The multifunctional silica nanomaterials have shown improved functions such as oil/water separation, photocatalysis, and antibacterial features for water treatment and purification. This improvement is due to an enhancement in their surface properties, increased porosity and surface area, as well as additional functional groups in their surface. Thus, these multifunctional silica nanomaterials have shown capability to remove diverse harmful aqueous pollutants, including metallic ions, organic compounds, and bacteria, as depicted in Table 7.3.

Graphene oxide (GO) exhibits a high adsorption capacity due to its functional groups and $\pi-\pi$ interactions with other compounds [161]. Several studies have combined the adsorption properties of GO with silica to achieve synergy between both components for water treatment and purification (Table 7.3). Galzerano et al. [162] combined multifunctional diatomite-based foams (MDFs) with carbonaceous nanomaterials (graphite, graphene, and graphene oxide) for water purification. These authors reported that the inclusion of carbonaceous materials in the MDF did not favor the removal of organic dyes (methylene blue and indigo carmine), but graphene (GE) and GO were highly efficient for Cd^{2+} uptake. This was attributed to synergy of the fine morphology, the larger foam surface, and the highly exfoliated GE and GO that were evenly dispersed in the MDF. Furthermore, pristine MDF showed the best performance for indigo carmine removal because of its intrinsic chemistry and hierarchical porosity. MDF also showed good Cd^{2+} uptake compared to MDF composites. Another study [46], reported maximum capacities of silica-decorated graphene oxide (SiO_2/GO) to remove Cd(II) and Congo red (43.45 and 333.33 mg/g based on Freundlich and Langmuir isotherms, respectively). According to the Langmuir and Freundlich isotherms, monolayer adsorption of Congo red and multilayer adsorption of Cd(II) on SiO_2/GO surface, respectively, were indicated. These authors indicated that the removal of Cd(II) and Congo red was spontaneous and exothermic in nature. Furthermore, the active sites of SiO_2/GO ($\pi-\pi$, hydroxyl, carboxyl, ketone, silane-based functional groups) contributed to enhancing the simultaneous removal of aqueous Cd(II) and Congo red. Another study carried out wastewater treatment to remove heavy metal ions (Pb^{2+}, Hg^{2+}, and Cd^{2+}) and organic dye (methylene blue [MB]) through nickel silicate and nickel silicate/nickel composite nanotubes (NiSNTs). The NiSNTs

Table 7.3 Multifunctional silica nanomaterials for wastewater treatment and water purification.

Synthesis method	Multifunctional nanomaterials	Pollutant	Findings	References
In situ hydrolysis	Silica-decorated graphene oxide (SiO_2/GO)	Congo red and cadmium (II)	- The maximum adsorption capacities of SiO_2/GO for Cd(II) and Congo red were 43.45 and 333.33 mg/g, respectively - The simultaneous adsorption of Cd(II) and Congo red showed enhanced the adsorption capacity of SGO adsorbent (~97% for both pollutants)	[161]
In situ impregnation	Multifunctional diatomite-based foams (MDF) with carbonaceous nanomaterials (graphite, graphene, and graphene oxide)	Indigo carmine dye, methylene blue dye, and Cd^{2+} removal	- Graphene and graphene oxide-MDF exhibited enhanced Cd^{2+} adsorption capacity - Poor organic dye removal with pristine diatomite powder was observed - The addition of carbonaceous material to the diatomite worsened the removal of the dyes	[162]
Hydrothermal process	Nickel silicate nanotubes (NiSNTs)	Heavy metal ions (Pb^{2+}, Hg^{2+}, and Cd^{2+}) and organic dye (methylene	- The NiSNTs showed excellent performance for the adsorption of the heavy metal ions and methylene blue in wastewater treatment	[163]

Continued

Table 7.3 Multifunctional silica nanomaterials for wastewater treatment and water purification.—cont'd

Synthesis method	Multifunctional nanomaterials	Pollutant	Findings	References
		blue) in synthetic wastewater		
Vacuum-assisted filtration and self-assembling process	SiO_2/graphene oxide (GO)	Oil—water separation and methylene blue dye removal	- Efficient and antifouling oil—water separation with a rejection rate of >99.4% and a high flux rate of 2387 L/m^2h for pure water and 470 L/m^2h for oil—water separation	[159]
Thermal decomposition of metal precursors in MSNs and subsequent methane CVD	Mesoporous silica nanospheres (MSNs) embedded with FeCo/graphitic carbon shell nanocrystals (FeCo/GC NCs@MSNs)	Removal of methylene orange and methylene blue dyes and Hg^{2+}	- High stability in 35% HCl and NaOH (pH 11) solutions - This magnetic composite showed excellent removal ability for dyes and Hg^{2+} - It is also a highly stable and magnetically recyclable multifunctional adsorbent	[160]
Chemical mixing, thermal treatment	Multifunctional clay-based ceramic filter	Nitrite, nitrate, total dissolved solids, total hardness, total organic pollutants, and pathogenic microorganisms	- It showed high filtration rates (about 50—180 m/h) compared to the common sand filter - Pathogens, nitrite, nitrate, and TDS in filtered water reduced to level of desired standards for drinking water	[158]

Sol–gel process	TiO_2–SiO_2@PDMS superhydrophobic films	Oil–water separation and dye waste water treatment (dyes: methylene blue, alizarine red)	- Excellent ability for oil–water separation and dye waste water treatment under UV light (colorless water in 30 min) - These superhydrophobic films can be used under high-temperature conditions	[165]
	SiO_2/ZnO core–shell NPs	Stearic acid (SA) and methylene blue (MB)	- Exhibited photocatalytic and H_2S chemisorption properties due to ZnO activity - Photocatalytic degradation of stearic acid (~85% in 30 min) and methylene blue (~90% in 3 h) under UV light - SiO_2/ZnO has potential use for purification operations coupling separation and photocatalysis or gas filtration and H_2S chemisorption at high temperature	[166]
Kheshti and Hassanajili method	Amino-functionalized mesoporous microsphere (Fe_3O_4@SiO_2@m-SiO_2–NH_2)	Cd^{2+} ions	- The maximum adsorption capacity of the adsorbent was ~885 mg/g: 92%–96% Cd^{2+} removal was obtained after 6 cycles - Cadmium ion desorption (in 1M HCl solution) and regeneration of	[167]

Continued

Table 7.3 Multifunctional silica nanomaterials for wastewater treatment and water purification.—cont'd

Synthesis method	Multifunctional nanomaterials	Pollutant	Findings	References
			Fe_3O_4@SiO_2@m-SiO_2 $-NH_2$ microspheres keeping their original capacity for metal removal was reported	
Grafting and cocondensation methods	Amino-functional mesoporous silica SBA-15 materials. Three amino groups: aminopropyl ($H_2N-(CH_2)_3-$), [2-aminoethylamino]-propyl ($H_2N-(CH_2)_2-NH-(CH_2)_3-$), and [(2-aminoethylamino)-ethylamino]-propyl ($H_2N-(CH_2)_2-NH-(CH_2)_2-NH-(CH_2)_3-$)	Heavy metals in wastewater [Cu(II), Ni(II), Pb(II), Cd(II), and Zn(II)]	- Negligible metal adsorption capacity was observed in materials prepared by cocondensation because amino active sites were not accessible to metallic species - Amine-grafted materials exhibited high amino groups content that adsorbed high amounts of aqueous Cu(II), Cd(II), Pb(II), Ni(II), and Zn(II)	[168]
Via a modified Stöber method	Multifunctional magnetic silica composites (MS, Fe_3O_4@SiO_2)	Metal ions (Cu^{2+}), bacteria (*E. coli*), and dyes (acid fuchsin) simultaneously	- Removal efficiencies for dye and Cu^{2+} were 100% and >98% for *E. coli*	[169]

showed excellent performance for the adsorption of the heavy metal ions and methylene blue in wastewater treatment [163]. The NiSNTs' maximum adsorption capacity for the ions was 203 mg/g (Pb^{2+}), 362 mg/g (Hg^{2+}), and 267 mg/g (Cd^{2+}) at pH = 7, based on the Langmuir adsorption model. Over 90% of the metallic ions were adsorbed inside of 5 min from the synthetic water solutions. Meanwhile, the NiSNTs exhibited a maximum adsorption capacity for MB of 198 mg/g (>90% of MB was adsorbed in 5 min). These results are attained due to the NiSNTs tubular hierarchical morphology and hollow interior structures conferring high surface areas and large pore volumes.

Recently, a comprehensive review of recent advances in multifunctional membranes with super-wetting features for oil and water separation and removal of harmful contaminants from water has been reported [164]. For instance, oil—water mixture separation and dye wastewater treatment with SiO_2-NPs/graphene oxide (GO) exhibited an efficient and antifouling oil—water separation with a rejection rate >99.4%, a high flux rate of 2387 L/m^2h for pure water, and 470 L/m^2h for oil—water separation. This was attributed to (1) the hydrophilicity and superoleophobicity interface of SiO_2-NPs and (2) the hydrophilic GO embedded with SiO_2-NPs that permitted rapid water permeation during the separation process [159].

Hong et al. [160] synthesized mesoporous silica nanospheres (MSNs) with FeCo/graphitic carbon shell nanocrystals (FeCo/GC NCs@MSNs) generating a highly stable (in 35% HCl and pH 11 solutions) multifunctional adsorbent and magnetically recyclable for dye waste water purification. Graphitic carbon provided noncovalent, hydrophobic interactions with the hydrocarbon chains of organic dyes (methyl orange and methylene blue dyes). The FeCo/GC NCs@MSNs adsorbent was functionalized with thiol groups (FeCo/GC NCs@MSNs-SH) to target metallic ions (Hg^{2+}) removal. These magnetic compounds showed excellent ability to remove the organic dyes and Hg^{2+}. However, FeCo/GC NCs@MSNs-SH exhibited slightly higher adsorption than FeCo/GC NCs@MSNs. This was attributed to the hydrophobic interaction between hydrocarbon chains of the mercaptopropyl group (giving thiol functionalization) and the dye molecules.

Shivaraju and coworkers [158] produced clay-based ceramic filters with 25% and 30% activated carbon and active components for drinking water treatment. These authors achieved the desired drinking water quality parameters by removing nitrite (98.5%), nitrate (80.5%), total dissolved solids (62%), total hardness (55%), total organic pollutants (89%), and pathogenic

microorganisms (100%) using such ceramic filters within a short duration. The high disinfection and purification efficiencies were ascribed to the high porosity, high surface area, high stability, and active NPs (TiO_2, Ag, and Cu) present inside the porous matrix of the ceramic filter. These authors found the low-cost clay-based ceramic filter to be easy to reuse and efficient for home drinking water treatment.

Wang et al. [165] produced versatile nonfluorinated TiO_2—SiO_2@PDMS (polydimethylsiloxane) hybrid films through a sol—gel process, possessing superhydrophobic and photocatalytic properties, for wastewater treatment. TiO_2—SiO_2@PDMS superhydrophobic films showed excellent ability for oil—water separation and methylene blue wastewater treatment under UV light (colorless water in 30 min). The anatase phase of semiconducting TiO_2, with high surface area, produced electron—hole pairs under UV irradiation to oxidize the methylene blue molecule. These superhydrophobic films can be used under high-temperature conditions [165]. ZnO is also a semiconductor oxide with photocatalytic properties exhibiting selective H_2S chemisorption with applications in photocatalysis and high-temperature gas, as reported by Naszályi et al. [166]. Naszályi and coworkers developed a multifunctional ceramic membrane through the sol—gel-derived mesoporous SiO_2 and ZnO coating active oxides (SiO_2/ZnO). These authors observed the UV-photocatalytic degradation of stearic acid (~85% in 30 min) and methylene blue (~90% in 3 h) reporting lower SiO_2/ZnO photoactivity compared to highly photoactive TiO_2 layers. Additionally, SiO_2/ZnO exhibited H_2S chemisorption properties due to ZnO activity. Thus, SiO_2/ZnO has potential use for purification operations coupling separation and photocatalysis or gas filtration and H_2S chemisorption at high temperature.

Novel amino-functionalized mesoporous microspheres (Fe_3O_4@-SiO_2@m-SiO_2—NH_2) were synthesized to remove Cd^{2+} ions from water [167]. These multifunctional microspheres showed high surface area (637.4 m^2/g), improving the adsorption capacity of the adsorbent (~885 mg/g) for the removal of Cd^{2+} ions (within 92%—96% for six cycles) at pH 6. This pH favored the adsorption capacity of Cd^{2+} ions because the lone pairs of free nitrogen atoms in the amino group enhanced the adsorption of the microspheres. However, in acidic pH solutions, the amino groups of the adsorbent were protonated, reducing its binding capacity to Cd^{2+} ions. The pseudo-second-order kinetic model and the Langmuir isotherm were used to model the experimental data. The Fe_3O_4@SiO_2@m-SiO_2—NH_2 microspheres were recycled in

HCl (1 mol/L) maintaining their original metal removal capacity, which confirmed their chemical stability and reuse, as well as their easy separation from the solution through an external magnetic field. Another study also employed amino groups to synthesize amino-functional mesoporous silica SBA-15 for efficient adsorption of heavy metals [Cu(II), Ni(II), Pb(II), Cd(II), and Zn(II)] in wastewater [168]. Two independent methods, grafting and cocondensation, were used to prepare the functionalized materials and three organic moieties were used to include the active amino sites: 2-aminoethylamino-propyl ($H_2N-(CH_2)_2-NH-(CH_2)_3-$), aminopropyl ($H_2N-(CH_2)_3-$), and [(2-aminoethylamino)-ethylamino]-propyl ($H_2N-(CH_2)_2-NH-(CH_2)_2-NH-(CH_2)_3-$). The Cu(II) adsorption rates showed that the adsorption process was fast and was modeled by the pseudo-second-order kinetic equation. Negligible metal adsorption capacity was observed in materials prepared by cocondensation because amino active sites were not accessible to metallic species. However, amine-grafted materials exhibited a high amino groups content that adsorbed high amounts of aqueous Cu(II), Cd(II), Pb(II), Ni(II), and Zn(II). All adsorbents exhibited a very good aqueous copper removal efficiency in both diluted and concentrated solutions. It was observed that having two amino positions in the same organic chain improved the adsorption capacity of copper.

Wu et al. [169] fabricated a water purifier composed of a magnetic silica (MS) core and a quaternary ammonium polymer (QAC) corona. The multifunctional water purifier (QAC-MS) was used for water disinfection (*E. coli*) and removal of harmful contaminants (copper ions and acid fuchsin anionic dye). *E. coli* was totally eliminated in contact with 3.5 g/L of QAC-MS but no disinfection was observed by the contact of *E. coli* with 3.5 g/L of any of the individual components of the water purifier. Therefore, QAC was responsible for the disintegration of *E. coli*. The disinfection mechanism of QAC-MS is based on the electrostatic attraction [170] of negatively charged bacteria upon adsorption on the surface of QAC-MS. Followed by penetration of the hydrophobic alkyl chain of the bacterial membrane with subsequent death of *E. coli* [171]. Regarding metal ion and anionic dye removal, QAC-MS exhibited excellent adsorption efficiencies of 100% removal of both dye and Cu^{2+} ions. According to these authors, this was attributed to (1) the protonation, under slightly acidic condition, of the amine groups present in QAC-MS forming positively charged $-NH_3^+$, which resulted from hydrophilic negatively charged $-SO_3^-$ groups in the anionic dye, and (2) the coordination complex formation between QAC-MS and Cu^{2+} ions.

6.3 Concluding remarks on multifunctional silica nanomaterials for water and wastewater purification

Silica, an inorganic porous material with silanol functional groups and a large surface area, has been used as an adsorbent material to eliminate aqueous pollutants. Several studies have modified or functionalized its surface with different nanomaterials to enhance its adsorption capacity to remove simultaneously a diverse number of aqueous pollutants. The improved capacity of the modified materials is due to an enhancement in their surface properties, increased porosity and surface area, as well as additional functional groups in their surface. Therefore, the modified silica adsorbents or multifunctional silica nanomaterials have shown additional functions such as oil/water separation, photocatalysis, and antibacterial features for water treatment and purification, as shown in the studies reported in this section. Very few works have been scaled to pilot plants for water purification.

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CHAPTER 8

Efficacy of biomass-derived nanocomposites as promising materials as corrosion inhibitors

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1. Introduction

The word corrode is derived from the Latin corrodore, which simply means to gnaw to pieces. However, the phenomenon of corrosion is gnawing at the efficiency of industrial sectors both "economically and environmentally." Corrosion is defined as the spontaneous destruction or wear of metals and alloys due to chemical or electrochemical reactions when in contact with an environment containing corrosive substances [1]. The most common form of corrosion is water-borne metal corrosion, in which a metal or alloy corrodes in an aqueous environment.

Corrosion is an undesirable phenomenon that badly affects the properties and beauty of materials and decreases their life. The Indian government spends around 3.5% of the nation's GDP to overcome corrosion losses [2]. Recent studies estimate that India and other countries are increasing their expenditure on corrosion inhibitors. Corrosion affects the surfaces of various infrastructures such as highways, bridges, buildings, chemical processing units, wastewater treatment facilities, and virtually all metallic objects used in our day-to-day life. There are multiple types of corrosion in aqueous environments [3]. The most important types of decay, such as uniform corrosion, galvanic corrosion, stress corrosion, pitting corrosion, crevice corrosion, intergranular corrosion, erosion-corrosion, and filiform corrosion illustrated in Fig. 8.1 [4]. The reactivity of metal, presence of impurities, air, moisture, gases like sulfur dioxide and carbon dioxide, presence of electrolytes, metal grain structure, composition during alloying, or the temperature during fabrication have a significant effect on the phenomenon of corrosion [5]. In 1824, Sir Humphrey Davy presented a

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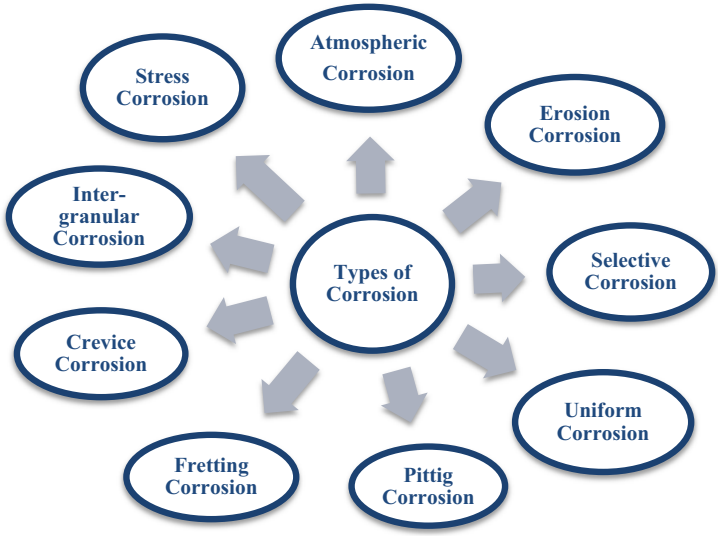

Figure 8.1 Schematic representation of types of corrosion.

series of papers to the Royal Society in London in which he described how zinc and iron anodes could prevent copper sheathing corrosion on the wooden hulls of British naval vessels [6]. The types and methods used to prevent corrosion are described herein.

Corrosion problems arise in pipelines due to the aggressiveness of the liquid carried by them. In various operations, these liquids may be in the form of petroleum-containing sulfur and water and high saline formations, with the utilization of these pipelines for heating and cooling purposes. However, some kinds of water that pass through these lines can contain very high chloride concentrations and a considerable amount of sulfates and other ions of different metals. For this, the inoculation of corrosion inhibitors through different locations of the pipes is very important. The list of destruction created by this phenomenon is part of human daily life, including wastage of valuable resources, plant shutdowns, and loss of contamination of products, costly maintenance, reduced efficiency, and expensive overdesigns. Mineral acids, especially hydrochloric acid, are commonly employed in industrial procedures such as acid cleaning, acid pickling, acid descaling, and oil well acidizing [7]. Because these acids are powerful corrosive substances, the study of corrosion prevention is always a topic of great theoretical and practical interest [8].

Corrosion can be prevented up to an extent by using corrosion-preventive methods. There are many ways to protect metals from corrosion. Over the past several decades, many corrosion testing methods and prevention techniques have been developed and applied in various laboratory and industrial fields. There are five primary ways to combat corrosion, including by selecting suitable materials and structural design [9], cathodic and anodic protection, i.e., impressed current and sacrificial anode are two essential methods for applying cathodic prevention [10], and by using protective coatings such as a sacrificial layer, organic/polymer coatings, ceramic coatings, corrosion/rust protective oils, gas-phase deposition processes, etc. [11]. Corrosion inhibition is the most practical, economical, and convenient technique to control corrosion on metal surfaces in different media by preventing metal dissolution and acid consumption [2]. These inhibitors work on the mechanism of molecular adsorption, i.e., the compound inhibits corrosion by controlling both anodic and cathodic reactions. The protonated species adsorb on the cathodic sites of the surface and decrease the evolution of hydrogen gas. Hence the rate of corrosion also decreases [12]. Inhibitors can be applied as a solution or as a protective coating using different techniques.

Corrosion inhibitors are very widely used to reduce corrosion processes in the environment and are substances that, when added in small amounts to aggressive environments, reduce the rate of corrosion. The adsorption of an inhibitor on a metal surface depends on the following factors:

- Nature of the metal;
- Surface charge of the metal;
- Adsorption mode and its chemical structure;
- Electrolyte solution.

For an inhibitive treatment to be an effective, certain important criteria must be met, as shown in Fig. 8.2. Most organic molecules tend to adsorb to metal surfaces, but in general, the most desirable properties when seeking corrosion inhibition relate to: the interaction of a double/triple bond or lone pair of electrons (N, S, P, or O) with an empty metal d orbital or a combination of some of the previous mechanisms [14–20]. It is frequently observed that the presence of electron-donating groups such as $-OH$, $-NH_2$, $-CH_3$, $-OCH_3$, etc. improves the inhibition performance of organic molecules, whereas the presence of electron-withdrawing substituents such as $-NO_2$, $-CN$, COOH, and $-COOC_2H_5$ decreases the inhibition efficiency of organic molecules. Electron-donating substituents such as $-OH$, $-NH_2$, $-CH_3$, $-OCH_3$, and others boost electron density

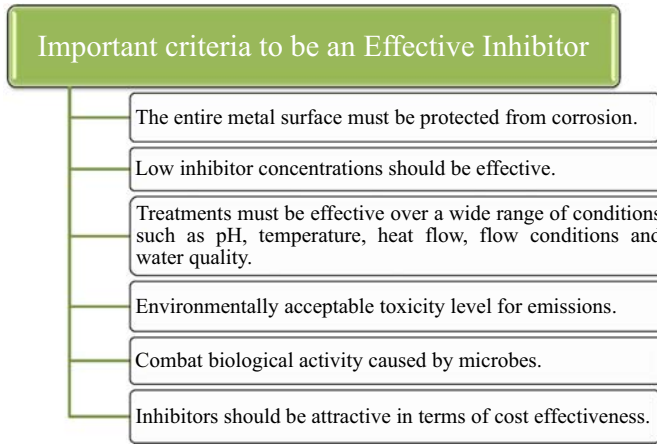

Figure 8.2 Important criteria for effective inhibitors [13].

at the inhibitor's adsorption site, increasing interactions between the inhibitor molecule and the metallic surface. Electron-withdrawing substituents, on the other hand, such as $-NO_2$, $-CN$, COOH, $-COOC_2H_5$, and so on, reduce the electron density at the inhibitor's adsorption site and hence the adsorption propensity on metallic surfaces [21].

Corrosion inhibitors are categorized according to how they suppress corrosion: cathodic, anodic, or mixed. Cathodic corrosion inhibitors reduce the corrosion potential to lower levels by preventing cathodic processes such as oxygen reduction and hydrogen evolution. Anodic corrosion inhibitors increase the corrosion potential and interact with reactive spots on the metal surface, passivating them. Mixed-type inhibitors are those that are neither cathodic nor anodic. These inhibitors can protect the metal surface by physisorption, chemisorption, or film formation. The electrostatic interaction between inhibitor molecules and the metal surface drives physisorption. Chemisorption, on the other hand, results via donor–acceptor interactions between unoccupied orbitals on the metal surface and free electron pairs in the inhibitor.

Different authors classify inhibitors in different ways. Some authors prefer top group inhibitors according to their chemical function, as shown in Fig. 8.3.

However, most of the compounds that make up inhibitors are expensive and toxic to both humans and the environment. They can cause temporary (reversible) or permanent (irreversible) destruction of organ systems. The risks associated with this can be seen in the synthesis or

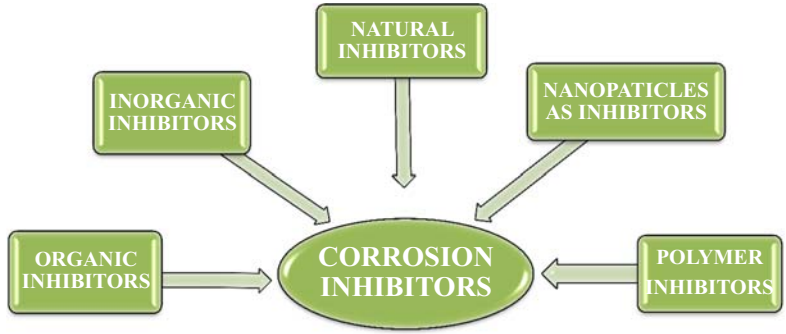

Figure 8.3 Classification of corrosion inhibitors.

application of these compounds. Safety and environmental issues related to corrosion inhibitors have always been a global issue. Therefore, it is important to find a way to prevent corrosion using environment-friendly inhibitors that are inexpensive and readily available.

Natural products are readily available and are safe for the environment because they are biodegradable in nature. Nontoxicity is a crucial criterion to consider when selecting an appropriate corrosion inhibitor, which many current organic/inorganic corrosion inhibitors do not meet [22]. The hunt for nontoxic efficient corrosion inhibitors is expanding due to increased awareness of the usage of ecologically benign chemicals in businesses and more stringent environmental protection requirements. Plant-derived products are generally the preferred choice for corrosion protection because they are environment-friendly, readily available, and inherently renewable [23]. In addition, these inhibitors are naturally biodegradable substances as corrosion inhibitors. Natural inhibitors are a rich source of ingredients with very high inhibitory efficiencies and when forming a protective layer, they can inhibit the action of reactive particles such as carbon dioxide, oxygen, chlorine, moisture, etc. [24].

For a reduction of the corrosion process, weight loss studies, electrochemical studies, characterization, and surface studies, etc. are the most popular techniques, by which the analysis of corrosion rate, inhibition efficiency, and other such parameters can be determined, as shown in Fig. 8.4.

2. Biomass as a corrosion inhibitor

Biomass in its different forms is also needed for animal and human nutrition, which means that other uses must be balanced. Preferably, the remaining biomass from nutrient biowaste provided as co-products for

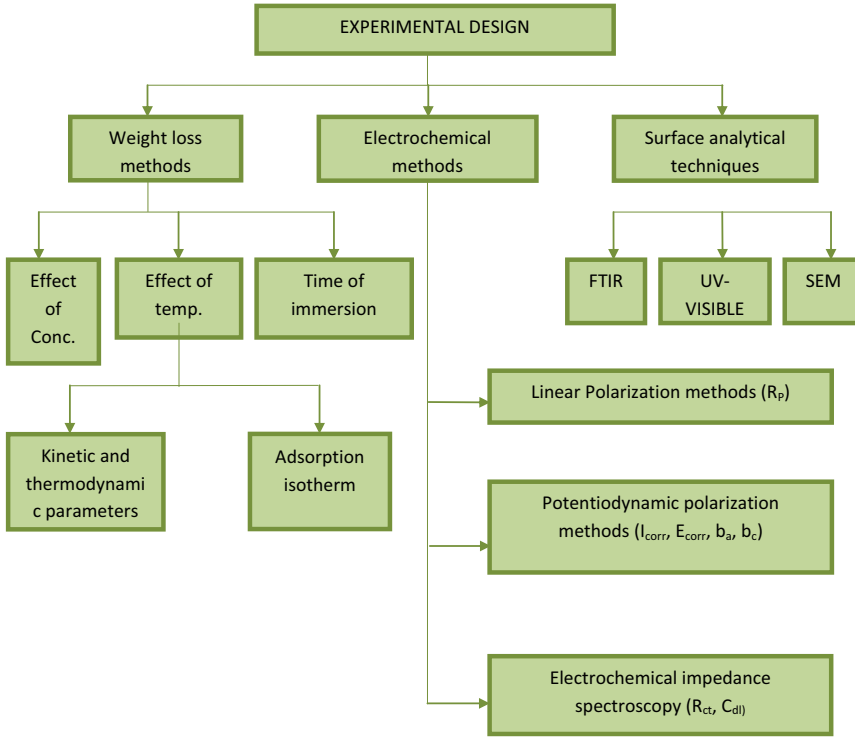

Figure 8.4 Various experimental designs.

many applications could be used in green chemistry. One of the areas of green chemistry, where an eco-friendly chemical frequently applied to biomass-derived products, offers innovations in terms of reducing environmental damage and waste, is related to metal surface protection.

With the advent of green chemistry, the concept of green corrosion prevention has been gaining increased attention. Plants are an excellent, inexpensive, and renewable source of natural products in the form of extracts or pure organic compounds (plant molecules). The key ingredient which enables plants and plant wastes to act as corrosion inhibitors are the groups of phytochemicals which block the active site on the metal surface by providing a protective film on it, causing an inhibitory effect due to the adsorption of inhibitory molecules over the surface. Plant extracts are composed of a very complex mixture of plant molecules belonging to various chemical classes such as flavonoids [25], terpenoids [26], alkaloids [27], anthocyanins [28], tannins [29], carotenoids [30], and saponins [31]. These plant molecules are rich in π electrons (benzene ring, double/triple

bond) and contain electrically negative functional groups in their chemical structure and heteroatoms such as oxygen, sulfur, and nitrogen [32] (Fig. 8.5).

The food business generates a high amount of by-products and waste, which poses disposal and pollution issues. The use of these agro-industrial by-products in bioprocesses provides a diverse variety of alternative substrates, assisting in the resolution of environmental pollution issues associated with their disposal. However, recycling and reprocessing of food-manufacturing by-products may provide a net benefit. Solving the food-processing companies' waste disposal problem through the valorization of by-products provides an opportunity for extra revenue generation. Tomato processing waste, which includes the cull, damaged fruits, and pomace, among other things, might be used to recover a range of chemicals such as colors, oil, protein, polysaccharides, animal feed, and so on. Not only this, but also large amounts of plant residue such as the stem are discarded carelessly after harvesting the fruits, missing the fact that they can be applied in generating useful biomass for other specific uses such as preventing corrosion, rather than creating another issue of dumping them as waste.

Renata F. B. Corderio et al. studied the corrosion inhibition of mild steel in hydrochloric acid media using coffee husk aqueous extract. The techniques employed for this study were gravimetric measurements, potentiodynamic polarization, and electrochemical impedance spectroscopy

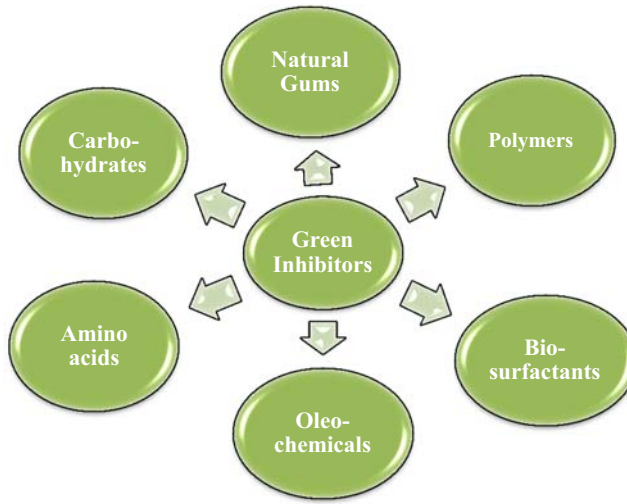

Figure 8.5 Various types of green inhibitors.

(EIS). The obtained result revealed that coffee husk aqueous extract was a good corrosion inhibitor for mild steel in hydrochloric acidic media and the maximum inhibition efficiency was found to be 89.2% at 800 mg/L with a 24-h immersion time [33]. Nouha M. Hiri et al. studied the corrosion inhibition effect of orange peel on carbon steel in 0.1 M hydrochloric acid solution, and for this purpose the experimental techniques of potentiodynamic polarization, EIS, Tafel, and SEM were adopted. The results obtained indicated that the orange peel as a biomass waste exhibited a higher efficiency of 78% [34]. K.K. Alaneme et al. extracted elephant grass extract and carried out an experimental analysis for corrosion inhibition using 1 M HCl as a medium on a test specimen with and without an inhibitor. They opted for weight-loss techniques, SEM, AAS, and FT-IR and the obtained results revealed that the test specimen with a greater amount of extract had a lower corrosion rate and showed a higher inhibition efficiency of 95% in 1 M HCl [35]. The study of Mish Gush on mild steel as a corrosion inhibitor was done by M.H. Sahini et al. They investigated the inhibition efficiency and the mechanism of corrosion also in 1 M HCl. Using potentiodynamic polarization, EIS, Tafel, DFT, SEM, AFM, and FT-IR, results were obtained and revealed that Mish Gush leaves extract acted as a mixed corrosion inhibitor and showed a 97% inhibition efficiency at 1200 ppm after 24-h immersion [36]. *Capsicum frutescens* biomass extract as a corrosion inhibitor on low carbon steel was studied by Emeka E. Oguzie et al. They carried out gravimetric and electrochemical analyses to measure the inhibition performance in 1 M HCl and 0.5 M H_2SO_4. The inhibition efficiency was found to be 85.6% at 1000 mg/L in 1 M HCl and 93.1% at 1000 mg/L in 0.5 M H_2SO_4 [37]. Imo E.O. et al. performed an experimental analysis for corrosion inhibition using *Aframomum melegueta* biomass extract on a test specimen with and without an inhibitor [38]. Victoria Vorobyova et al. studied the corrosion inhibition of steel in sodium chloride media using tomato pomace extract. The techniques employed for this study were gravimetric measurements, potentiodynamic polarization, and electrochemical impedance spectroscopy (EIS). The obtained results revealed that tomato pomace extract was a good corrosion inhibitor for steel in sodium chloride media and the maximum inhibition efficiency was found to be 98% at 500 ppm after 48-h immersion time [39]. *Allium sativum* L. acted as a corrosion inhibitor on mild steel in a study by Harish Kumar et al. They carried out gravimetric, electrochemical, and DFT analyses to check the inhibition performance in 5 M HCl. The inhibition efficiency was found to be 94.76% following the

physio-chemisorption mechanism [40]. Rajesh Haldhar et al. studied the corrosion inhibition effects of the aerial parts of *Solanum surattense* which showed 93% efficiency at an inhibitor concentration of 500 mg/L [41]. Harish Kumar et al. studied the corrosion inhibition of mild steel in 0. 5M HCl by *Morus nigra* (mulberry) leaves. The techniques employed for this study were FTIR, UV-visible, NMR, weight loss, EIS, potentiodynamic polarization (PDP), and DFT. The obtained results revealed that *Morus nigra* was a good corrosion inhibitor for steel in HCl and the maximum inhibition efficiency was found to be 91.67% following both physical and chemical modes of adsorption [42].

3. Nanocomposites as corrosion inhibitors

In the modern age, nanotechnology is increasing in use at a very high rate with its applications in research. It is a technology that works on the nanometer scale. It deals with atoms, molecules, or macromolecules having a size of approximately 1−100 nm to create and use materials that have novel properties [43]. Nanoparticles have various approaches in different areas such as in the industrial sector as inert additives or fillers [44], biomedical uses in drug delivery and blood purification [45], food industries for food nano-structured ingredients as food additives, carriers for intelligent delivery of nutrients, anticaking agents, antimicrobial agents, fillers for improving mechanical strength and durability of packaging materials, food nano sensing [46], and also agricultural and environmental areas for the removal of hazardous pollutants from wastewater [47], etc.

Nanotechnology has come into being as a technological advancement to enhance and transform the agri-food sector and increase global food production with high potential. Additionally, it is used to evaluate food's nutritional value, quality, and safety [48]. Nanotechnology is gaining attention in almost all areas, i.e., chemistry, physics, engineering, and technology, but most people are unaware of its existence in daily life. Still, its extensive usage is found in medicine, engineering, environment, electronics, defense, security, etc. Although much work has been carried out using this technology, there remains some space for developing novel nanomaterials with high efficiency in various fields for the progress of humankind. Thin-film coatings through mixing or blending with organic materials, such as polyurethane [49], polyamide [50], polyester [51], PVC [52], acrylics [53], alkyds [54], and epoxies [55], play a crucial role as a protective layer by delaying the transition of corrosive species in different

environments such as chlorine and hydroxyl ions, water, oxygen, pollutants, and pigments, which have an affinity to react with the material surface [56]. Nanomaterials and their additives have been proven to be good corrosion inhibitors due to their higher surface-to-volume ratio compared with conventional macroscopic materials [57]. These compounds stop the reaction on the surface to the environment, control the corrosion rate by blocking active sites of the metal surface, and provide properties such as hardness, straightness, durability, optical qualities, thermal stability, etc. These types of compounds are eco-friendly and degradable in the environment.

Nanocomposites are a form of heterogeneous multiphase solid materials, in which one phase has a nanoscale structure such as nanotubes, nanorods, nanoflowers, and nanospheres, and these type of materials are produced by incorporating one matrix into another by various methods such as in situ polymerization, precipitation, solution mixing, and the sol–gel process [50]. When these two different types of materials are mixed in different compositions, a new type of material is created with unique important properties that are advanced compared with the bulk materials. Some of the unique characteristics of nanocomposites are summarized in Fig. 8.6.

Nanomaterials have a great advantage in showing higher corrosion-inhibitory properties because their surface-to-volume ratio is increased. These materials stop the reaction on the surface and mitigate the rate of corrosion by blocking active sites of the metal surface, and provide hardness, strength, durability, optical qualities, and thermal stability, etc. [58].

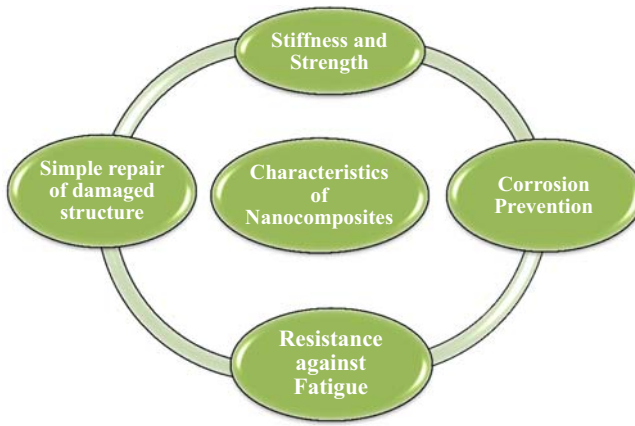

Figure 8.6 Characteristics of nanocomposites.

Ag nanoparticles with PVP and PEGSH as a thin film on carbon steel alloy acted as good corrosion inhibitors in 1 M HCl, as studied by A.M. Atta et al., who investigated this by UV-vis, Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM)/EDAX, TEM, potentiodynamic polarization (PDP), electrochemical impedance spectroscopy (EIS), and DLS measurement. The results obtained from electrochemical measurement indicate that the Ag nanoparticles with PVP exhibit 90.95% inhibition efficiency [59]. Gamal A. El-Mahdy et al. studied the corrosion inhibition of steel in 1 M HCl by magnetite (PAMPS-Na-co-St/Fe_3O_4) nanocomposite. The techniques employed for this study were FTIR, TEM, thermogravimetric analysis (TGA), EIS, and PDP. The obtained results revealed that this nanocomposite was a good corrosion inhibitor for steel in HCl and the maximum inhibition efficiency was found to be 99.7% [60]. A study of polystyrene organo clay nanocomposite on carbon steel as a corrosion inhibitor by L. A. Al Juhaiman et al. investigated the inhibition efficiency and the mechanism of corrosion also in 1 M HCl. Using EIS, Tafel polarization, water permeation process, FTIR, XRD, and TEM results were obtained and the results revealed that polystyrene organo clay nanocomposites showed a 99.94% inhibition efficiency in 3.5% NaCl [61]. An investigation was done on aluminum-titania nanocomposite as catalysts for electrochemical generation of H_2 by Mohammed A. Amin et al. They opted for techniques such as XRD, XPS, EIS, SEM, and EDX, and showed a maximum inhibition efficiency of 99.9% in 0.5 M H_2SO_4 [62]. M.M. Solomon et al. studied the corrosion inhibition of mild steel in hydrochloric acid media by carboxymethyl cellulose/Ag nanocomposites on St 37 steel. The techniques employed for this study were UV-vis, FTIR, TEM, SEM, EDS, weight loss measurements, EIS, PDP, dynamic EIS, and AFM. The obtained results revealed that carboxymethyl cellulose/Ag nanocomposites were a good corrosion inhibitor for mild steel in hydrochloric acidic media and the maximum inhibition efficiency was found to be 96.37% [63]. S. John et al. deliberated on the corrosion inhibition effect of chitosan–polyvinyl alcohol nanocomposite films on mild steel with a 0.1 M hydrochloric acid solution and for this purpose FTIR, XRD, SEM, DSC, TGA, PDP, LPR, and EIS were adopted. The results obtained indicated that the chitosan–polyvinyl alcohol nanocomposite films exhibit a higher maximum inhibition efficiency of 98.47% [64]. N. Palaniappam investigated GO-Pr nanocomposite decoration as a corrosion inhibitor on Mg AZ31 alloy and used techniques such as UV-vis, FTIR, FE-SEM, HR-TEM, Raman spectroscopy, XRD, DLS measurements, and EIS, which

showed a higher inhibition efficiency of 72.3% [65]. M. Srivastava et al. studied the corrosion inhibition of steel in 1 M HCl by chitosan−cobalt and chitosan−SnS_2 nanocomposites. The techniques employed for this study were FTIR, TEM, TGA, EIS, and PDP. The obtained results revealed that this nanocomposite was a good corrosion inhibitor for steel in HCl and the maximum inhibition efficiency was found to be 95% with chitosan−cobalt and 80% with chitosan−SnS_2 nanocomposites [66]. K. Haruna et al. investigated the cyclodextrin−GO nanocomposite decoration as a corrosion inhibitor on carbon steel and used techniques such as UV-vis, FTIR, FE-SEM, HR-TEM, Raman spectroscopy, XRD, EFM, and EIS, which showed a higher inhibition efficiency of 81.17% [67]. K. Haruna et al. studied the corrosion inhibition of mild steel in hydrochloric acid media by dopamine−GO nanocomposites on C-steel. The techniques employed for this study were UV-vis, FTIR, Raman spectroscopy TEM, SEM, EDS, weight loss measurements, EIS, PDP, LPR, and AFM. The obtained results revealed that a dopamine−GO nanocomposite was a good corrosion inhibitor for C-steel in hydrochloric acidic media and the maximum inhibition efficiency was found to be 91.05% [68].

4. Biomass-derived nanocomposites as corrosion inhibitors

Nanostructured materials have been establishing themselves as the modern generation of high-performance materials, being used in areas from automotive engineering to bioengineering, owing to a vast array of unique properties due to their ideal grain size, larger surface-to-volume ratio, and high grain boundary volume fraction [69]. They are used from self-cleaning glass to high-performance components for aerospace applications. Nanocoatings of biomass waste provide materials with improved strength, durability, optical qualities, and thermal stability. Nanomaterials as a corrosion inhibitor are the most effective and economical method to protect metal from corrosion and increase its durability [70]. Synthetic organic and natural inhibitors effectively reduce steel dissolution, but their usage is limited due to environmental risks and lack of availability [71]. Thin-film coatings of nanomaterials through mixing or blending with biomass waste materials, such as soya oil, orange peel, coffee husk, onion mesocarp extract, etc. form a protective layer by delaying the transition of corrosive species in different environments such as chlorine and hydroxyl

ions, water, oxygen, pollutants, and pigments, which have an affinity to react with the material surface [56].

Ekemini Itueri et al. investigated onion mesocarp extract—Ni nanocomposites as a corrosion inhibitor on X60 steel. Using EDAX, FT-IR, UV-vis, DLS, XRD, SEM, TEM, weight loss measurements, EIS, and the H_2 evolution technique, results were obtained and these results revealed that onion mesocarp extract—Ni nanocomposites were a good corrosion inhibitor for X60 steel in 1 M HCl and achieved a higher inhibition efficiency of 88.1% [72]. S. John et al. studied the inhibitive action of chitosan—TiO_2 nanocomposites dip coating on mild steel in 0.1 M HCl and carried out the experiment using FTIR, XRD, EIS, TGA, and contact angle measurements techniques. The obtained results revealed that nanocomposites acted as a good corrosion inhibitor as these nanocomposites showed an inhibition efficiency of 84.69% in 0.1 M HCl [73]. K. L. Palanisamy et al. studied the corrosion inhibition of mild steel with a carrier oil, i.e., olive oil, stabilizing iron-oxide nanoparticles incorporated into a paint. Using weight loss measurements and SEM, the results were obtained and revealed that the nanocomposites of iron oxide with olive oil showed a higher inhibition efficiency of 80.88%, and so proved to be a good corrosion inhibitor [74]. S. Bioumy et al. investigated the electrochemical corrosion behavior of a graphene oxide/chitosan/silver nanoparticle composite coating on stainless steel utensils in aqueous media, and to complete their investigation they used techniques such as SEM, EDAX, EIS, PDP, cyclic voltammetry, weathering test, and hardness and thickness measurements. The obtained results revealed that the nanocomposites formed a protective layer on the stainless steel and showed an inhibition efficiency of 99.4% [75]. E. A. Essien et al. synthesized an olive leaf extract—titanium nanoparticle composite using the chemical precipitation method and characterized the extract using UV-vis, FTIR, and also to check their anticorrosive property they used SEM/EDAX, XRD, weight loss measurements, and AFM. From the results of the weight loss measurements, it was shown that these nanocomposites had an inhibition efficiency of 94.3% in acidic medium at 10×10^{-2} g/L [69]. Ekemini Ituen et al. synthesized walnut husk extract and formed nanocomposites with silver nanocomposites for the removal of heavy metals from petroleum wastewater, and studied the anticorrosion property on steel used in pipework. This was investigated using electrochemical, weight loss, FT-IR, and SEM/EDS analyses. The obtained results revealed that this nanocomposite follows the physical adsorption mechanism and showed a higher inhibition rate at 88.6% for 5 h of inversion [76]. Xiang Gao et al. studied a novel high-performance and long-life anticorrosion coating with tannic acid

(TA)-grafted biomass carbon nanosheets. Their characteristics were based on waste biomass-derived carbon nanosheets. The obtained results revealed that the anticorrosion and service life of the smart coating were evidently improved and the coating exhibited a self-repairing property [77]. The superparamagnetic inhibitor Fe_3O_4@MoO_4-LDH was synthesized by ion exchange and investigated as a good long-term corrosion inhibitor as it shows 71.96% inhibition efficiency at 24 h on Q235 steel [78]. Mohammad Mobin et al. investigated an almond gum—silver nanocomposite as a novel, cheap, and green inhibitor, and to complete their investigation they used techniques such as FT-IR, UV-vis, XRD, DLS, SEM, TEM, EDAX, EIS, PDP, TGA, gravimetric analyses. The obtained results revealed that the nanocomposites acted as a good corrosion inhibitor as they showed an inhibition efficiency of 96.5% at 60°C at 150 ppm for a mild steel surface in 1 M HCl following the Langmuir Adsorption Isotherm model [79]. Bo Chen et al. investigated epoxidized biomass *Eucommia* gum as a nanofiller in an epoxy composite coating with excellent anticorrosive performance [80].

5. Conclusion

A great deal of research is on-going in the fields of biomedicine, electronic storage devices, and sensors for nanocomposites, however there remains scope for the development of research in the field of corrosion. Because of their environment-friendly behavior and high inhibition efficiency, biomass-derived nanocomposites are the preferred choice in the field of corrosion protection systems. Most organic solvents are expensive, and their use for inhibitory action cannot be done in a cost-effective way. Many investigations have shown that the modification of biomass waste can be used to enhance the corrosion inhibition efficiency and diminish the corrosion rate. Adsorption on metallic substrate obeyed the Langmuir adsorption isotherm, and Temkin and Freundlich's adsorption was also addressed. Natural and biopolymers emerge as highly effective inhibitors for corrosion in the future due to their easy availability, low-cost, environment-friendly, and nontoxic nature.

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CHAPTER 9

Adverse effects of nanoparticles on human health and the environment

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Nanoscience has transformed the world through the introduction of chemical substances/materials with particles (known as nanoparticles) between 1 and 100 nm in size in at least one dimension [1]. On the basis of their overall shape, these particles can be 0D, 1D, 2D, or 3D [2], which makes their properties dissimilar to those of the bulk products of similar chemical compounds [3,4]. By examining the functions and interactions of cellular biomolecules, these nanoparticles (NPs) have different shapes and compositions that characterise their distinctive properties and interactions with human cells. As a result, target-based therapies are currently being replaced by this first line of therapy [5]. Nanotechnology is utilized in our daily lives with the manipulation of nanometer-scale materials into a wide variety of areas [6], and these innovations have relevance in a number of domestic and industrial sectors which include the design, characterization, production, and application of materials and devices in different fields of agriculture, foodstuffs, healthcare including diagnosis, treatment, and drug delivery, cosmetics and sunscreens, paints, bio-labeling, electronics, sensors, fiber optics, imaging, and many more [7–12]. Despite their unique advantages and applications in the domestic and industrial sectors, the use of resources with dimensions in nanometers has raised concerns about their safety for users, customers, and the environment.

There are several types of NPs that are capable of posing health hazards to humans and, while determining the toxicity of NPs, the size of the NPs is most important, followed by the surface area, agglomeration state, structure of crystals, surface charge, and porosity. Environmental NPs are also ultrafine particles and major air pollution occurs due to combustion process derivatives (i.e., burning of coal, petroleum, and wood), generation of aerosols from different atmospheric processes, automobile exhausts, and the pollution caused by volcanoes [13]. Hence, environmental NPs have diverse chemical compositions and types of toxicity. On the contrary,

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industrial NPs have homogeneous shape and a defined chemical composition; these can be engineered or released incidentally into the environment. Engineered NPs are commercially produced materials with at least one particle dimension less than 100 nm [14] Nano-sized materials have sparked a major revolution in the fields of science, engineering, and industry (pharmaceutical, food, etc.) and in the field of medicine nanoparticles are being used as a new delivery method for drugs, proteins, DNA, and monoclonal antibodies [15–17]. They are usually composed of heavy metals and their oxides (e.g., nickel, zinc, cadmium, manganese, silicon, titanium, gold, antimony), carbon, and many others [18]. Metal NPs enter the human body mostly through the respiratory, circulatory, dermal (skin adsorption/penetration), gastrointestinal, immunological, and neurological tracts [19]. Once absorbed, NPs can exert their toxic effects instantly or following translocation to the target organ.

The key factors that evaluate the toxicological effects of NPs in the human body depend on the properties, which may include the uniqueness of the exposure (penetration, duration of exposure, and concentration) and of the exposed organisms (individual vulnerability, specific route the NPs follows inside the body, the activity at the time of exposure), as well as their inherent toxicity such as catalytic activity, chemical composition, structure, capability to bind or coat surface species, and the surface area of NPs [20]. The behavior of NPs in diverse environments and their interactions with biological organisms are of major importance.

1. Types of NPs (Fig. 9.1)

1. Organic

   Carbon-based nanomaterials: These nanomaterials are the most attractive and widely used for an application point of view [21]. The commonly used nanomaterials are:

   (a) Fullerene–carbon derivatives

   (b) Carbon nanotubes (single- or/and multilayered) are emerging as a significant novel class of multifunctional building blocks for the advancement of nanotechnology with their unique one-dimensional hollow nanostructure and extraordinary properties.

2. Inorganic

   Metal-based nanomaterials

   (a) **Metals** (mainly gold and silver): metal NPs have particular catalytic properties [22] and have extensive applications. Metal NPs can be

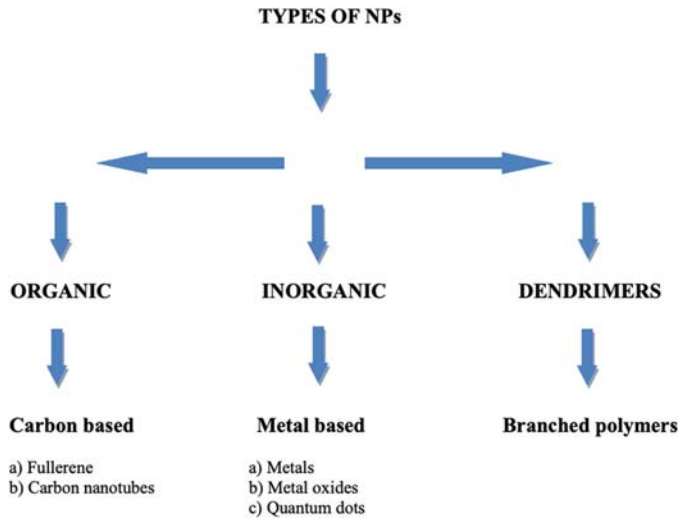

Figure 9.1 Types of nanoparticles.

found in the fields of biotechnology [23], food safety [24], biosensing [25], clinical diagnosis and therapy [26], and water and sewage treatment [27]

(b) Metal oxides (aluminum, copper, iron, zinc, titanium, etc.)

(c) Quantum dots.

3. **Dendrimers** (branched nanosized polymers with high potential for medical applications).

2. Potential routes of human exposure to NPs

NPs can enter the body through various routes, including inhalation, ingestion, injection, implantation, or penetration through the skin (Fig. 9.2).

Inhalation is the major route of human exposure to airborne NPs [28,29]. Materials which by themselves are not very injurious may perhaps be toxic if they are inhaled in the form of NPs. Once they move inside the body they may diffuse throughout the body through the blood circulation, reaching organs including the liver or heart, and they may also cross cell membranes. Another possible route of inhaled NPs within the body is the olfactory nerve; NPs may cross the mucous membrane present within the nose and reach the brain via the olfactory nerve. The different areas of the respiratory tract (nose, larynx, airways, lungs) function as a filter for

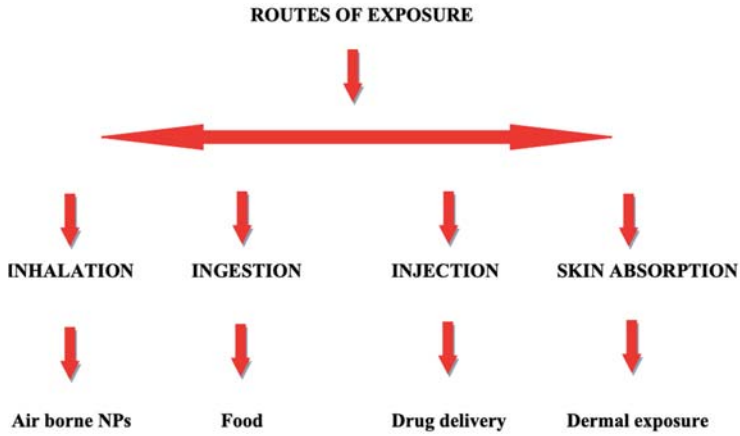

Figure 9.2 Potential routes of human exposure to NPs.

NPs. Their distribution in the body may depend on their size and surface characteristics, such as polarity, catalytic activity, lipophilicity, and hydrophilicity [30,31]. As the size of NPs decreases, the surface area per unit mass increases and, consequently, the NPs are anticipated to exhibit increased chemical and biological activities in the body [32,33]. As a consequence, it is hypothesized that smaller NPs might be more toxic than their larger counterparts. It is generally believed that the smaller NPs are taken up by cells faster than larger ones. Insoluble NPs are of greater health concern as they can be retained in the body for longer.

The effects of **inhaled NPs** in the body may include lung inflammation and heart problems. Studies in humans show that breathing in diesel soot causes a general inflammatory response and that is alters the system that regulates the involuntary functions of the cardiovascular system, such as control of the heart rate.

Ingestion is another important route of human exposure to NPs. This could be both directly through food or indirectly either by dissipation of NPs from food containers or by secondary ingestion of inhaled NPs [34].

Injection and implantation are used in the medical area, usually as carriers for drug delivery both by the oral and parental (subcutaneous, intramuscular, intraarterial, intravenous) routes, biosensors, imaging contrast, and via the skin [35].

Skin absorption is another significant route of human exposure to NPs [36,37]. NPs may enter dermally by penetration from accidental exposure or when they are present in cosmetics, skin care products, hair

care products, lip balms, or other topical applications. Even through the stratum corneum (the outer layer of the epidermis), which protects the skin against environmental exposures, nanosized (5–20 nm) titanium dioxide (TiO_2) particles have been reported to penetrate and also through hair follicles, and then to interact with the immune system [38,39].

3. Characterization of NPs

Two of the main parameters studied in the characterization of NPs are their size and shape.

The essential physical properties of NPs include:

- Size, shape, surface charge, specific surface area
- State of agglomeration and degree of aggregation
- Size distribution
- Surface morphology/topography
- Structure, including crystallinity and defect structure
- Density
- Optical and electronic properties.

The important chemical properties of nanomaterials include:

- Chemical composition
- Purity
- Surface chemistry
- Solubility.

4. Potential mechanisms of NP toxicity

There are several mechanisms of NP toxicity, some of which include the following:

(1) Direct association of NPs with the cell surface of an organism, where the membrane might be damaged or initiate the internal signaling pathways that damages the cell.

(2) Dissolution of the material resulting in releasing of toxic ions that influence the organism, usually through impairment of vital enzyme functions or through direct interaction with the DNA of the cell.

(3) NPs generate reactive oxygen species (ROS) causing consequent oxidative stress on an organism, which can also damage important enzymes or cause a change in the genomic material and hence may influence subsequent generations by hereditary factors [40].

5. Toxicity assessment of NPs

The functions of exposure route, dose, concentration, time, and/or frequency may cause NP toxicity, and these parameters are widely used in the evaluation of nano-toxicology. Conventionally, these elementary factors of NP toxicity are pertinent for the evaluation of small-molecule drugs and other compounds.

5.1 In vitro assessment

In vitro assessment of NP toxicity is an important factor. It can help in establishing possible differentiations in the toxic actions of NPs and traditional forms of substances. The advantages of in vitro assessment include lower cost, quicker, and fewer ethical concerns [41]. Assessment can be performed by different assays, such as:

(a) Proliferation assay: This assay is used to measure the cellular metabolism by assessment of metabolically active cells. For in vitro toxicity assessment of NPs the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) is the most frequently used tetrazolium salt [42]. The technique is beneficial due to fast yield, reproducible results, and least manipulation of the model cells [43].

(b) Necrosis assay: Necrosis assay fulfills the need for the consistent, speedy, economical, and reproducible quantitative in vitro assay assessment of NPs. The integrity of the membrane is assessed to determine the necrosis present in the cell and it is generally used to establish the viability of cells. The integrity of the membrane is most commonly measured by uptake of the dye for example, neutral red [44] and trypan blue [45].

(c) Apoptosis assay: Apoptosis is one of the major markers observed in the in vitro assessment of NP toxicity. The generation of excessive free radicals is considered the cause of apoptosis and DNA damage [46,47]. Evidence has suggested that apoptosis and DNA damage can be caused by oxidative stress in cell culture systems [46].

(d) Oxidative stress assay: One probable mechanism of toxicity of NPs is the induction of ROS and the consequential oxidative stress in cells and organs, but the rationale of various methods is hindered due to their high cost.

(e) Cell viability/lethality: Among the various NPs, carbon NPs are used most often for the assessment of cell viability and lethality.

5.2 In vivo assessment

The in vivo toxicity assessment of NPs is usually performed on animal models, such as rats and mice. The assessment methods for in vivo toxicity include the following:

Biodistribution: Scrutinize the localization route of NPs to the tissue or organ. The detection of NPs is made through radiolabels in killed or live animals [48].

Clearance: Clearance of NPs is performed by the assessment of excretion and metabolism of NPs at different time intervals after exposure [49].

Serum chemistry/hematology: This is another common method for in vivo toxicity assessment. The assessment of changes in the serum chemistry and cell type is carried out after exposure of NPs [50].

Histopathology: To establish the toxicity level caused due to NPs, histopathology of the cell/tissue/organ after exposure is performed [51]. Histopathology has been used for NP-exposed tissues such as lungs, heart, brain, liver, kidneys, eyes, and spleen [50,52,53].

Advanced techniques: The innovation of toxicity evaluation includes utilization of micro-electrochemistry and microfluidics [54].

6. Adverse effect of NPs on human health

The new fast-emerging field of nanotechnology has become a major risk to human life, as from childhood we are exposed to different nanomaterials [55]. As explained earlier, NPs due to their small size can travel and easily enter the human body through different routes and cross the cell membranes, and may reach the lungs and gastrointestinal tract as well as the liver, brain, heart, and spleen [56–59]. The physicochemical properties of NPs, as defined earlier, namely shape, size, specific surface area, chemical composition, surface charge/chemistry, solubility, purity, roughness, and many more have an impact on their uptake and accumulation in target organs [60–62]. Any extracellular material makes first contact with cells either through the lipid (e.g., phospholipid) or the protein components (e.g., membrane receptors) present in the cell membrane, and due to their minute size NPs have greater permeability of the skin, cell membranes, and mucous membranes [63]. NPs pose more of a risk to human health as compared to large-sized particles of similar chemical substance, and it is generally indicated that the toxicity of NPs is inversely proportional to their size [64–66]. The interaction of NPs with living structures depends on several key factors which include dose and solubility of the NPs as well as the potential of NPs

to spread inside the body. Several NPs degrade easily, whereas some others do not degrade or dissolve readily, and they may accumulate in the body as a substitute and persist for a long time, causing toxicity. The major target organs of NPs identified up till now are the lungs, dermal system, and the liver and spleen. The secondary target organs of NPs are the heart, brain, kidneys, etc. [58,67]. The toxic effects of NPs on human health are described in Table 9.1.

6.1 Pulmonary toxicity of nanomaterials

The lungs are one of the major routes of entrance for particulate matters into the body with the average person breathing 11,000 L of air every day, hence it is expected that after the inhalation of NPs, they may be deposited throughout the entire respiratory system, from the nose to within the lungs, which has airways that transport inhaled air combined with NPs in and out of the body. Because of the large surface area of the lungs, NPs have a prime entrance route. Though larger particles (size more than 10 μm) are inclined to be deposited in the upper part of the respiratory system and can be removed effortlessly by the body through coughing and sneezing, smaller NPs can reach the gas exchange surfaces and remain there for a long time initiating disturbances [68]. Inside the lung, broken surfaces and other damage and injury to various parts of the respiratory system can accelerate the penetration of NPs into adjacent tissues, resulting in rapidly exacerbated diseases of the lung [69]. Earlier studies, both in in vitro and in vivo models, have revealed that exposure to NPs not only initiates considerable oxidative stress-mediated cellular dysfunction [70,71], but also consistently stimulates upregulation of proinflammatory cytokines [72–75] that are responsible for the pathogenesis of complications of the pulmonary organs and may cause pulmonary fibrosis [76], asthma [77,78], chronic obstructive pulmonary disease (COPD) [79,80], and pulmonary edema [81]. Pulmonary complications cause NPs to become more aggravated by the lack of the clearance process that is performed by alveolar macrophages, which depend on the rate of deposition of NPs and the rate of clearance of macrophages, and due to pulmonary inflammation the accumulative burden of NPs on the lungs causes thickening of the pulmonary wall, cystic lesions, and macrophage infiltration [82].

6.2 Dermal toxicity of nanomaterials

NPs can enter inside the human body through several applications in different modes. The skin is the largest organ in living organisms and behaves as a first-line barrier in connecting the internal body organs to

Table 9.1 Nanotoxicological outcomes of NPs on human health.

Toxicity	Disease caused	Exposure	Mechanistic paradigm	NPs responsible
Pulmonary toxicity	Asthma, chronic obstructive pulmonary disease (COPD), emphysema mesothelioma, lung cancer	Toxic inhalation	Oxidase stress, inflammation, fibrosis and genotoxicity	Titanium dioxide (TiO_2), carbon nanotubes, etc.
Dermal toxicity	Abrasion, reduction in skin thickness, and skin sensitization and irritation	Disturbances in skin integrity, transcellular and follicular penetration, lipophilic infiltration, percutaneous absorption	Membrane damage, DNA damage, oxidative stress, epigenetic modulation, autophagy, apoptosis	ZnO, TiO_2, SiO_2, Ag, Au, Co, Ni, etc.
Cardio-toxicity	Increased blood pressure and decreased heart rate, cardiac arrhythmia, myocardial infarction, ischemic heart disease, dysrhythmias, heart failure, and cardiac arrest	Diesel exhaust, wood smoke	Oxidative stress, ROS	Engineered carbon NPs, etc.

Continued

Table 9.1 Nanotoxicological outcomes of NPs on human health.—cont'd

Toxicity	Disease caused	Exposure	Mechanistic paradigm	NPs responsible
Neuro-toxicity	Neurodegeneration, altered function of neuronal networks reduced neuroplasticity, and potentially cumulative damage	Products containing nanomaterials, occupational exposure, consumer products	Synaptic degeneration oxidative stress; mitochondrial injury; cytoskeletal changes, apoptosis necrosis, ROS, inflammation	Nanogold, CNTs, TiO_2, SiO_2, nanoresins, nanoclay, nanoalumina, metal oxides, etc.
Nephro-toxicity	Vacuolar degeneration, renal fibrosis, necrobiosis glomerular degeneration, and proximal tubular necrosis.	Adsorbed, internalized, circulated, and distributed in the renal system	ROS, protein expression, genotoxicity, oxidative stress, apoptosis, necrosis	Fullerene, CNTs, metal oxide NPs, quantum dots, etc.
Gastro-toxicity	Autoimmune, inflammatory, and gut diseases, colorectal cancer, irritable bowel disease, celiac disease, colitis	Drinking water and/or unintentional consumption of food containing NPs	Altered microbiota, increased proinflammatory cytokines, bacterial invasion	Inorganic NPs, metal and metal oxides, TiO_2, SiO_2, ZnO, Ag, etc.

external substances. Numerous compounds are able to pierce and invade this first-line barrier, and they may have local effects, such as pain, irritation, and sensitization. It has been reported that entrance of NPs into the body through inhalation and ingestion is more hazardous as compared to exposure through the skin [83].

Several chemicals can come into contact with the skin; these chemicals can be either large in size or in the nanoscale range. Entrance of NPs through the skin is size dependent, as those >45 nm cannot pierce the skin and hence are unable to permeate it while those with a size between 21 and 45 nm can pierce and invade only injured skin, NPs between 4 and 20 nm can possibly permeate through both undamaged and injured skin, while those $\leqslant$ 4 nm are capable of penetrating and invading through intact skin [84].

Skin is typically exposed profoundly to solid NPs present in cosmetics and through the application of several lotions and creams which usually contains metals and their oxides as photo-protection, photo-thermal, photo-dynamic products, hair follicle disorders treatment, etc. [85].

6.3 Cardiotoxicity of nanomaterials

Cardiovascular disease is second after pulmonary diseases caused due to NP exposure. Inhaled NPs reach the blood circulation by crossing the air—blood barrier and accumulate in secondary organs, including the heart [70,86]. It has been consistently shown that there are adverse effects of NP exposure on human health, predominantly to the cardiovascular system with numerous mechanisms being projected to account for the increased morbidity, including oxidative stress, endothelial dysfunction, arrhythmia, systemic inflammation and thrombosis [87,88]. NP exposure triggers decreased cardiac output due to oxidative stress, neutrophil-mediated cardiac inflammation, and obstruction of the pathways such as the calcium signaling pathway and cardiac muscle contraction pathway that play a vital role in sustaining cardiac function [89].

A key limitation of research into the cardiovascular system is the inadequate accessibility of human adult cardiomyocytes due to restricted possibility for regeneration and proliferation, which explains the profound dependence on the utilization of animal models or animal-derived cells for studying NP-induced toxicity.

6.4 Neurotoxicity of NPs

NPs inhaled within the body may cross the mucous membrane inside the nose and then reach the brain via the olfactory nerve. The complex

character of potential exposures to known environmental sources of NPs that are accumulated in specific time and sources, the uptake and movement of NPs across the olfactory nerve, the respiratory system, and then entering the gastrointestinal tract, and the transportation of NPs to the brain may cause damage to the molecular and cellular structures of the central nervous system (CNS).

Due to the miniature size and properties of NPs, substantial investigations have been focused on their probable translocation through the functional blood supply to the rest of the body, including the brain, and on the pathological consequences caused in the brain subsequently, and the ultimate findings suggest the injurious effect of NPs on the brain [90–93].

6.5 Nephrotoxicity of nanomaterials

Adequate research has been carried out to explore the toxic effects of NPs on primary target organs, but their effects on renal tissue are not well explained. The kidneys are the main organ prone to xenobiotics, and NPs are expected to be eliminated through renal excretion. Recent in vitro and in vivo studies have established that the kidneys are a key secondary target organ of toxicity induced by NPs [94], and like other organs, in the kidneys too the NPs are adsorbed, circulated, and distributed to different parts of the renal system according to their physicochemical properties [95].

Different NPs which have been reported to causes toxicity in the renal system include fullerene [96], CNTs [97], metal oxide NPs [98,99], and quantum dots [100].

NPs may cause adverse effects on the renal system. In vivo studies have revealed that NPs can exhibit a significant nephro-toxic effect both at the tubular and glomerular levels. Toxic effects at the tubular level include deterioration of the tubular epithelial cells through degeneration, the presence of cellular fragments and protein-rich liquid in the tubule lumen, and renal fibrosis, while at the glomerular level the toxic effects of NPs include distended glomeruli, alterations in Bowman's space, and proliferated mesangial cells [101].

6.6 Gastro-toxicity of NPs

Exposure of NPs to the gastrointestinal tract (GIT) occurs mainly through drinking water and/or unintentional consumption of food containing NPs. The stability, surface characteristics, and other physiochemical properties of NPs may be regulated by their interactivity with the GIT, any alterations to the NP will manipulate their absorption in the gut and therefore they can

affect the gut microbiota [102]. It has been reported that in an archetypal Western diet, approximately 10^{12}–10^{14} NPs are ingested every day and roughly ~1% of NPs are taken up by the mucosal membrane [103]. Consumption of NPs through drinking water or food may modify the composition of the microbiota of the gut and GIT, and probably by encouraging pathogenesis is causative of different autoimmune, inflammatory, and other gut diseases. In some industries, including the food industry, the use of NPs has increased due to the enhanced use of nanomaterials [104]. Inorganic NPs are extensively used in processing and packaging of food materials [105].

Therefore, various industries should be instructed to follow guidelines and apply modifications in the utilization of NPs to reduce their negative impacts on human health.

6.7 Hepatotoxicity of NPs

The liver is the largest organ in the human body and has more than 500 different roles including some vital functions. The most significant function is the filtration of blood, another is eliminating and detoxifying waste products, namely alcohols, drugs, and NPs, from the body. The liver is reported to filter around 30%–90% of dispensed NPs from the bloodstream. These NPs, when accumulated in the liver, may alter its function and cellular morphology. The liver function biomarkers (enzymes) serum alanine transaminase (ALT) and alkaline phosphate (AKP) levels, in humans have been found to be increased during long-term exposure to air pollution, and also reported to be secreted into the blood upon liver injury [106,107].

6.8 Reproductive toxicity of NPs

NPs have been reported to exert several toxic effects on various organs including the reproductive organs. Increased production of engineered NPs may enhance the risk of intrusion with the reproductive organs [108]. They affect both the male and female reproductive systems.

6.9 Male reproductive system

The male reproductive system is reported to be susceptible to oxidative stress and inflammation, and both these factors lead to exposure to NPs [109]. Oxidative stress is a key factor which contributes to male reproductive toxicity after exposure to NPs [110]. NPs generate ROS, which is another major factor reported to cause 30%–80% of total infertility

concerns in men [111]. The enhanced production of ROS leads to apoptosis of cells and impaired spermatogenesis [112]. Exposure to different NPs such as silver NPs [113,114], copper NPs [115], and nickel NPs [116] and coexposure to metal oxides such as TiO_2 NPs and ZnO NPs [117], have been reported to cause NP-induced oxidative stress in male reproductive organs.

6.10 Female reproductive system

NPs may enter the female reproductive system and, as with other organs, accumulate according to their size in the cells and organs of the female genital system and causes damage to fertility. After entering the blood circulation, NPs may arrive at the uterus and ovary cause injury to them [118,119].

Currently, the extensive use of NPs raises concerns about their toxic effects on the human body, mainly on the reproductive systems and fetal well-being, particularly given the tiny dimensions of NPs, easiness of penetrating, and their potential for crossing the placental barrier, they may cause injury and/or toxicity to the fetus [120].

The mechanism of reproductive toxicity due to NPs remains unclear. As explained with the male reproductive system, NPs generate ROS. They traverse the membrane and produce ROS in the ovary and other germ cells, and finally cause cell death or deformity. These ROS can damage the DNA/cells and lead to alterations in genomic material through heredity in subsequent generations [121].

NPs can also cause immunotoxicity and genotoxicity, but the potential mechanism for this is yet to defined.

7. Adverse effects of NPs on the environment

As during the modern era of nanotechnology nanoscale materials are becoming increasingly smaller, it is becoming more difficult to detect toxic NPs in waste that might contaminate the environment. Consequently, the exposed population of NPs continues to increase due to the expansion of their applications. Further, after their accumulating in organs, significant quantities of nanomaterials are excreted and released into the environment [122]. Although there are evident benefits to the use of NPs there remain several questions about how the use of NPs in everyday life may influence the environmental conditions. One of the major concerns that have to be addressed in the near future, before immense use of NPs, is their toxicity

impact of human health and the environment [123]. Therefore, before the wider use of nanomaterials is allowed in everyday activities, it is imperative to discover how these NPs influence the surrounding environment so that their damaging impacts can be avoided.

8. Types of environmental NPs

8.1 Natural

(a) Atmospheric: These NPs are inorganic in nature, e.g., volcanic ash
(b) Terrestrial
(c) Aquatic

8.2 NPs are both organic and inorganic in nature

Examples of inorganic NPs are silicates (clay and mica), oxides/hydroxides (MnO), carbonates ($CaCO_3$), phosphates, metal sulfides (ZnS).

Organic examples include macromolecules, biocolloids (bacteria), cellular debris.

1. Engineered
   (a) Intentional: Intentional application of NPs in the environment includes their use in remediation of the environment [124,125] or in agricultural applications [126,127]. They may be carbonaceous (SWCNTs), metal oxides (ZnO,TiO_2), semiconductor materials (QD), zero-valent metals, and nanopolymers (dendrimers).
   (b) Unintentional: Unintentional emission of NPs into the environment includes the following:
      (i) Release due to the life cycle of products incorporating NPs, such as paints, cosmetics, sunscreens [128,129];
      (ii) Accidental spills or industrial liquid effluents, for instance, those released by textile industries during the washing of nanotextiles [130]. It has been projected that of the NMs produced worldwide, 63%–91% reach landfills, 8%–28% are released into soils, 0.4%–0.7% in natural water bodies, and 0.1%–1.5% are emitted into the atmosphere [131]. These may also be wear and corrosion products, and waste and combustion products.

There are four ways in which NPs can interact with the environment and become toxic and harmful to the surrounding environment [132]:

1. **Hydrophobic and hydrophilic NPs**: A nano-coating of TiO_2 powder will reduce the weathering effects, such as salt rain degradation on

composite materials. A concern was reported about the effect of TiO_2 NPs and it should be assessed when leaked into the environment [133].

2. **Mobility of contaminants:** NPs can easily be attached to contaminants and transported to a more sensitive environment such as aqueous environments. They can be emitted into the atmosphere by two common methods [134]:

   Primary emission: into the air directly from the source which is the major basis of total emissions.

   Secondary emission: secondary particles are emitted naturally.
3. **Solubility:** Many NPs are soluble in water, and are difficult to separate from waste if not handled properly.
4. **Disposal:** Any waste product, including NPs, can cause environmental toxicity if disposed of inappropriately.

9. Pathways of NPs into the ecosystem

NPs are released into the ecosystem in three emission situations:

1. Release of NPs during the production of raw materials and nano-enabled products
2. Release of NPs during the use of products
3. Release of NPs after disposal of NP-containing products [135–137].

Emissions of NPs can occur either directly to the ecosystem or indirectly using a technical system. Indirect emissions probably take place either via the sewage of wastewater treatment plants (WWTPs), application of biosolids to the soil, or leachates from landfills. It also affects the fate of NPs [138–141].

10. Effects of NPs on the environment

10.1 Effect of NPs on dust cloud formation and decrease in sunlight intensity

NPs, after being emitted into the environment, are considered to play a significant role in the formation of dust clouds. After release they coagulate and form dust clouds [142].

10.2 Effects of NPs on the concentration of environmental hydroxyl radicals and ozone depletion in the atmosphere

Hydroxyl radicals are among the most reactive free radicals in the environment that play a vital role in the photochemical degradation of natural

organic matter along with organic pollutants in the environment. NPs are very reactive and instantly bind with hydroxyl radicals, which ultimately results in the overall reduction of hydroxyl radicals [143,144]. Hydroxyl radicals are known to degrade many pollutants as they are strong oxidants, and thus their reduction in the atmosphere is responsible for the increase in greenhouse gases. These greenhouse gases are eventually responsible for ozone layer depletion and cause severe damage to the environment [145]. Additionally it increases exposure to UV radiation [146], which leads to increased incidences of different types of skin cancer.

10.3 Effect of NPs on the decrease in the environmental stratospheric temperature

Molecular hydrogen is released by accident from hydrogen fuel cells and other sources, and NPs in the troposphere interact with it [147,148]. Molecular hydrogen after interacting with NPs moves up to the stratosphere and forms a great deal of water vapor in the stratosphere which causes cooling of the stratosphere, enhancement of the heterogeneous chemistry which obliterates ozone, an increase in noctilucent clouds, and alterations in the chemistry of the troposphere and atmosphere—biosphere interactions.

The appearance of noctilucent clouds, and their regular increase could might be linked to changes in the climate [147].

11. Fate of nanoparticles in the environment

Nanomaterials can undergo chemical, physical, and biological alterations as well as interact with macromolecules after being discharged into the environment [148—150]. NPs in the environment go through various aging processes, for instance, chemical transformation, aggregation, and disaggregation. The interchange among these processes and the transport of NPs establishes the fate and finally the eco-toxicological prospective of NPs [151—153].

NPs may interact with the environment in numerous ways; they may be attached to a carrier and by bio-uptake transported in underground water, by contaminants, or by organic compounds. Potential aggregation will permit conventional transportation to sensitive environments where the NPs are capable of breaking up into colloidal NPs.

11.1 Current challenges

Nanotechnology has emerged with direct advantageous applications in the field of human health and the environment; however like other novel

technologies it can have adverse effects on living beings and the ecosystem although these may be unintentional.

Over the last few decades, concerns about health, the environment, and safety risks of NPs have increased tremendously and efforts has been made through extensive research to prevent the risks posed by the utilization of and/or exposure to NPs responsible for toxicity and to overcome the probable mechanisms of toxicity of NPs, which is a major challenge as the mechanisms are neither known yet nor explained by traditional toxicology [154]. Several methods are accessible which describe and characterize the toxicological properties of NPs, and the correlation between the effects of NPs with their physicochemical characterization remains a challenge.

To decrease the dissolution of NPs to toxic ions, toxic species may be substituted with less toxic ions having properties comparable to the former; for this NPs can be sealed with a shell material, the morphology of the NPs can be selected to reduce their surface area and consequently minimize dissolution.

One of the challenges arises when NPs developed and applied in medicine cross human body barriers. There are materials that are developed to pass through barriers, not to enter cells, while there are others that are designed to act within them [155].

Due to extensive usage in industry, the expansion of novel nanomaterials is increasing rapidly and the availability of sufficient high-quality scientific data is the major challenge in the development of the safety evaluation of NPs. For the estimation of risks, different models and strategies have to be developed to systematize the existing data on the effects of NPs on human health and the environment, along with methods, and to finally integrate them into a policy.

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SECTION 4

Functionalized nanoparticles-based antimicrobial coatings for textile application

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CHAPTER 10

Functional finishing of textile materials using silver-based functionalized nanoparticles: Health perspectives

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1. Introduction

The textiles industry has been in place for thousands of years. Textiles product were manufactured domestically until the 17th century, from sources which included cotton, hemp, and flax, and also from animal sources such as wool and silk. Then, during the Industrial Revolution, the manufacturing process was altered, providing fascinating, smarter products and faster processes [1]. With the advent of new technology, new fibers have been introduced from time to time keeping in view the needs of society and humankind. Clothing is not merely a product to cover the body with beautiful-looking materials. Today, new materials and technology are being developed to meet the growing demands for modern functional textiles.

The existence of functional textiles is in fact the inspiration for the development of new products to fulfill the specific needs of the textile industry. The use of technology is not limited to improving the look of clothes but has also moved to specific Health perspectives. The day is not far away when medicines will be administered through clothes using transdermal routes. Under certain humidity and temperature conditions, natural fiber textiles, such as cotton, are good carriers of a variety of bacteria, causing discoloration, loss of mechanical strength, foul odor, and even negative health effects to the human body. Antimicrobial agent modification of cotton fabrics has become a popular method for providing unprecedented textile performance. Nanotechnology research has provided

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fresh insights into antimicrobial agents and resulted in the development of functional nanomaterials with distinct chemical and physical properties, and has generated significant prospects for ecologically benign finishing chemicals and sustainable developing technologies to replace traditional hazardous finishing chemicals and nonsustainable finishing procedures, taking into account product quality, economy, ecology, and social factors. Metal nanoparticles in the development of multifunctional fabrics have proven to be among of the most significant methods. Because only a small percentage of bacteria are resistant to silver (Ag), Ag in the form of nanoparticles (AgNPs) or ions (Ag^{+}) has the highest antibacterial activity and has been utilized for medicinal and health purposes. In textile manufacturing, functional finishes have become more significant in the acquisition of multifunctional properties such as antistatic, durable, antimicrobial, dirt resistant, flame resistant, water repellent, wrinkle recovering, self-cleaning, ultraviolet protection, and conductivity. In this chapter, functional finishes of textiles that are highly interesting due to their high therapeutic potential for practical and industrial applications are highlighted.

2. Various types of textile materials

In this section, various types of materials are introduced which are used in the production of yarn for textiles, which are categorized into two main classes: natural materials which include silk, hemp, wool, and cotton fibers, and synthetic materials including nylon, polyester, and rayon [2–4]. In Fig. 10.1 the types of materials used for producing yarn of textiles are described. Textile finishing involves procedures for improving the appearance of textiles [5].

Simply put, the goal of finishing is to make the textile more appealing to the consumer and to achieve a number of goals, including preparation through purification, activation, and functionalization, increased added value, improved quality, repeatability, variety, improved attractiveness through appearance modification, changed handling, increased comfort, dimensional stability, protection, and improved performance [6]. Imparting various specific characteristics to textiles is generally carried out during a chemical finishing step. Significant progress has been made in this respect, and functional finishing of textile materials in nanotechnology has been introduced with potential properties associated with current nanotechnology research for use in textiles including: aesthetics, shrink resistance, antimicrobial, stain resistance, electrical conductivity, static protection, fire

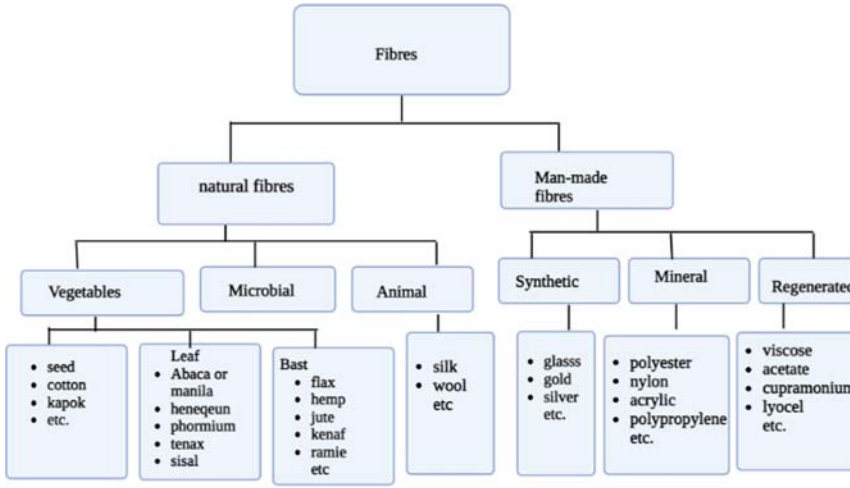

Figure 10.1 Types of materials used in the production of yarn for textiles.

resistance, ultraviolet (UV) protection, fragrance release, water repellent (hydrophobic), high strength, wrinkle resistance, moisture management, and self-cleaning properties. Different methods can be included in nano-finishing ranging from various deposition techniques such as electroless deposition and vapor deposition to layer-by-layer coating, sol–gel, ex situ and in situ synthesis, and fabrication of nanomaterials [7]. Choudhury defined functional finishing as any operation which improves the performance properties of a fabric such as durability, strength, etc. Property-changing functional finishes provide the added qualities desired for a particular fabric or they may be used to change an undesirable property to a more desirable one. Many such finishes add more than one property to a fabric [8]. Finishing procedures can be divided into two categories. Simple operations like drying on a steam-heated cylinder to various types of calenders, elevating for soft effects on the fabric's surface, and breaking the finishing of filled products for a comfortable feel are examples of physical or mechanical processes. Optical finishing, brushing and napping, softening, shearing, and compacting of textile structures are examples of physical finishing procedures for textiles. Chemical finishing, often known as "wet finishing," is the process of applying chemicals to textiles in order to obtain a certain outcome. The chemical methods have changed remarkably with time, and newer finishes are being developed continually [9].

3. Silver-based functionalized nanoparticles in antipathogenic finishes

Silver is the most frequently used metal in textiles, as well as wound dressings. Heavy metals are toxic to microbes even at very low concentrations, whether in bulk or nanoparticles. They kill microbes by binding to intracellular proteins and inactivating them. Other metals, such as copper, zinc, and cobalt, also have received attention as effective antimicrobial agents for textiles. The antimicrobial property has developed into an essential prerequisite for all textiles and household products because of the recent COVID-19 pandemic which resulted in an enhancement in awareness about hygiene and health [10]. Factors that influence microbial growth include environments that are humid and warm. Fibers from natural sources such as cotton and linen are susceptible to microorganisms such as bacteria and fungi. Fibers which are synthetic are not completely resistant to microorganisms; for example, polyurethane fibers and coatings can be infested. Chemical processes can promote microbial growth. Sweat, sebum, blood, dust, dirt, and food stains on fabric provide a nutrient-rich environment for microbial growth. Microbial growth on textile fabrics causes disgusting odors to be released from the infected fabric. It may also cause fabric pigmentation or discoloration, and in extreme cases, the growth of microorganisms may cause fabric weakness and the transmission of infections to humans. Functional clothing, such as cycling shorts or bodysuits, causes increased deposits of bodily excretions such as perspiration, fat, and traces of feces and urine. Microorganisms found on the skin can thrive in textiles, making them an ideal breeding ground. Most microorganisms thrive in conditions of high moisture and body heat, and their numbers can double every 20–30 minutes [11]. In Fig. 10.2 various properties of silver-based functionalized nanoparticles are highlighted.

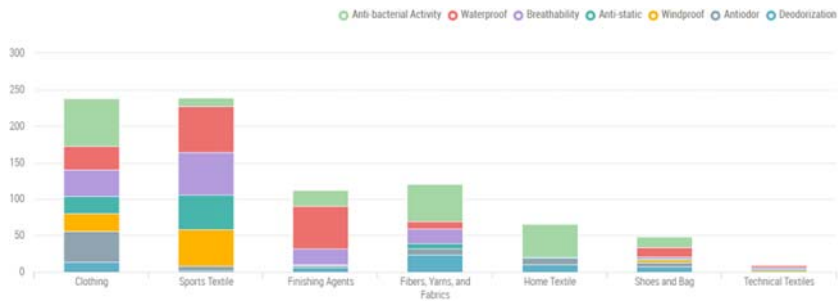

Figure 10.2 Properties of silver-based functionalized nanoparticles.

The antimicrobial activity provided by chemical finishes can be categorized into two types [12]:

a) The antimicrobial protection of the textile user against pathogenic or odor-causing microorganisms and

b) The antimicrobial protection of the textile itself from damage caused by mold, mildew, or rot-producing microorganisms.

Depending on the requirements of the finished product, a variety of antimicrobial finishes is available and applied. Antibacterial finishing which is either bactericidal or bacteriostatic finishing, and antimicrobial finishing which is either hygienic finishing of household textiles, such as deodorant finishing, or antimicrobial finishing of technical textiles, such as germicidal or antimycotic finishing. Antimycotic finishing may be fungicidal or fungistatic finishing [13]. Silver nanoparticles have antibacterial capabilities and can damage bacteria's cellular barriers. One benefit of silver nanoparticles over antibiotics is that they impact bacteria that are resistant to medicines. Silver nanoparticles' antibacterial capabilities are determined by their size and concentration. In general, increasing the concentration improves the antibacterial capabilities. According to research, when silver nanoparticles get tiny enough, they may eliminate germs at extremely low quantities. Numerous researches on the influence of nanoparticle shape on antibacterial capabilities have been conducted. According to one study, nanoplate particles have the greatest antibacterial impact and activity.

Despite several researches on the mechanism of silver nanoparticles' impact on bacteria, there remain many unanswered concerns. Silver nanoparticles have been shown in the past to destroy bacterial cellular walls. Changes in the cellular membrane of bacteria enhance the diffusivity of the cells, resulting in the bacterium's demise. Another process involves the generation of free radicals by silver nanoparticles. These radicals wreak havoc on the cellular wall. The presence of silver ions in the environment, on the other hand, produces an interaction between these ions and thiol groups in enzymes and alkaline agents of bacteria, resulting in cell death. Some biological functions, such as DNA replication, are also inhibited by this contact. The antibacterial mechanism of silver nanoparticles (AgNPs) may be considered as the continual release of silver ions and because of their electrostatic attraction and affinity to sulfur proteins silver ions adhere to the cell wall and cytoplasmic membrane. The interaction of silver ions with the sulfur and phosphorus of DNA result in termination of the microorganisms [14]. The proposed mechanism of action has been described in Fig. 10.3.

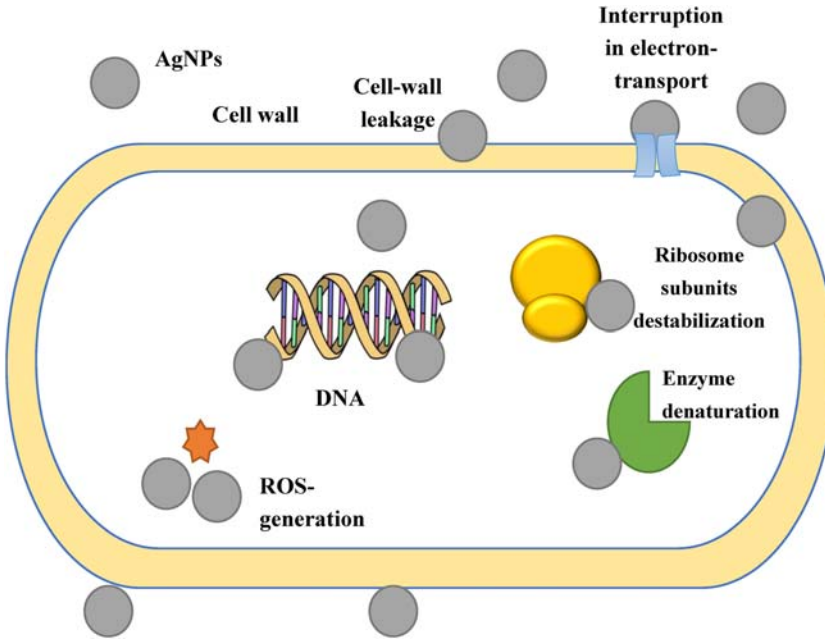

Figure 10.3 Mechanism of action by AgNPs.

When compared to disc and triangular plate morphologies, spherical AgNPs had a larger specific surface area and a better capacity to discharge metallic ions, resulting in superior antibacterial properties [15]. When compared to larger AgNPs, smaller AgNPs have higher antibacterial activity. In comparison to the larger nanoparticles, the smaller AgNPs aggregate more quickly and have a higher effect on the target organelle [16]. Table 10.1 describes the effects of AgNPs against pathogenic bacteria.

The interaction of AgNPs with viruses is still an underexplored field, especially in the textile industry. Against various enveloped viruses, the mechanism of action of AgNPs as an antiviral and virucidal has been investigated. According to Elechiguerra and colleagues, nanoparticles bind to the disulfide bond regions of the CD4 binding domain within the HIV-1 viral envelope glycoprotein gp120 and inhibit the virus by binding to the disulfide bond regions of the CD4 binding domain within the HIV-1 viral envelope glycoprotein gp120 [21]. The fact that AgNPs inhibited a variety of HIV-1 isolates shows that their method of action is independent of cell tropism and that AgNPs are anti-HIV-1 drugs with a broad spectrum of

Table 10.1 Mechanism of action for AgNPs against pathogenic bacteria.

Bacteria	Fabric type	Mechanism of action	References
E. coli	Cotton fabric	Inhibit the growth of bacteria	[17]
S. epidermidis	Cotton fabric	Inhibit the growth of bacteria	[17]
C. haemolyticum	Cotton, polyester, and nylon fabric	Inhibition zones of 5.67 ± 0.58, 2.33 ± 0.58, and 2.00 ± 1.00 mm	[18]
B. cereus	Cotton, polyester, and nylon fabric	Inhibition zones of 2.00 ± 0.00, 2.33 ± 0.58, and 2.33 ± 0.58 mm, respectively	[18]
S. aureus	Synthetic copolymer	Shows antibacterial activity by inhibition of growth	[19]
Pseudomonas aeruginosa	100% cotton woven	Shows antibacterial activity	[20]

activity. Table 10.2 describes the effects of AgNPs against pathogenic viruses.

Fabrics' antibacterial and antifungal characteristics are mostly determined by the composition and dosage of the impregnation solution. Paszkiewicz reported that after 5, 10, 15, and 20 washing/impregnation cycles, all tested materials had a very high antibacterial activity and a lasting antibacterial capacity against *Escherichia coli* and *Staphylococcus aureus*. After 18 hours of incubation, the proportion of dead cells in *Escherichia coli* and *Staphylococcus aureus* had already reached 100%. After 5 (99.99%) and 15 (100%) washing/impregnation cycles, the antifungal tests revealed that only the textile sample impregnated with solutions containing Ag^{+}/Cu^{2+} and AgNPs/Cu^{2+} displayed substantial inhibition of *Candida albicans* development [36] Table 10.3 describes the effects of AgNPs against pathogenic fungi.

Table 10.2 Mechanism of action of silver nanoparticles against various pathogenic viruses.

Name of virus	Mechanism of action for silver nanoparticles against various viruses	References
Herpes simplex virus (HSV-1)	Inhibit cellular attachment and intracellular replication	[22]
Type 2 HSV	Directly block viral glycoproteins and interact with viral DNA	[23]
Epstein–Barr virus	Induce ROS generation and activating autophagy	[24]
Human immunodeficiency virus 1 (HIV-1)	Interfere with HIV-1 replication	[25]
SARS-CoV-2	Inactivation of viral particles upon short exposure	[26]
Human papilloma virus (HPV)	Induce formation of free radicals	[27]
Rotavirus	Direct inhibitory action on virus production	[28]
Zika virus	Protein deactivation and denaturation	[29]
Dengue virus	Penetrate into vector cell	[30]
West Nile virus	Penetrate into vector cell	[31]
Chikungunya virus	Penetrate into vector cell	[32]
Monkeypox virus	Blocking of virus–host cell binding and penetration	[33]
Hepatitis B virus (HBV)	Interaction with double-stranded DNA and/or binding with viral particles	[34]
Tacaribe virus (TCRV)	Inactivation of virus particles prior to entry	[35]

4. Silver-based functionalized nanoparticles in nonmicrobial protective finishes

The UV protection feature has received great attention because over exposure to UV radiation increases the chances of developing premature skin aging, sunburns, allergies, and skin cancer. A UPF (UV protection factor) value of 40–50 means outstanding UV protection feature as per standard regulations in the United States [45]. A recent study at the Department of Molecular Biology and Human Genetics, Tzu-Chi

Table 10.3 Mechanism of action of silver nanoparticles against various pathogenic fungi.

Fungus	Mechanism of action for silver nanoparticles against various fungi	References
Trichophyton rubrum	Geometric mean of MIC values = 1·19 and 2·89 μg/mL, respectively, showed high antifungal activity	[37]
Sclerotinia sclerotiorum	Inhibiting sclerotia germination and mycelial growth	[38]
Helminthosporium sp., *Alternaria alternata*, *Phytophthora arenaria*, and *Botrytis* sp.	Nano-Ag antifungal activity may be related to damaging the fungus membrane lipid bilayer, leading to intracellular ion efflux resulting in cell death	[39]
Fusarium sp.	AgNPs, with an MIC in the range of 0.125−4.00 μg/mL, showed significant antifungal activity against all tested fungi	[40]
Aspergillus niger, *Aspergillus fumigatus*, *Fusarium soleni*	ROS generation and changes in intracellular calcium levels	[41]
Botrytis cinerea, *Fusarium oxysporum*, *Aspergillus parasiticus*, *Alternaria alternata*, *Aspergillus niger*, *Penicillium chrysogenum*	AgNPs-Alt revealed inhibitory effects to pathogenic strains at 0.25 mg/mL concentration and this activity was observed to be concentration dependent	[42]
Fusarium solani	Cellular and organelle structure damaged by AgNPs. AgNPs even possibly permeated into the cell across the membrane, resulting in cell death due to their small size	[43]
Candida krusei, *Candida parapsilosis*, *Candida tropicalis*, *Candida albicans*, *Candida glabrata*, *Fusarium oxysporum*, *Trichophyton interdigitale*, *Trichophyton rubrum*, *Microsporum canis*	AgNPs were able to inhibit the growth of all evaluated fungi at a concentration below that considered cytotoxic (81.37 mg/L)	[44]

University Taiwan revealed that AgNPs can protect skin from UVB-induced damage in both cell cultures and mouse models [46]. Cuk reported the synthesis of cotton using natural extracts-functionalized fabrics with in situ synthesized AgNPs showing better UV protection properties than the samples treated with only a reducing agent, and the overall rating was excellent (UPF > 50). The reason for the high UPF values of the samples treated with only a reducing agent is due to the organic compounds of the natural extracts which act as UV absorbers [47].

The fabrication of super-hydrophobic materials with oil/water-repellent properties has been receiving great attention in the textile industry. Super-hydrophobic surfaces have been developed using hydrothermal, solution-immersion, chemical vapor deposition, electro-spinning, layer-by-layer assembly, and pad-dry methods. Of all these techniques, the solution-immersion method has many advantages such as efficiency, scalability, minimal equipment requirements, and cost-effectiveness [48]. Super-hydrophobic surfaces prepared with the AgNPs-coated fabric, had an increased water contact angle (CA) and decreased water shedding angle (SHA). Super-hydrophobicity properties with CA of 158 ± 4.3 and SHA of 7 were reported. The increased hydrophobicity can be attributed to the increase in surface roughness of the fabric as a result of its coating with AgNPs. Hydrophobicity was stable and did not reduce over time. A super-hydrophobic surface with high CA and low SHA was prepared, ascribing to the two-level surface structure of the fabric [49]. Super-hydrophobic fabrics are being developed by fabric nanoparticle deposition and polymer grafting. However, due to the weak attachment between the incorporated particles and fibrous substrates, the micro-/nanostructures constructed using the above-mentioned approaches are easily destroyed by mechanical forces, such as finger pressing, washing, and mechanical abrasion, making the fabrics lose their super-hydrophobicity during normal use [50].

The conductive fabrics have been a large field of research in the biomedical and safety communities. The naturally conductive yarns can be spun directly from conductive materials or metals to make conductive fabrics [51]. The higher concentration of silver nitrate solution caused an increase in the electrical resistivity of coated fabric samples. This behavior can be attributed to the formation of large silver particles at a higher concentration of silver nitrate solution. The lower concentration of silver nitrate produced more conductive fabrics due to the formation of a percolated network by the creation of continuous connectivity between the small silver particles [52]. A conductive fabric was prepared by padding 3-

mercaptopropyltriethoxysilane-modified cotton with silver 2-ethylhexylcarbamate/methanol, followed by a thermal reduction process at 130°C. AgNPs with a size of 20−100 nm endowed the fabrics with electric resistance as low as 3.92 Ω and inhibition zones of 22.0 and 21.2 mm against *E. coli* and *S. aureus*, respectively [53].

5. Application of silver-based functionalized nanoparticles for healthcare in textiles

In this chapter, we want to emphasize the available first line of defense, i.e., use of face masks and hand sanitizers against microbial attack, especially COVID-19, particularly for those who are immune-compromised. Researchers have collaborated to design various curative/preventive treatments, however there remain a number of barriers to the supply and mass-production of well-tested and safe nanomaterial-based products around the world. Furthermore, because this pandemic has demonstrated the world's inability and limits in delivering the required supply of face masks, it was vital to combine forces and create alternative tactics and strategies to combat COVID-19 and any future pandemics. Over the last 2 decades, the world has experienced various pandemic respiratory infections, ranging from SARS and swine flu (H1N1) to the most recent coronavirus disease 2019 (COVID-19 or SARS-CoV-2 virus), with the latter showing greater infection rates and substantial medical problems [54]. As per numerous reports, small liquid particles released by infected persons during sneeze, coughing, talking, and breathing disseminated the virus via the air. As a result, wearing suitable facemasks that cover the mouth and nose is one of the most efficient preventative strategies against infection. Another study discovered a 0.12 relative risk of infection while using masks in a meta-analysis of four investigations [55]. As a result, researchers and manufacturers collaborated on manufacturing reusable face masks to meet the market demand. Many people resorted to making their own domestic masks, recycling older masks, or utilizing masks that provide less protection. Research has been conducted to improve the performance of cloth face masks by discovering novel materials with sufficient filtration efficiency, breathability, and comfort, as well as imparting new qualities like hydrophobicity, antibacterial, and antiviral capabilities [56]. Since the antibacterial capabilities of some nanomaterials became widely recognized, novel designs of respiratory protection equipment and facemasks have involved the coating of natural fibers previously employed as filter barriers with specific

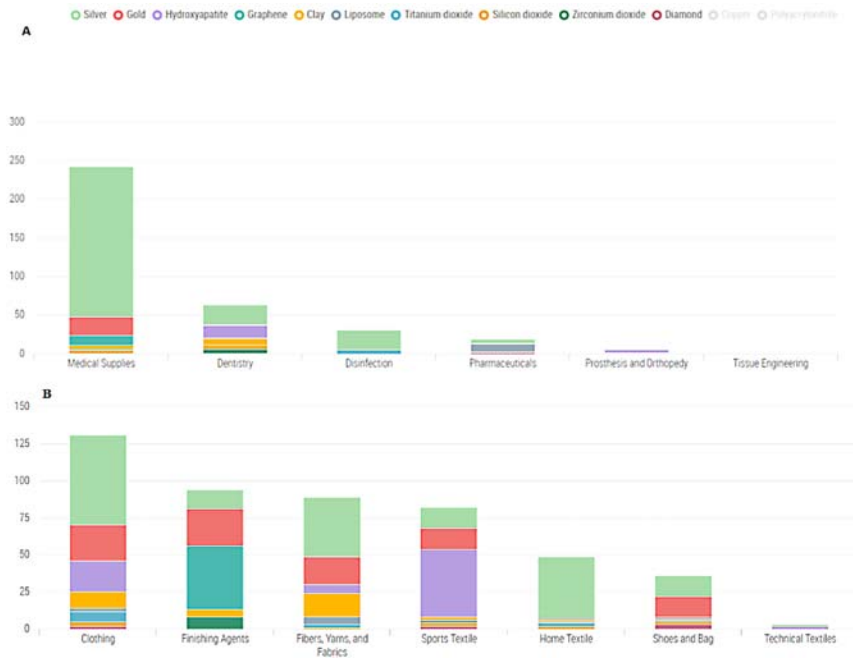

Figure 10.4 (A) Nanomaterial-based products used in healthcare; (B) nanomaterial-based products used in the textile industry. Data available on the Nanotechnology Product Database (NPD).

nanoparticles. Silver nanoparticles (NPs) and graphene are two of the most commonly employed nanomaterials in facemasks [57]. According to research on the Nanotechnology Product Database (NPD), silver nanoparticles are employed in 75% of medical products. According to the data, silver nanoparticles are extremely important in the creation of nanotechnology goods in the healthcare sector. Silver nanoparticles are the most widely employed nanostructures, with significant differences to other nanostructures. According to the Nanotechnology Product Database, silver nanoparticles have been employed in 238 commonly used items. Fig. 10.4 illustrates statistics on nanomaterials used in the healthcare and textile industries.

A variety of technologies are used in the disciplines of health and medicine because the market in these sectors and the strategic relevance of hygiene to governments drive researchers to utilize technology development to improve living quality, particularly in the healthcare profession. As a result, nanotechnology goods in the field of medicine from the

Nanotechnology Products Database (NPD) were investigated. According to the results, wound dressings were the main goods in this category, with 62 nanosilver products, 15 atopic eczema textiles, 20 respiratory masks, 9 medical scrubs, 6 lab coats, and 1 arm sleeve. The products in the textile industry are 22 socks with nanosilver items, 21 sports jackets, 13 underwear socks, and 12 fabric. According to projections, silver nanoparticles will have a market value of almost $3 billion in 2024, owing mostly to their antibacterial and antifungal capabilities. It should be noted that the uses of these nanoparticles are not restricted to the medical industry but also have applications in the textile and packaging industries. A large share of market of these materials is in the United States and the UK, while South Korea and China have a developing market in Asia [58]. Tables 10.4 and 10.5 describe silver nanoparticles-based products and their applications in the healthcare and textile industries in various countries.

6. Safety of silver-based functionalized nanoparticles

A number of investigations into risk detection of silver NPs in face masks and other garment materials that come into contact with the human body have been undertaken. Silver NPs were examined for skin sensitization, neurotoxicity, and genotoxicity in a recent research and were determined to be safe for all three risks [59]. Silver-based functionalized nanoparticles, because of their antibacterial and antifungal properties against pathogens, have been widely employed in a variety of textile applications. This occurs as a result of the release of Ag^+ ions, which inhibits respiratory enzymes. Once within the cell, silver nanoparticles intercalate into the bacterial DNA and suppress pathogen growth. AgNPs are environmentally friendly and nontoxic to humans [60]. Cloth masks treated with silver ions provide a powerful tool against viral infection, with the virus being destroyed in one of three ways: the metal nanoparticles create a free radical-like OH ion that is toxic to the virus's cell, the metal chelates with N, O, and S in the virus's cell, or the metal damages the electron transport chain because silver is a transition element with a d-block [61]. The impact of different fabric materials, number of layers, and hybrid layers on the air permeability and breathability of cloth masks was explored in a recent study to assess their comfortability. The physiological effects of wearing the suggested face masks were also assessed by monitoring the users' oxygen saturation of hemoglobin (SpO^2 percent) and heart rate while performing routine tasks such as office work and walking. The physiological implications of wearing

Table 10.4 Nanosilver products, properties, and applications in textile-based healthcare products.

Product name	Therapeutic properties	Application	Country
Nanordica wound dressing	Antibacterial activity, environmentally friendly, cost effective, long-term effective, breathable, hypoallergenic, wound healing	Wound dressing	Estonia
Nano Silver Adult Mask 2 Pack	Antibacterial activity, antimicrobial activity, antifungus, durable antibacterial effect, antidust, antiodor	Face mask	USA
Heenrgy Bio Immunity Mask	Washability, antimicrobial activity, antiodor, antiviral, reusable	Face mask	India
ZOONO Triple Layer Face Mask	Antibacterial activity, washability, long-term effective, reusable, anti-germ	Face mask	New Zealand
Anatomical antibacterial drape NANO guard	Antibacterial activity, washability, durable antibacterial effect	Face mask	Czech Republic
Dony Mask	Antibacterial activity,	Face mask	Vietnam

Table 10.4 Nanosilver products, properties, and applications in textile-based healthcare products.—cont'd

Product name	Therapeutic properties	Application	Country
	washability, UV protection, breathability, waterproof, eco-friendly, antiviral, reusable, dust filtration		
MONOmask	Antibacterial activity, soft, comfortable, hypoallergenic, recyclable, air pollutants resistant	Respiratory face mask	China
Antibacterial face mask with pocket for nanofiber filter 6C	Antibacterial activity, washability, breathability, antimicrobial activity, antiviral, particulate removal, antiodor	Face mask	Czech Republic
Wet Wipes	Antifungal activity, durable antibacterial effect	Wipes	South Korea
NM Membrane for Mask	Antibacterial activity	Respiratory protection, coronavirus, COVID-19	India
Nano-HEPA Mask	Antimicrobial activity, virus removal, bacteria removal, germ removal	Face mask	Malaysia
		Knee guard	USA

Continued

Table 10.4 Nanosilver products, properties, and applications in textile-based healthcare products.—cont'd

Product name	Therapeutic properties	Application	Country
Nano Flex Calf Support	Antibacterial activity, circulation improvement, antiodor		
Arm Sleeve	Antibacterial activity, UV protection, flexibility, antiodor	Arm sleeve	Taiwan
Antiviral face mask for children (2.5–5 years)	Chemical-free, virus removal, allergen-free, bacteria removal	Respiratory mask for children	Czech Republic
Hemoflex	Durable antibacterial effect, biodegradability, biocompatibility, sterile	Medicine, wound dressing	Russia
PADYCARE Neck Collar for atopic eczema	Antibacterial activity, antiinflammatory	Atopic eczema textile	Germany
ADYCARE Antibacterial sock—navy-black	Anti-bacterial activity, antiinflammatory	Atopic eczema textile	Germany
PADYCARE Ladies Slip	Antibacterial activity, antiinflammatory	Atopic eczema textile	Germany
PADYCARE Gloves for atopic eczema	Antibacterial activity, antiinflammatory	Atopic eczema textile	Germany
PADYCARE Kids Feet Liner for atopic eczema	Antibacterial activity, antiinflammatory	Atopic eczema textile	Germany
Snap Front Warm-Up Jacket	Antibacterial activity, antimicrobial activity	Medical scrub	USA

Table 10.4 Nanosilver products, properties, and applications in textile-based healthcare products.—cont'd

Product name	Therapeutic properties	Application	Country
Mid Rise Moderate Flare Drawstring Pant	Anti-bacterial activity, anti-microbial activity	Medical scrub	USA
Padycare Fitted sheet for eczema	Antibacterial activity, antiinflammatory	Atopic eczema textile	Germany

face masks while undertaking diverse activities, on the other hand, have only recently been explored. Several studies have looked at the physiological effects of surgical face masks on SpO^2, heart rate, and CO_2 levels when worn during work [62–66]. On the other hand, research has shown that the cytotoxic and genotoxic effects of AgNPs are based on their concentration, size, exposure period, and environmental variables, according to the findings. Furthermore, nanosilver surface-coating agents such as citric acid, amino acids, acetyl trimethyl ammonium bromide, and sodium dodecyl sulfate are noncovalently attached to nanosilver particles and can be released into the environment and biological media with or without interaction with biological macromolecules, and inorganic and organic ions make NPs unstable in media [67]. Ag^+ ions and Ag^0 are released into the media as a result of particle aggregation, surface oxidation to form silver oxide, and oxidation of silver oxide, resulting in ionic silver accumulation in the environment, biological media, and inside the cell via diffusion or endocytosis, causing mitochondrial dysfunction [68]. According to Hasse et al. AgNPs subsequently engage with cell membrane proteins, activating signaling pathways to produce reactive oxygen species (ROS), which causes damage to proteins and nucleic acids due to silver's great affinity for sulfur, eventually leading to death and cell proliferation suppression. AgNPs cause DNA damage, apoptosis, and necrosis by lowering glutathione (GSH), increasing lipid peroxidation, and activating ROS-sensitive genes in the mitochondrial pathway [69].

The possibility of nanosilver penetrating the skin when used in textiles is a source of worry. According to a study in cosmetics, the skin is semi-permeable by nature; even nanoparticles will not flow through it easily. The study conclusively proved that nanoparticles used in modern cosmetics

Table 10.5 Nanosilver-based textile products with therapeutic properties and application in various countries.

Product name	Therapeutic properties	Application	Country
T-shirt Hipster Nano Comfort	Antibacterial activity, UV protection, softness, antiodor, durable antibacterial effect, moisture elimination, thermoregulatory	T-shirt	Czech Republic
Thermal boxer briefs nanosilver	Antibacterial activity, nontoxic, antifungal activity, flexibility, breathable, sweat absorption, unpleasant odor elimination, moisture absorption	Underwear	Czech Republic
Women's fitness tank top, nanosilver-active black with strip	Antibacterial activity, flexibility, deodorization, mold resistance, lightweight, breathable, sweat absorption, durable antibacterial effect, moisture absorption	Sportswear, clothing	Czech Republic
Neckerchief nanosilvercoolmax imprinted	Antibacterial activity, deodorization, breathable, soft, sweat absorption, durable antibacterial effect	Bandana	Czech Republic
Antibacterial-Antiodor Socks	Antibacterial activity, antiodor	Socks	Iran
Klepper stretch pants	Antibacterial activity	Pant	Germany
Benita Antibacterial Chador	Anti-bacterial activity, anti-fungal activity, deodorization, microorganism removal	Chador	Iran
Nano silver thread anti-radiation fabric for veil	Radiation resistance	Headwear	China Australia

Table 10.5 Nanosilver-based textile products with therapeutic properties and application in various countries.—cont'd

Product name	Therapeutic properties	Application	Country
ASAT Elite Extreme Layer Zip Mock	Antibacterial activity, antiodor, hydrophobe	Military clothes	
Magic Tie of the 21st century	Stain resistance	Tie	Czech Republic
Youleg Nano silver 420 Den Compression Stockings Pantyhose	Antibacterial activity, anti-odor	Pantyhose	Taiwan
Premium non-iron shirts non-care	Antiwrinkle	Shirt	Japan

do not enter human skin, even when the epidermis is injured [70]. Human skin is impervious to silver nanoparticles. Ag nanoparticles on the skin surface, on the other hand, may infiltrate the skin if the barrier function of the human skin is broken. It is probable that 0.2%–2% of Ag nanoparticles will get through the skin (0.002–0.02 ppm). At these concentrations, Ag nanoparticles showed no toxicity. When nanoparticles (20–200 nm) come into contact with intact or partially injured skin, they are unable to breach the skin barrier and permeate to the lower strata, making them safe to use. Nanoparticles with a diameter of less than 10 nm could reach the stratum corneum's deeper layer, but nanoparticles bigger than 40 nm could not. Chromium, silver, TiO_2, and ZnO nanoparticles do not penetrate deeper than the stratum corneum [71,72].

It seems that the respiratory and gastrointestinal systems, as well as the skin, are the major routes of NP penetration into the body. Researches into NP toxicity are mostly conducted in vitro, and with human and animal models. Male and female rats were used in an in vivo study to test lung function, and the results showed that while the male rats in the high-dose group displayed persistent inflammation over the course of the 12-week recovery period, the female rats were able to recover gradually from the lung inflammation [73]. Mild pulmonary fibrosis and inflammation are brought on by acute and subacute exposures to AgNPs, and the ongoing production of AgNPs can result in subchronic damage responses [74,75]. Studies on animals showed that oxidative stress is involved in this process and causes lung tissue damage [76]. The rate of intracellular Ag ion release is

one of the most crucial variables that can impact AgNPs' lung toxicity [77]. Smaller AgNPs (10 nm) are more harmful to human lung cells than larger AgNPs, according to research using varied AgNP sizes [78]. The bioavailability, size, and surface of the coating, together with the duration of exposure, are some parameters that might collectively affect AgNP lung toxicity.

Previous research has shown that one of the crucial NP absorption mechanisms is gastrointestinal exposure. Assar et al. [79] investigated how intraperitoneal injections of AgNPs at various doses and for varied amounts of time affect every bodily physiological process as well as histological structure and defense mechanisms. The current study found that the first sign of AgNP toxicity was a decrease in body weight, particularly in rats given 0.5 and 1 mg compared to the control group. In a dose-dependent manner, AgNPs decreased the RBC count, Hb, and HCT in all treated groups. When compared to the control group, only the high dose-treated group's mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) measurements decreased and showed a microcytic hypochromic anemia [79].

Wang et al. [80] examined the effects of 20 nm polyvinylpyrrolidone-coated nanosilver (PVP-AgNPs) and 20 nm bare nanosilver nanoparticles (AgNPs) on the micronucleus of mouse bone marrow, as well as DNA damage and chromosomal aberration in the human hepatoma cell line (HepG2). These findings demonstrated that, to varied degrees, cell DNA damage and chromosome aberration were brought on by 20 nm AgNPs and 20 nm PVP-AgNPs. Given that the toxicity of nanosilver can be brought on by silver ions produced on the surface of the particles, the amount of silver ions released from the two types of nanosilver may be connected to this [80].

AgNPs' potential neurotoxicity is being investigated by researchers in cellular and animal models [81–84]. Hong investigated the neurotoxicity caused by polyvinylpyrrolidone- and citrate-coated AgNPs (AgSCs and AgSP). The findings revealed that the neurotoxicity caused by AgNPs varied depending on the coating and dose. Compared to AgSP, AgSC exhibited higher neurotoxicity. Metal-binding protein metallothionein (1F, 1E, and 2A) was dramatically upgraded by AgSC. This protein is important for metal homeostasis, heavy metal detoxification, and cellular antioxidative defense [85]. The degree of exposure, particle size, surface coating, aggregation state, and the kind of cell or organism employed to assess its

toxicity all have a role in the toxicological consequences of silver nanoparticles.

It has been proposed that skin exposure to NPs found in beauty goods could serve as a viable pathway for nanocarrier-based medication delivery. However, it has been discovered that skin absorption of nano-titanium dioxide in vivo and in vitro is extremely poor, typically below the detection level [86]. According to studies, the majority of NPs can enter the testis, epididymis, and seminiferous tubule in male mice reproductive tissues or organs in various ways [87]. Garcia, however, noted that there were no variations in the body and testis weights after intravenous administration of AgNPs in male CD1 mice [88].

The use of nanofinishes in textiles is completely prohibited under the 2014 version of the environmental mark GOTS (Global Organic Textile Standard) [89]. Although nanoparticles are not inherently dangerous, the Scientific Committee on Emerging and Newly Identified Health Risks has determined that there is ongoing scientific ambiguity on several aspects of their safety, necessitating a case-by-case analysis of the chemicals' safety. The type of fabric, aging of the nanoparticle functionalization process, engineering parameters used during production, prior and subsequent finishing treatments of the textile fabric, and nanoparticle type (chemical composition, form, etc.) are used to assess and determine the safety of the textile [90].

A study reported cotton fabrics which were utilized to deposit silver nanoparticles after being coated with conducting polymers, such as polypyrrole and polyaniline. However, after being coated with polypyrrole, cotton's cytotoxicity decreased, which was likely due to the removal of contaminants from neat cotton during the in situ coating technique. On the contrary, the polyaniline coating of the cotton increased the cytotoxicity of the finished product. According to an article, it was discovered that polyaniline was extremely poisonous [91]. According to numerous studies, perspiration from antibacterial fabrics depends on the fabric's quality, pH, and temperature [92–95]. Other essentials needed for functionalized nanoparticle fabrics are [96]:

1. Exhibit a preference for a certain cloth or fiber type.
2. Apply easily to textile substrates.
3. Being able to kill off harmful germs while keeping desired microorganisms unaffected.
4. Chemically inert, which means they won't harm the textile when they are processed.

5. Capable of withstanding frequent washing, dry cleaning, ironing, and long-term storage, as well as resistance to the detergents used to clean the textiles.
6. Without deteriorating into dangerous byproducts while being used.
7. Neither the user nor the environment will be negatively impacted.

Metal release levels from various materials have regularly been measured using artificial sweat. However, the makeup of sweat differs not just across people but also depending on their body area, age, season, level of acclimatization, nutrition, infection status, and amount of activity [97,98]. Initially Kulthong et al. reported that the amount of silver coating, the fabric quality, pH, and artificial sweat formulas all had an impact on how much silver leaked out of the materials into the synthetic sweat [92]. Size-dependent, surface-dependent, shape-dependent, aggregation- or agglomeration-dependent, and dose-dependent are some of the physicochemical features associated with nanotoxicology [99–105]. A study reported that physiological electrolyte content and an acidic pH invariably cause micron-scale aggregation, which can be facilitated by the creation of biomolecular coronas. Surprisingly, larger particles showed more resistance to outside stimuli than their smaller counterparts. AgNP bioactivity can be diminished or, in severe circumstances, totally eliminated by aggregation, according to research on cytotoxicity and antibacterial agents. Because it might prevent aggregation brought on by external factors and protect toxicity, biomolecular corona formation turned out to be a fundamental feature [106].

7. Conclusions and future prospective

From the above compilation it is very clear that the use of nanoparticles is not only limited to improving the looks of clothes but has also moved to specific Health perspectives. The day is not far away when medicines will be administered through clothes using transdermal routes. As nanoparticles are increasingly included into common consumer goods such as textiles, to lessen the potential risk connected with the use and application of NPs on human health, rules and restrictions are required. Prior to the development of any regulation pertaining to nanotextiles, additional research involving experts in the fields of textiles, safety and health, and toxicology is required. Silver is thought to be reasonably safe for people and is not hazardous to the immunological, cardiovascular, neurological, or reproductive systems despite being present in the body in low amounts through nutrition,

drinking water, and air particulate inhalation [107–111]. Recently, with more research being conducted throughout time, adverse consequences of AgNP exposure in animal models have been identified [112–116]. Tests have suggested that AgNPs may be hazardous to humans through mammalian toxicity studies, despite the lack of precise mechanisms and conclusive clinical trials. The liver, kidneys, and lungs are particularly susceptible to the accumulation of silver nanoparticles in the body's organs. The liver may be particularly at risk if there are silver nanoparticles present. Additionally, there may be long-term consequences from the purported buildup of silver nanoparticles in the lungs. Different mechanisms may result in exposure to AgNPs used as antibacterial drugs [117–120]. AgNPs used in filtration systems result in exposure through touch, ingestion (air filtration systems), and ingestion (water filtration systems) (antibacterial fabrics). In this chapter, functional finishes of textiles that are highly interesting due to their high potential for practical and industrial applications have been reviewed.

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CHAPTER 11

Synthesis and functional finishing of textile materials using zinc-based functional nanoparticles

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1. Introduction

Natural cotton textiles and garments are a common commodity in human life. The desirable features of cotton textiles such as breathability, durability, and biodegradability have augmented their usage in diverse areas as apparel, canvas, medical gowns, home decor, etc. [1]. Textiles are manufactured from natural polymers and an extensive range of synthetic polymers due to their exceptional fiber-forming properties [2]. However, the natural fibers, which are essentially made of cellulose and proteins, are the main causes of the growth of various microorganisms and are an ideal platform for pathogens to spread when exposed to a contaminated environment [3]. On the other hand, there is a rich source of hydrocarbons in the cellulosic fibers with low limiting oxygen index (LOI) value which can undergo immediate thermal combustion when ignited and pose a risk to life and the environment [4]. Nevertheless, continuous research efforts are being made to imparting multifunctional properties on cotton textiles, which could enhance their potential for multiple applications. In this context, the impregnation of functional nanoparticles into textiles has been the subject of research interest to impart diverse functionalities.

Progression in nanotechnology and the advent of the Industrial Revolution have synergically made a significant transition in the textile

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manufacturing sector and upgraded its legacy to a new dimension: so-called smart/technical textiles. The global market for technical textiles in 2019 was $201.2 billion and it is expected to reach $274.1 billion by 2027, with a CAGR of 5.1% [5]. The demand for technical textiles has been found across different domains, namely antibacterial, flame retardancy, medical healthcare, ultraviolet (UV) blocking, water repellency, flexible electrodes, and wearable electronics applications. When compared to their bulk form, nanoparticles offer inimitable physical, chemical, thermal, and mechanical properties by virtue of the particle size reduction [6]. The functional coatings of such nanostructured materials can produce multifunctional textiles for different practical applications. In addition, they can also provide improved durability to surface-modified fabrics as a consequence of the large surface area and high surface energy [7]. Despite their functional performance, it is essential to study and confirm that nanomodified textile finishing does not cause any hazardous effects to the wearer [3] or the environment. Second, fixation of the nanoparticles within the textile surface should be sustained and allow them to adhere [3] under practical conditions such as dyeing and laundering.

To date, several nanoparticles of metal and metal oxides have been exploited for functional coatings for cotton textiles [8,9]. For instance, silver nanoparticles have shown sturdy antibacterial activities against both Gram-positive and Gram-negative bacteria including *Staphylococcus aureus* (*S. aureus*) [10,11] and *Klebsiella pneumoniae* (*K. pneumoniae*) [11]. Nevertheless, most metal nanoparticles possess agglomeration, poor adhesion, leaching, and unstable nature, which hinder their range of applications [3]. On the other hand, metal oxide nanoparticles have shown much better performance. Al_2O_3 has displayed exceptional wrinkle resistance and flame-retardant behavior [12], and TiO_2 nanoparticles [13,14] have provided excellent protection against UV radiation. Among the metal oxides, research trials into zinc oxide (ZnO) nanoparticles have been highly investigated for textile finishing due to their unique features, namely antibacterial, superhydrophobic, photocatalytic, and UV blocking properties. The noncentral symmetry characteristics of wurtzite ZnO nanoparticles results in a piezoelectric effect, which extends its application in the domain of piezoelectric sensors and mechanical actuators [6]. The photocatalytic property enables ZnO nanoparticles to be utilized as the most effective chemical agent to degrade dyes and surfactants present in textile industry wastewater [15]. To this end, the favorable features for textile finishing such as biocompatibility, innocuous nature [7], eco-friendly, and

better air permeability [16] have increased ZnO functionality to diverse applications as illustrated in Fig. 11.1. The advantageous applications and drawbacks associated with ZnO-modified cotton fabrics are listed in Table 11.1.

Functional coating of ZnO to cotton textiles is the next foremost method to generate multifunctional textiles. The techniques, namely sol–gel [25], pad-dry-cure [26], dip-coating [27], spray coating [28], chemical bath [29], layer-by-layer (LbL) assembly [30], and electrospinning [19], have been utilized for an effective coating process. The surface modification process can be performed either by direct growth of ZnO nanoparticles or in situ synthesis of ZnO followed by deposition on the textile substrate based on the desired application. In addition, several prefatory and rudimentary strategies, namely pretreatment, neutralization, curing, functionalization, laundering, and fastness tests have been carried out in an attempt at efficacious nanoparticle fixation [28]. In this context, this chapter contextualizes the fundamentals and recent advancements in textile finishing processes for the development of standalone ZnO-functionalized textiles. Furthermore, the deposition strategies followed on

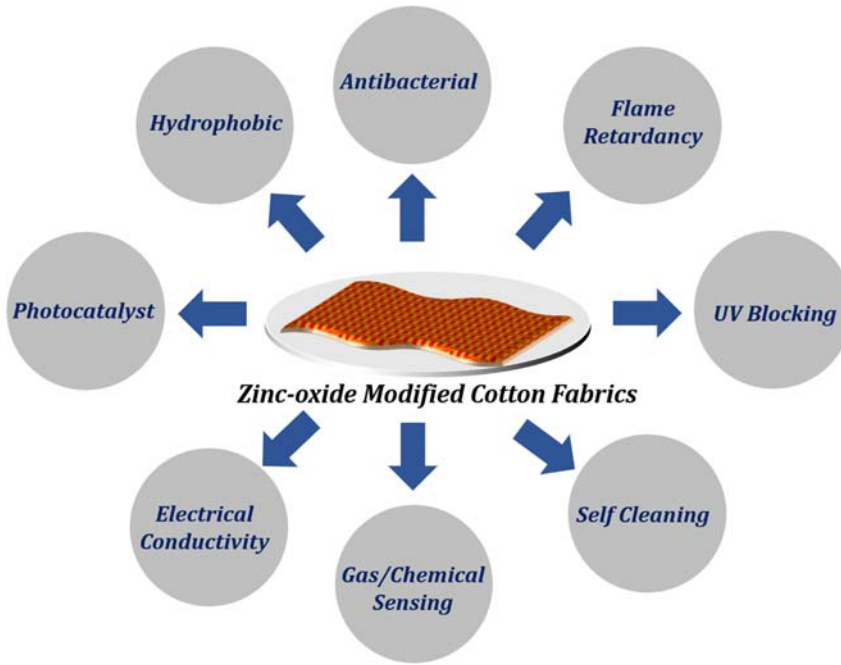

Figure 11.1 Schematic representation of zinc oxide functionalized fabrics applications.

Table 11.1 Advantages and disadvantages of surface-modified fabrics with ZnO nanoparticles.

S. no.	Description	Advantages	Disadvantages	References
1.	Nano ZnO—acrylic binder	86%—92% bacterial reduction and 90% UV blocking	Low tensile strength	17
2.	ZnO—polyester knitted fabrics	Strong antibacterial activity	Requires more cytocompatibility	18
3.	Electrospun ZnO	Excellent UV blocking	Low wash durability	19
4.	In situ synthesized nano ZnO	Antibacterial activity (>99%)	Reduced tensile strength	20
5.	ZnO—sodium dodecyl sulfate and ZnO —praepagen HY	High antibacterial and antifungal activities	Low wash durability	21
6.	ZnO-coated fabric	High antibacterial efficiency (75% —99.9%)	Lesser abrasion resistance	22
7.	Nano-ZnO	75% UV blocking efficiency and high air permeability	Low tensile strength	23
8.	CF_4 plasma-assisted ZnO fabric	High ultraviolet protection factor (>50)	Low finishing durability	24

each of the surface modification techniques and challenges associated with them also have been highlighted. The final section precisely describes the improvement in functional behavior of ZnO nanoparticles-finished cotton textiles for antibacterial applications. To this end, the likelihoods and implications of such surface-modified textiles for next-generation electronic textiles (e-textiles) are discussed.

2. Synthesis and characteristics of ZnO nanoparticles

ZnO is a direct and wide bandgap (~3.37 eV) and n-type semiconductor material coupled with a large excitation binding energy of 60 meV [15]. It typically comprises of Zn^{2+} and O^{2-} ions that are ionically bonded together to a greater extent and covalently to a lesser degree [31]. ZnO nanoparticles are most commonly found in three crystallite structures, namely cubic rocksalt, cubic zinc blende, and wurtzite hexagonal. Among these structures, wurtzite hexagonal structure (space group $P6_3mc$) is the most commonly available one due to its thermodynamically stable nature under ambient conditions [15]. For the synthesis of ZnO nanoparticles, various methods such as hydrothermal, sol–gel, microwave irradiation, microemulsion, and sonochemical have been attempted and these are discussed in the following subsections. The parameters including precursors, reagents, concentration, processing temperature and time, and pH value during the synthesis influence the size and shape of the resultant ZnO nanoparticles that are ultimately reflected in their functional performance [31]. ZnO exhibits a wide range of shapes such as nanobelts [32], nanospheres and donut-shaped structures [33], hexagonal plates [34], nanosheets [35], and nanoleaves [36] with respect to the synthesis parameters. In addition, the functional performance can also be tuned by means of doping with metal/nonmetal, other semiconductors, and nanocarbon components [37].

2.1 Hydrothermal method

The hydrothermal method is a solution reaction-based approach in which nanoparticles have been synthesized under a wide range of temperature and pressure conditions. The morphology of the nanoparticles can be controlled by varying the pressure conditions between low and high, which depend on the vapor pressure of the core composition in the reaction [38]. Talebian et al. [39] have demonstrated the morphology-dependent antibacterial action of ZnO nanoparticles against *S. aureus* and *E. coli*. From their results,

it was found that physiochemical properties of solvents, namely 1-hexanol, ethylene glycol, and water, have a significant impact on the crystal growth and exhibited different morphologies such as hexagonal rods, spheres and flower structures. In the presence of light illumination, flower-like ZnO nanoparticles with reduced crystallite size and high surface defects showed greater bacterial inactivation against *S. aureus* and *E. coli*.

On the other hand, the green biomimetic synthesis of ZnO—silver (Ag) nanocomposites assisted with the extract of *Thymus vulgaris* (*T. vulgaris*) leaf has been attempted by Zare et al. [40], wherein the synergetic impact of *T. vulgaris* and Ag inclusion into ZnO toward their antibacterial activity has been highlighted. The results of this study revealed that an increase in the concentration of ZnO-Ag nanocomposites showed substantial antibacterial action by effectively inhibiting the growth of *S. aureus* and *E. coli*. Instead of evaluating the antibacterial efficiency of ZnO nanoparticles in powder form, Alashti et al. [41] ventured to analyze its performance by depositing them onto cotton fabrics. Two batches of ZnO were synthesized, with and without the addition of a capping agent, starch, and the same has been followed for deposition of ZnO on cotton fabrics. The addition of starch made the modified surface more superhydrophobic and it exhibited substantial antibacterial action toward *E. coli*. Still, the antibacterial reaction between *E. coli* and modified cotton fabrics needs to be analyzed or investigated to formulate its performance action.

2.2 Sol—gel approach

Sol—gel synthesis is the most versatile wet chemical approach for the synthesis of various nanoparticles, which involves the colloidal solution of molecular precursors, so-called sol, transformation from a sol to a gel-like biphasic structure from the hydrolysis/alcoholysis process and subsequent solvent removal by drying [42,43]. Herein, the controlled morphology of nanoparticles can be achieved by varying the synthesis parameters, namely precursors, solvent, temperature, pH value, and so on [44]. Khan et al. [45] investigated the effect of mechanical stirring on the morphology of ZnO nanoparticles and their action against the microbial strains including *Bacillus subtilis* (*B. subtilis*), *E. coli*, and *Candida albicans* (*C. albicans*) has been evaluated through the disc-diffusion method. A significant growth inhibition of microbial strains was observed for the thorn-like ZnO sample stirred at 2000 rpm as a consequence of reduced size, which allows greater interaction with microbes and resulted in enhanced antimicrobial performance.

Silva et al. [46] examined the influence of size and surface modification of ZnO nanoparticles and their antibacterial activity through minimum bactericidal concentration assay (MBC) and minimum inhibitory concentration assay (MIC). Two strategies have been followed for the synthesis: (1) variation in reaction time and (2) surface modification with 3-glycidyloxypropyl trimethoxysilane (GPTMS). From the results, it was found that an increase in the reaction time resulted in the reduced particle size that led to enhanced bactericidal action toward *S. aureus* and *E. coli* with MICs of 0.0456 and 0.3125 mg/mL, respectively. Toward the development of self-protecting antibacterial garments, Shaban et al. [47] have employed the sol–gel and spin coating approaches synergically for textile finishing with ZnO nanoparticles. The typical surface modification process involves the preparation of ZnO sol from the sol–gel method and the various batches of prepared sol were deposited over the cotton fabric using a spin coating technique. The physical and chemical parameters including deposition cycle, precursor concentration, pH value, and doping concentration were optimized toward the uniform distribution of ZnO on the cotton surface. The antibacterial activity of treated cotton fabric at optimum conditions has shown appreciable performance against a number of bacteria including *Bacillus subtilis* (*B. subtilis*), *Klebsiella pneumoniae* (*K. pneumoniae*), *E. coli*, and *Salmonella typhimurium* (*S. typhimurium*). This is attributed to the abundance of surface defects and charges of ZnO, which may in turn inhibit the bacterial growth.

2.3 Microwave-assisted synthesis

Microwave synthesis of nanoparticles involves the direct interaction of electromagnetic waves with polar molecules or ions, leading to the alignment or orientation of dipoles of molecules as a consequence of rotational or vibrational motion and, thereby, causing homogeneous heat generation within the material [48]. The degree of energy transfer in the reaction depends on the molecules' dielectric properties, whereas the production of internal heat greatly reduces the processing time and energy requirement [49,50]. It also offers some other advantages, such as higher yield, high purity, and narrow particle size distribution [48]. The antibacterial performance of ZnO microspheres prepared with respect to the reaction time at constant microwave irradiation has been studied by Shinde et al. [51]. The formation of nanoplates to microspheres was achieved by increasing the reaction time from 1 to 5 min. It was found that the ZnO synthesized with

a reaction time of 5 min showed greater inhibitory efficacy of 95%–98% toward *S. aureus* and *E. coli* with zones of inhibition (ZOI) of 17.6 and 25.7 mm, respectively.

Ahammed et al. [52] demonstrated the synergetic effect of microwave irradiation and additive agents toward the synthesis of ZnO spherical nanoparticles. The microwave irradiation greatly reduced the particle size to 70–90 nm as compared to 580–630 nm with conventional heating. Henceforward, nanoparticles with reduced particle size have been tested in antibacterial studies against *S. aureus*, *E. coli*, *Salmonella typhi* (*S. typhi*), and *Klebsiella* spp. *SK4*. Among these, ZnO has shown high biocidal activity against *S. aureus* with a maximum ZOI of 14.5 ± 0.04 mm and a low against *E. coli* of 10.5 ± 0.04. Toward the surface functionalization with cotton fabrics, Tanase et al. [53] employed microwave irradiation to synthesize ZnO nanoparticles by varying the precursor concentration, pH stabilizer, reaction temperature, and time. The same methodology has been followed for in situ growth toward the surface functionalization of cotton fabrics. Nearly all the consequential ZnO-modified fabrics inhibited the growth of tested strains including *S. aureus*, *E. coli*, and *Candida albicans* (*C. albicans*). From the analysis, it was observed that antibacterial efficiency was effective based on the type of target strain, and the size and morphology of the synthesized ZnO samples.

2.4 Active chemical species of ZnO

The venerable attributes of ZnO such as high quantum efficiency, high redox potential, elevated electron lifetime (>10 s), and increased photosensitivity offer unique properties, making it ideal for photocatalysis application [37]. During irradiation, electrons from the valance band of ZnO get excited and transferred to the conduction band (e^-_{CB}) by leaving holes behind in the valence band (h^+_{VB}), resulting in the generation of electron–hole pairs. Herein, the simultaneous photochemical reactions, oxidation and reduction, occur at the surface of ZnO in the presence of water and dissolved oxygen molecules, which produce highly reactive oxygen species (ROS) such as •OH and $\bullet O_2^-$ radicals [15]. The whole reaction is schematically represented in Fig. 11.2A. In the photocatalytic degradation of dye molecules, the photo-induced electrons of ZnO react with dissolved oxygen molecules, which in turn produce superoxide radicals ($\bullet O_2^-$) which further undergo reaction with water and form hydroxyl

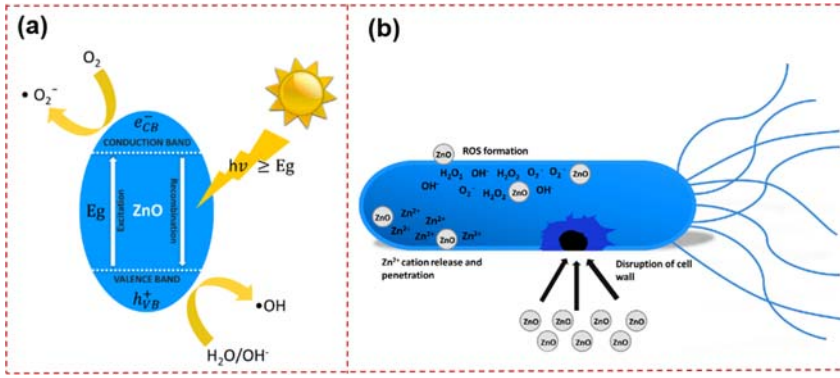

Figure 11.2 Proposed multifunctional mechanism of ZnO nanoparticles: (A) photocatalytic and (B) antimicrobial. *(Reprinted with permission from Ref. [15].)*

radicals (•OH). The hydroxy radicals tend to react with the organic dye molecules and degrade it (Eq. 11.1). On the other hand, the photo-induced positive holes in the valence band of ZnO react with water molecules and generate •OH radicals that further degrade the organic dye molecules (Eq. 11.2) [54]. The proposed photocatalytic mechanism of ZnO by Rakibuddin et al. [54] is as follows:

$$\mathrm{ZnO} + h\nu \rightarrow \mathrm{ZnO}(h^+) / \mathrm{ZnO}(e^-)$$
$$\mathrm{ZnO}\ (e^-) + \mathrm{O_2} \rightarrow \mathrm{O_2^{\bullet -}}$$
$$\mathrm{O_2^{\bullet -}} + \mathrm{H_2O} \rightarrow \mathrm{H_2O_2} + \mathrm{OH^{\bullet}}$$
$$\mathrm{H_2O_2} \rightarrow \mathrm{OH^{\bullet}}$$
$$\mathrm{OH^{\bullet}} + \mathrm{Organicdye} \rightarrow \mathrm{CO_2} + \mathrm{H_2O} \quad (11.1)$$
$$\mathrm{ZnO}(h^+) + \mathrm{H_2O} \rightarrow \mathrm{OH^{\bullet}}$$
$$\mathrm{OH^{\bullet}} + \mathrm{Organicdye} \rightarrow \mathrm{CO_2} + \mathrm{H_2O} \quad (11.2)$$

The photocatalytic behavior of ZnO is also attributed to its self-cleaning properties. The photo-induced positive holes and ROS cause direct and indirect photooxidation of the organic compounds and lead to their decomposition [55]. For an antimicrobial action, it is believed that the release of ions from the nanostructured metal-oxides reacts with the thiol group (−SH) of protein in bacteria, which makes them inactive [31]. In the case of ZnO, the generated ROS, i.e., H_2O_2 and •OH hydroxy radicals and liberated Zn^{2+} ions from the surface, are assumed to be important for the

antimicrobial action. ZnO nanoparticles can be directly absorbed to the cell surface during interaction with the bacterial cells and, as a consequence, the cell wall gets disrupted. Moreover, the generated ROS causes disruption of the cellular components via oxidative stress [15]. The exact antimicrobial mechanism of ZnO is not yet completely addressed due to multiple antimicrobial action, as represented in Fig. 11.2B.

The inconsistency in antimicrobial action of ZnO nanoparticles is most likely due to the difference in synthesis parameters and the resultant morphology. Also, it was alleged that bacteria cell wall structures also play a momentous role [15,56]. Some of the results from the attempts of ZnO antibacterial behavior include: (1) antibacterial action of ZnO is shape dependent, where nanorod structures possess enhanced activity against bacteria relative to hexagonal structures [57], (2) reduced particle size with increased surface-specific area improved the antibacterial action [58], and (3) ZnO nanoparticles cause more effective antibacterial action in Gram-positive bacteria than Gram-negative bacteria [56], whereas an increase in the exposure time of ZnO to bacterial growth medium displayed increased effectiveness against both Gram-positive and Gram-negative bacteria [59]. On the whole, it is inferred that the identification of optimal synthesis conditions are crucial to tailoring the functionality of ZnO nanoparticles. Hence, it is essential to monitor the physical and chemical parameters of the ZnO synthesis process as well as in the growth/deposition stages on cotton fabrics to impart the functional performance toward the desired applications.

3. Textile finishing of ZnO nanoparticles

Textile finishing with functional nanomaterials involves the development of protective garments with multifunctional properties to protect them from harmful UV exposure, antibacterial infection, fire hazards, and so on. Textile finishing can be classified into two broad categories: mechanical and chemical finishing. In this chapter, we have focused only on chemical finishing and discussed the same in detail. For such finishing, various chemical methods have been employed to impart the desired functionalities, along with other requirements such as durability, breathability, and repeatability. Each of these finishing methods are distinct from each other on the basis of coating and deposition practices and are discussed in the following subsections.

3.1 Pad-dry-cure

The pad-dry-cure method is the most common finishing technique for durable and uniform surface modification which entails three systematic stages: (1) padding; (2) drying; and (3) curing. At the first stage, the pristine cotton textiles are dipped into the functional sol and allowed to pass through a squeezer under constant nip pressure. Then the removal of water molecules and impregnation of nanoparticles onto the textiles are done at the drying and curing stages in the presence of constant temperature [60]. The terms "fabric pickup" and "wet pickup" are significant in evaluating the finishing efficiency, which refers to the amount of the desired chemical/finishing solution loaded onto the textiles, and the corresponding relations are represented in Eqs. (11.3) and (11.4) [60,61]. The wet pickup and effective functional coating over a large area depends on fabric properties, sol solution level, padder speed, nip pressure, and temperature.

$$\%\ \text{Pickup(PU)} = \frac{\text{Wet fabric weight} - \text{Dry fabric weight}}{\text{Dry fabric weight}} \times 100 \quad (11.3)$$

$$\%\ \text{Wet Pickup(WPU)} = \frac{\text{wt of solution applied}}{\text{wt of dry fabric}} \times 100 \quad (11.4)$$

Faisal et al. [62] demonstrated the surface modification of cotton fabrics with as-synthesized ZnO nanoparticles through the pad-dry-cure technique. The pristine cotton fabrics were immersed into a suspension of ZnO in citric acid and padded by passing through a padding mangle to enable 100% wet pick-up. The antibacterial performance was tested against *S. aureus* and *E. coli* through an agar diffusion method, where more significant bacteriostatic action was observed toward *E. coli* than *S. aureus*. Another research study by Arputharaj et al. [20] investigated the multifunctional behavior of ZnO-finished fabrics in which it showed exceptional antibacterial action against the pathogens *S. aureus* and *Klebsiella pneumoniae*. Also, it displayed a greater UPF value with an average of 40, even after 30 washing cycles. Karthik et al. [58] evaluated the various functionalities such as UV protection, antibacterial, and hydrophobicity of ZnO-finished fabrics. A green synthesis of ZnO from *Acalypha indica* was carried out and calcined at three different temperatures (100, 300, 600°C). The synthesized nanoparticles were coated uniformly over the cotton fabrics using a pad-dry-cure method. The finished fabrics with highly calcined ZnO nanoparticles possessed excellent antibacterial activity toward *E. coli* and *S. aureus*. In addition, an enhanced UPF value of 87.8 and greater

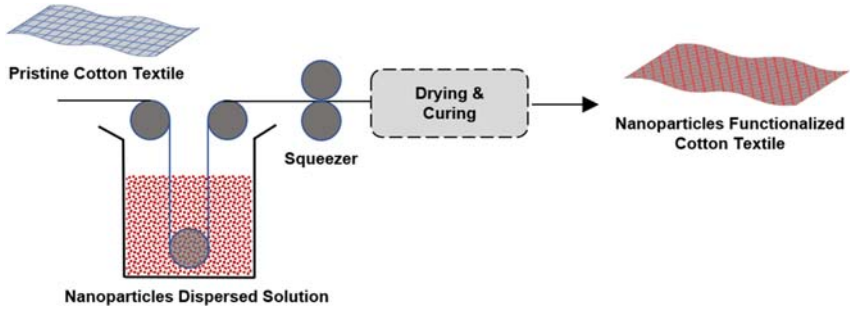

Figure 11.3 Functional coating of nanomaterials on cotton textiles using a pad-dry-cure method.

hydrophobicity of contact angle of 155 degrees were observed. A schematic representation of the pad-dry-cure process is shown in Fig. 11.3.

Yae [63] examined the functionalization of cotton fabric with ZnO/polyvinyl alcohol (PVA) and its antibacterial property. Various concentrations of ZnO/PVA were used for this study in which the optimized ratio between them was shown to have better tensile strength and antibacterial action toward *S. aureus* and *E. coli* with ZOIs of 4.77 and 3.85 mm. The increase in the concentration of ZnO in the cotton fabric increased the ROS concentration and thus penetrated the cell, leading to cell death. The addition of PVA makes the ZnO disperse homogeneously and avoid agglomeration with each other. From the above discussions, it is clearly seen that the fabric finishes using the pad-dry-cure method are utilized for various applications. However, it allows the deposition of the same chemicals/functionality on both sides and not on a single side, where an impartment of multifunctionality becomes more of an issue. For example, the outer side of a sportswear outfit has to be water repellent, whereas the inner structure has to be hydrophilic in nature to absorb sweat or water during body motion. In such a case, each side has to be imparted with different functionalities. The formulation of providing multifunctionality by mixing different chemicals as a single recipe results in undesired functionality or shortening of the expected efficiency [64].

3.2 Dip coating

The impregnation of nanomaterials by dip coating is one of the most promising approaches for uniform textile finishing. In this process, the cotton substrate undergoes surface modification through dipping into a bath solution of the desired functional nanomaterials suspension. The

viscosity of the suspension is customarily low viscous in nature, which makes the excess solution return back to the bath solution once the textile is removed. The excess functional materials over the textile surface are squeezed out using nip rolls or by a couple of doctor blades [65]. The dip coating process is schematically represented in Fig. 11.4. The advantages of this process include that there is no stress in the fabric as well as no distortion to yarn of the textiles during coating, and it therefore could be the most opted method for the deposition of aqueous-based coating solutions to any substrates [65].

Souza et al. [66] developed a single-stage process of ZnO coating onto cotton fabrics, which exhibits exceptional antibacterial action against *Pseudomonas aeruginosa* (*P. aeruginosa*) and *S. aureus*. In this process, a set of three cotton fabrics were dip coated for 1 min each with respect to the reactional solution aging time. The cotton fabric treated with reactional solution for 1 h aging time showed faster bacterial inhibition. This greater antibacterial action has been attributed to the immediate adherence of large ZnO nuclei and the presence of growth units promoting the growth of ZnO nanoparticles on the cotton fabrics. Roy et al. [27] developed ZnO-impregnated cotton fabrics for antibacterial and antifungal applications. Different mole concentrations (1, 1.5, 2, 2.5, and 3 M) of ZnO solution have been prepared in which the cotton fabrics were dipped into the solution for up to 10 cycles as the surface coating process. Among them, ZnO of 2 M concentration showed the most significant antimicrobial performance against *Aspergillus niger*, *S. aureus*, and *E. coli* and exhibited appreciable ZOIs of 14, 24.5, and 22 mm.

Muhammad et al. [67] utilized hydrothermal and dip coating for the impregnation of ZnO nanoparticles on cotton fabrics. At first, ZnO nanoparticles were synthesized by a hydrothermal method and were

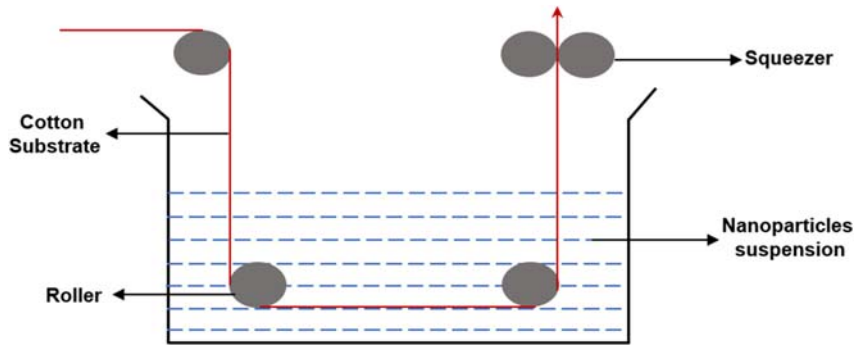

Figure 11.4 Dip coating of nanoparticles into cotton textiles.

functionalized with a coupling agent. Further, the nanoparticles were applied for the surface modification process using dip coating. The dipping of cotton fabrics was carried out with different concentration levels and dipping times. From the results, it was found that the UPF value of ZnO-modified cotton fabrics increased up to 90.9 with dipping time. Also, the surface coating of fabrics with functionalized ZnO nanoparticles showed greater ZOI as a consequence of a devastating effect on bacteria. In other work, Ran et al. [68] adopted polydopamine (PDA)-templated ZnO on cotton fabrics toward antibacterial and UV protection applications. In this work also, ZnO nanoparticles were grown on the cotton fabrics using a hydrothermal technique assisted with dip coating. The PDA-templated cotton fabric was dipped in ZnO seed solution and squeezed using a rubber roll and dried. Then, the seeded cotton fabric was immersed into the ZnO growth solution for 5 h at 90°C and the resultant fabric was rinsed and then dried for the proposed application. PDA-templated ZnO cotton fabrics showed a 99% reduction in bacterial load against *Gluconobacter cerinus* (*G. cerinus*). Even though functional coating through dip coating is easier, it is quite unpopular in the surface modification process and, moreover, an additional technique such as hydrothermal and exhaust dyeing is needed for effective deposition.

3.3 Electrospinning

Electrospinning is a well-known technique to produce ultrafine one-dimensional nanofibers. In this process, a high static voltage has to be applied to the capillary solution which contains polymer and a strong electrostatic force has been induced on that, leading to the formation of a "Taylor" cone at the nozzle edges. From the Taylor cone, a fiber jet is ejected when the applied electric field strength breaches the surface tension of the subjected liquid. The solvent(s) in an ejected fiber jet gets evaporated while allowing through atmosphere and leads to the deposition of a solid polymer fiber mat on the collector. Neamjan et al. [19] investigated the effect of various shapes of electrospun ZnO on cotton fabric toward the UV protection performance. Different structures of ZnO were obtained by altering the synthesis parameters and those nanoparticles were added to the PVA to prepare a homogeneous solution. The resultant ZnO/PVA solution was subjected to electrospinning at the optimized deposition conditions, where three different ZnO/PVA fiber mats were coated over the cotton fabrics. From the results, it was found that all ZnO nanofibers

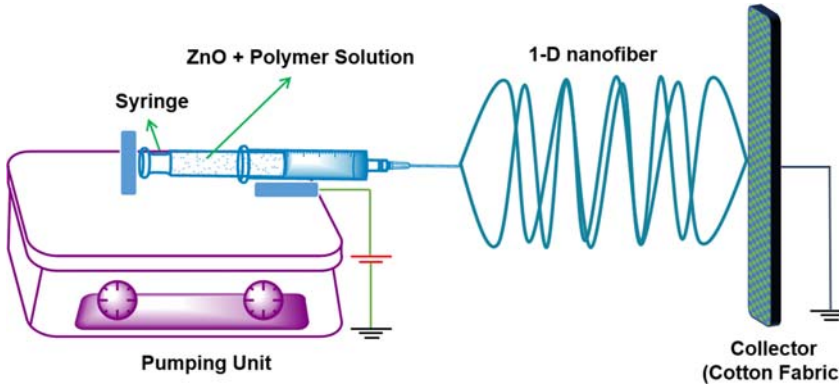

Figure 11.5 Electrospinning of ZnO nanofibers to the cotton fabric.

exhibited greater UV-blocking ability, especially in the UV region of 250–315 nm. The process set-up for electrospinning is shown in Fig. 11.5.

Instead of using cotton fabric, Li et al. [69] used cotton cellulose directly for the preparation of a one-dimensional fiber substrate to embed ZnO nanoparticles on it. At first, cotton cellulose was added to the N,N-dimethylacetamide solution of lithium chloride and then stirred at 80°C for a homogeneous mixture, prior to electrospinning. The homogeneous solution is electrospun at constant applied potential and the subsequent nonwoven cotton fabric collected by a rotating mandrel in the collector side. The nonwoven nanofiber fabric then underwent seed layer growth of ZnO and was immersed into the precursors of ZnO for further growth. The ZnO-impregnated cotton nanofibers showed high absorption toward the wavelength of 350 nm, which implied its UV-blocking performance. Similarly, Zhang et al. [70] followed the same methodology with the slight modification of adding copper sulfate (CuS) at the final stage in the preparation of ZnO/CuS nanocomposite fiber fabric for photocatalytic application. The nanocomposite fiber fabric exhibited remarkable photocatalytic action against methylene blue (MB) dye due to direct interfacial charge transfer phenomena. From all the above discussions, it is clearly seen that the development of free-standing nanofiber fabrics is quite possible with the aid of electrospinning. Also, the electrospun ZnO cotton fabrics have not so far been reported for antibacterial activity. Because of the availability of multiple polymers and the choice of further optimization in process parameters, various attempts have to be made toward the realization of ZnO-impregnated fabrics for multifunctional applications including antibacterial function.

3.4 Layer-by-layer (LbL) assembly

LbL assembly is a unique surface finishing approach in which sequential adsorption of oppositely charged materials (i.e., cations and anions) in an adjacent manner leads to an ultrathin layer of polyelectrolyte nanocomposites [71]. The basic principle behind such effective deposition is the electrostatic interaction between those charged materials. In this process, the substrate subjected for surface modification gets immersed into the cation and anion solutions, alternately. In the intervals of each layer adsorption, the layered surface is immersed into a washing solution. The same cycle is repeated until the desired multilayer deposition is achieved [30,71]. A schematic representation of LbL deposition is shown in Fig. 11.6. The LbL assembly technique offers a wide range of opportunities to incorporate various functional molecules including dyes, charged nanoparticles, proteins, and so on within the multilayers. A relatively very few studies have analyzed the possibilities of utilizing the LbL technique toward the deposition of ZnO nanoparticles on cotton textiles [72,73].

Ugur et al. [30] attempted to improve the antibacterial and UV protection properties of cotton textiles with the aid of multilayer ZnO nanoparticles using an LbL assembly technique. For the initial adsorption, the surface of the cotton fabric should be charged. Henceforth, the cationization of fabric has been performed to generate cationic sites on the surface by treating it with an aqueous solution of 2,3-epoxypropyl trimethylammonium chloride (EP3MAC). Then, the resultant cationic fabrics

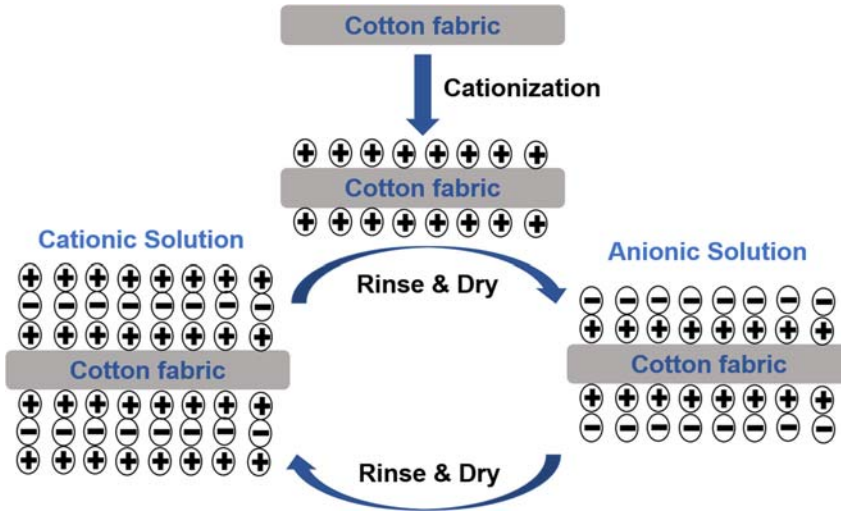

Figure 11.6 Layer-by-layer assembly of ZnO on cotton fabrics.

(positively charged) were immersed into the anionic ZnO colloidal solution, deionized water, cationic ZnO colloidal solution, and again with deionized water, consecutively. This adsorption process indicates one complete cycle which was repeated for 10 and 16 multilayer depositions. Finally, the ZnO multilayered cotton fabrics were dried at 60°C and cured at 130°C prior to the characteristic study. From the results, it is clearly seen that the antibacterial activity of the treated fabrics was increased toward *S. aureus* with an inhibition zone of 1.2 and 1.3 cm, for the increase in layers of ZnO to 10 and 16 on the fabric surface, respectively. Also, the same was reflected in the UV-blocking characteristics with an enhanced UPF value for the increased multilayers of ZnO. Owing to this, nanocomposite-layered cotton textiles have been developed to be utilized for a protective clothing application. As with electrospinning, the attempts at ZnO-functionalized fabrics by LbL assembly have been less pronounced. Hence, further attempts at surface modification using this approach could be helpful for the development of layered ZnO fabrics.

4. Conclusions, opportunities, and future trends

Textile finishing is an imperative tool to impart multifunctionality into cotton fabrics for the development of technical textiles. Undoubtedly, there have been continuous research efforts over the years to develop multifunctional textiles with durable, efficient, breathable, and biocompatible properties. The future trend of high-performance textiles implies the need for chemical finishes to meet the multifunctional requirements. From the existing literature reports, it is clear that textile finishing with nanoparticles will improve the performance of the finished products. In this regard, the potency of ZnO nanoparticles toward their antibacterial activity has been overviewed in this chapter. Also, the synthesis and finishing techniques so far have been made to develop technical textiles with multifunctional properties have been discussed. The generation of reactive oxygen species, shape and morphology of nanoparticles, and the nature of target bacteria are the key findings to evaluate the antibacterial performance. The antibacterial assessment clearly proved that microbial growth in a medium is greatly inhibited by ZnO-functionalized cotton fabrics. However, the exact mechanism for antibacterial action is not clearly understood and all the reported mechanisms are proposed anonymously. Henceforth, further insights to analyze the bacterial inhibition process are vital to developing protective garments to safeguard humans from a bacteria-contaminated environment.

To date, multiple finishing methods have been evolved for the modern industry for the development of multifunctional textiles. It is noteworthy that certain challenges remain in each of the finishing techniques to meet the requirements of target application as well as customer demand. Also, the antibacterial action of ZnO nanoparticles has shown more inhibition of Gram-positive bacteria than Gram-negative bacteria. Hence, there are large potential opportunities available to overcome these obstacles by upgrading the existing nanoparticles via functionalization with other nanoparticles, and through the use of new auxiliaries and dispersing agents. Likewise, the essential features like durability, compatibility, stability, and air permeability could also be increased. These features are required for protective garments like medical gowns, bed linen, and ultraviolet filters, which should be comfortable for the wearer. Continuous efforts on the improvement of ZnO nanoparticles in combination with other organic and inorganic materials may synergistically pave multifunctional properties to the resultant nanocomposite structures.

Concerns over exposure to harmful microbes, UV light rays, toxic gas/chemicals, and so on, have augmented the burgeoning of self-protective garments in the current lifestyle scenario. Owing to the advancements in nanotechnology and textile industry standards, functionalities of nanoparticle-finished fabrics will be further advanced in the future. Undeniably, the perception of cotton fabrics toward simple apparel will definitely be transformed into flexible and wearable garments for multifunctional applications. The textile finishing of cotton fabrics with nanocomposite materials of a multifunctional nature will be the forerunner for the emergence of nanoengineered textiles for diverse applications such as textiles-based supercapacitors, gas/chemical sensors, and triboelectric and piezoelectric nanogenerators. Together with the progression in nanoparticles and nanofinishing methods, sophisticated and innovative multifunctional smart textiles can be developed.

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CHAPTER 12

Antimicrobial textiles based on nanoparticles and composite, antiviral and antimicrobial coatings based on functionalized nanomaterials

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1. Introduction

Nanomaterials must have a dimension between 1 and 100 nm [1]. The term "nano" is derived from the Greek "nanos" and Latin "nanus" meaning "dwarf," which relates to their small size, but scientifically "nano" means one in a billion [2]. The properties nanomaterials display are mainly due to the nanometer size of the material [3]. When compared with bulk materials, their nano size provides them with the large surface energy with fewer imperfections [4]. Nano dimensions provide a high surface area to volume ratio with a high volume of surface atoms, leading to the "surface"-dependent properties of the nanomaterial [5]. Nanomaterials research approaches nanotechnology from a materials science perspective, leveraging advances in materials metrology and synthesis developed to support microfabrication research. Nanoscale materials frequently have unique optical, electronic, thermophysical, or mechanical properties. Because of their distinctive chemical and physical properties, such as a vast surface ratio and significant mechanical strength, they play a crucial role in the fabrication of many devices and made amendments.

Facile synthesis of nanomaterials and their easy integration with current technologies have resulted in advancement of nanoscience in the last few decades. Nanoparticles are complex molecules composed of three layers:

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(a) the surface layer, which has the ability to be functionalized with various other molecules, metal ions, plant extracts, surfactants, biomolecules, and polymers, (b) the shell layer, which is different material from the core in all chemical aspects, and (c) the core, itself known as nanoparticles and consisting of the central part of the nanomaterial [6]. Nanoparticles can be categorized into various classes. The categorization depends on their physical, chemical, and biological properties. Based on the physical and chemical characteristics, some of the well-known classes of nanoparticles are carbon-based nanoparticles, nanocomposites, metal nanoparticles, and polymeric nanoparticles [7]. When one type of nanoparticle is combined with another nanomaterial or bulk-type material, it is known as a nanocomposite. Nanomaterials are classified on the basis of their dimensions also. On the basis of their dimensions, we can divide them into four types, which are 0D (solid nanoparticles, nanoparticles, and quantum dots), 1D (nanowires, nanorods, fibers, and carbon nanotubes), 2D (layered nanostructured sheets, films, patterned surfaces, and coatings), and 3D (pillars, electrochemical system, MEMS devices, 3D composites, and polycrystals); zero-dimensional nanomaterials are basically nanoparticles [8].

These remarkable physical properties result in a wide range of applications such as metallic nanoparticles can be used as very active catalyst [9], and nanoparticles and nanowires are used to enhance the sensitivity and sensor selectivity of chemical sensors [10]. Nanomaterials are used in different areas, which are nanofabrics, cosmetics, drugs and medicines, biosensors, defense and security, imaging, cancer treatment, catalysts, packaging, health care, and electronics [11]. Recently, high-quality filters have been prepared using nanostructures capable of removing particulates which are as small as a virus [12].

Leveraging advances in materials metrology and synthesis lead to the developments in support of microfabrication and textile research. The unique properties of nanomaterials impart textiles with features like water repellence, wrinkle resistance, UV protection, soil resistance, antibacterial, antiviral, antistatic, improvement of dyeability, and self-cleaning fabrics. Among these, the antimicrobial and antiviral properties are of major importance for the textile industry. Antimicrobial and antiviral textiles may kill or inhibit the growth of microorganisms and viruses on the surface of fabrics or inhibit the formation of biofilms, reducing the risk of infection that may be created by using functionalized nanoparticles [13]. Antimicrobial textiles are high-performance textiles, with the potential to either kill or inhibit the growth of microorganisms on their surfaces. Textiles with

antimicrobial properties show a wide range of applications such as in air filters, water purification, storage, curtains, healthcare fabrics, wound-healing bandages, food packaging materials, hygiene, and sportswear [14]. Fig. 12.1 depicts the journey of textiles from natural fabrics to functionalized fabrics.

As per the available literature, small-sized nanomaterials exhibit remarkable and extraordinary properties, extending their use to numerous applications. Nanoscience has also benefited the areas of textiles and apparel. The utilization of nanomaterials in the textile field is described in Table 12.1.

Organic UV blockers are less stable than metal oxides when it comes to blocking UV radiation. The increase in surface area and absorption in the UV range of nano-ZnO has led to improved UV-blocking properties. Zinc oxide nanoparticles are more economical and effective than nanosilver when it comes to antibacterial finishes. Titanium dioxide and zinc oxide are also used to impart antibacterial properties. Metal ions and metal compounds have antimicrobial effects. It is believed that some of the oxygen in the air and water is converted into active oxygen by catalytic action with metal ions, dissolving organic matter, and exerting a bactericidal action.

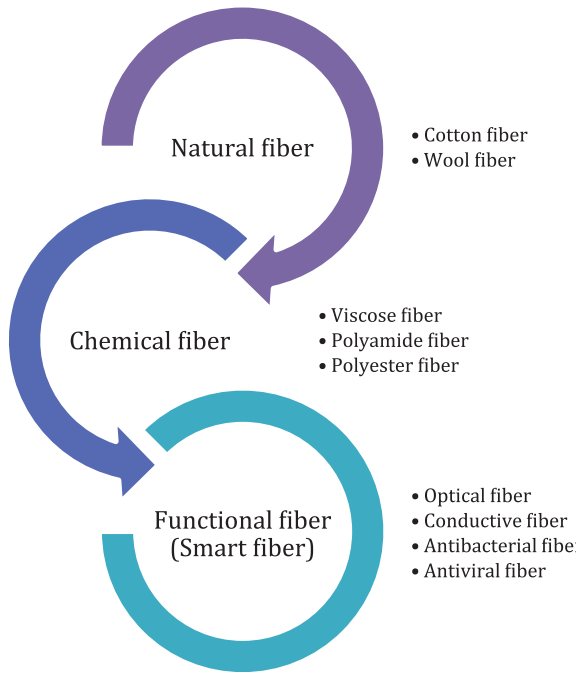

Figure 12.1 :Journey of textiles from natural fabrics to functionalized fabrics.

Table 12.1 Utilization of nanomaterials in textiles.

S .no.	Nanomaterials	Functions	References
1.	Aluminum oxide	Flame retardant and resistant to abrasion	[15]
2.	Silicon dioxide	Hydrophobic and dirt repellence	[16]
3.	Zinc oxide	UV protection, antistain, self-cleaning, antimicrobial property	[17]
4.	Silver	Antibacterial properties	[18]
5.	Graphene-gallium	Smart e-textile	[19]
6.	Gold	Antibacterial and antifungal	[20]
7.	Zinc oxide and titanium dioxide	UV protection	[21]
8.	Copper and copper oxide	Antibacterial properties	[22]

The nanomaterials such as carbon nanotubes, bio-based nanomaterials, and metal nanoparticles (Ag/Au, TiO_2, ZnO and CuO) show their use in textiles to enhance textile utility and properties like conductivity, hydrophobicity, antimicrobial activity, increased strength, self-cleaning, etc. Although nanoscience has had a huge positive impact in the textile industry there remain some challenges that need to be addressed. Scalability, manufacturing cost, stability, biocompatibility, and toxicity of the nanomaterials should to be evaluated for environmental safety and consumer safety. In this chapter we have summarized the types and utility of nanomaterials in various fields with a focus on their use as antibacterial and antiviral agents. The functionalization of nanomaterials for enhancement of biological properties and their incorporation in the textile industry along with their future perspectives are also discussed in the chapter.

2. Types of nanomaterials and their applications

Nanomaterials can be classified into four types, which are inorganic-based nanomaterials, organic-based nanomaterials, carbon-based nanomaterials, and nanocomposites. Fig. 12.2 shows different types of nanomaterials.

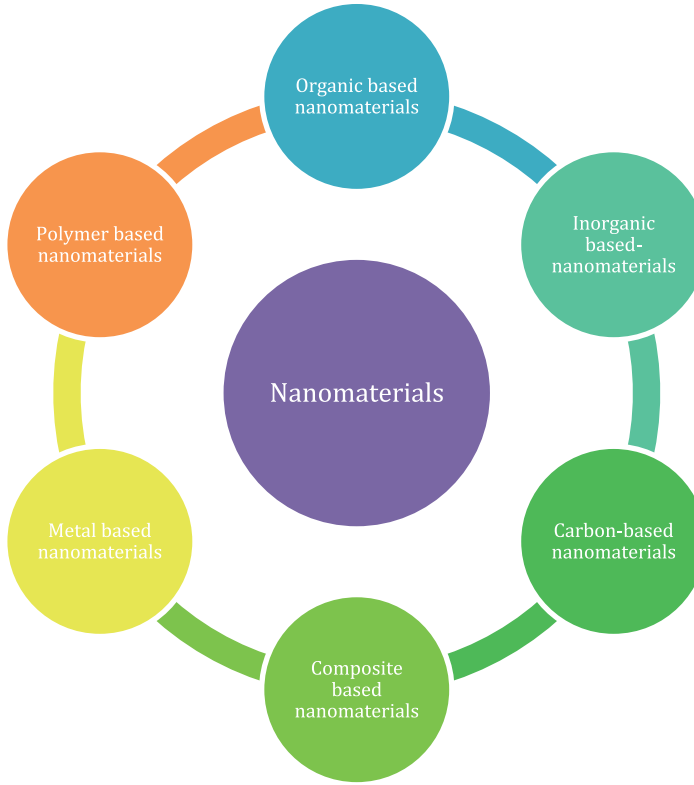

Figure 12.2 Different types of nanomaterials.

Inorganic-based nanomaterials are those formed when a metal and a nonmetal element take the form of an oxide, hydroxide, chalcogenide, or phosphate compound [23]. Nanoparticles may be used for various applications such as nano zinc oxide as an antibacterial additive, iron oxide nanomaterials as hyperthermia agents and MRI contrast agents [24,25], and quantum dots as bioimaging contrast agents. The properties of organic nanoparticles like biocompatibility, biodegradability, and ease of surface modification, lead to their application in drug administration and therapeutic applications in humans [26]. Polymeric nanoparticles are the most prevalent organic nanoparticles, with a size below 1000 nm [27]. Polymeric nanoforms have properties which make them useful for medical applications [28]. Carbon-based nanomaterials are composed of carbon, and include fullerenes, graphite and its derivatives, carbon nanotubes, etc. [29]. Carbon-based nanomaterials are utilized in different forms for various

purposes, including as an antimicrobial agent, water disinfectant, antimicrobial surface coating, slow-release fertilizer or pesticide, and in the delivery of therapeutics, biomedical imaging, biosensors, tissue engineering, and cancer therapy [30].

The carbon-based composite nanomaterials embedded in ceramic, metal, or polymer materials also show a wide range of applications, such as drug deliveries, imaging, biosensors, and medical implants [31]. The nanocomposites of carbon nanotubes, iron oxide nanoparticles, gold nanoparticles, mesoporous liposomes, dendrites, micelles, and quantum dots may be used as nanocarriers. The multifunctional composite nanomaterial is used for magnetic/electric purposes, textile engineering, biomedical engineering, and in sensors [32,33]. There are many advantages of nanomaterials in composite material, viz., chemical resistance, thermal conductivity, thermal expansion, dimensional stability, gas barrier, synergistic flame retardance, enhanced mechanical properties (tensile) strength, stiffness (toughness), etc. [34]. Various biomedical applications of nanomaterials are shown in Fig. 12.3.

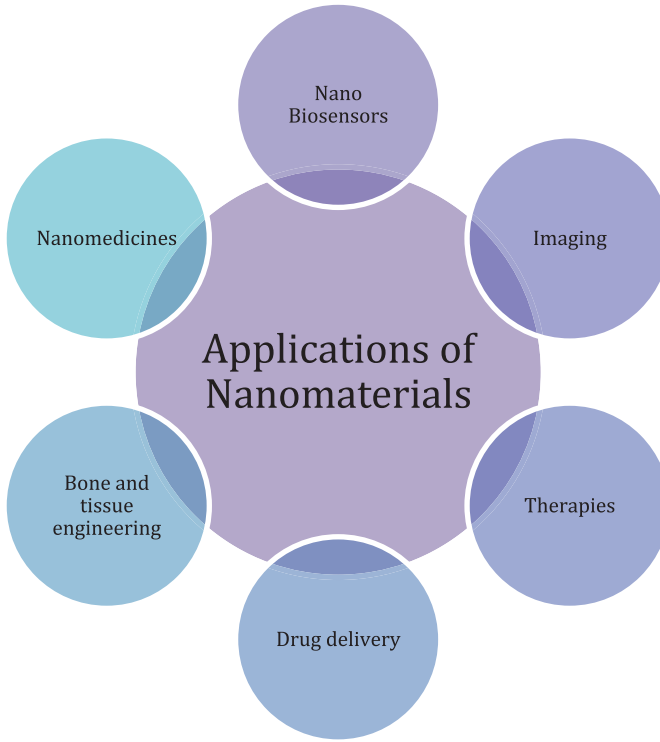

Figure 12.3 Various biomedical applications of nanomaterials.

Further, nanocomposites are divided among three matrix-based nanocomposites, which are polymer—matrix or metal—matrix nanocomposites or ceramic nanocomposites [34]. Metal—matrix nanocomposites contains metal(s) as the matrix (this can be aluminum, magnesium, iron, and copper) and ceramic as reinforcement (something added to provide more strength or support). It can be of two types, organic and inorganic, organic reinforcement includes Redmond and fly ash, while inorganic reinforcement includes oxides, nitrides, carbines, bromides and others. They are mainly used in the automobile and aerospace industries due to their advanced features like mechanical strength, sustainability, light weight, flexibility, simplicity, and recyclability [35]. Ceramic—matrix nanocomposites are those that comprise ceramics as a matrix (oxides, carbides, nitrides, phosphate, carbonates, silicate, and halides) reinforced with ceramic/metal fibers (metal, glass, ceramic, and polymer). They have matrices of alumina, calcium aluminum silicate (CAS), and lithium alumina silicate (LAS). They have high strength and thermal stability. Some of their important properties include tensile and compressive behavior, fracture toughness, fatigue resistance, corrosion resistance, higher chemical stability hardness, and lightweight [34,36].

Polymer matrix composites (PMCs) are composite materials composed of a large number of short or continuous fibers held together by a matrix of polymers. PMCs are designed to transfer loads between the fibers of the matrix. Polymer—matrix nanocomposites are materials consisting of fibers that are embedded in a polymer matrix. They are used in materials to enhance their properties. Fig. 12.4 describes the types of nanocomposite

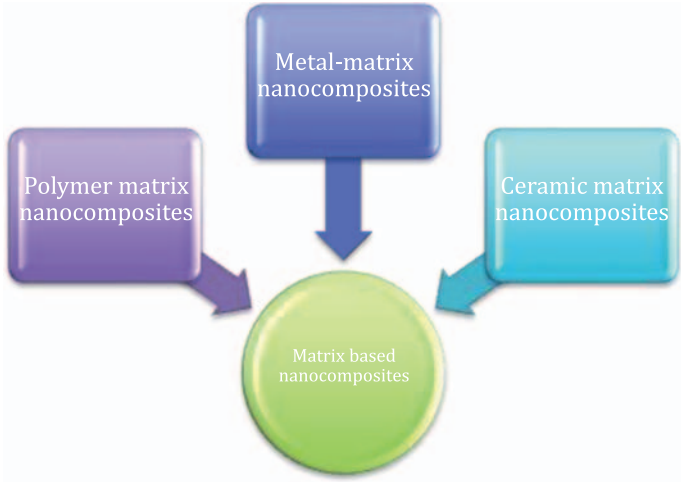

Figure 12.4 Various types of nanocomposite materials.

materials. In polymer—matrix composite, the matrix phase is known as a continuous phase, whereas the reinforcement phase is a discontinuous phase. Some of the factors which affect the properties of the polymer—matrix composite are their proportions of composition, the geometry of reinforcement, and the type of interphase used. The aim of preparing polymer—matrix composite is to provide strength, thermal expansion, thermal stability, stiffness, great toughness, and corrosion resistance. They are used for various applications in the automotive industry, aircraft industry, aerospace industry, marine, biomedical application, and industrial areas [35,37]. Among these, biomedical applications are of great demand and necessity.

Coating is an important part of various products and a variety of coating materials as well as methods are used to provide protection and other structural properties [38]. Nanocoating not only reduces pollution, in comparison to regular hairspray, nano-hairspray is required only in one-tenth of the amount, hence saving material through using these ultra-thin coating materials. Reduced use of solvents and other toxic compounds in paints and lacquers also helps in reducing pollution. Nano-coated surfaces are easy to clean or self-cleaning, thus reducing energy and detergent consumption [39]. Nano-coating on mirrors, bricks, glass, metal, wood, timber, paint, tiles, and textiles provides the product with aesthetic value, speedy drying, transparency, antifouling, fire-retardance, elasticity, corrosion-free, self-cleaning, high conductivity, hydrophobicity, excessive water vapor permeability, and antimicrobial activity water repellence, etc. [39—42].

2.1 Carbon-based nanomaterials

Nanomaterials made of carbon are incredible scientific advancements with distinct characteristics (high mechanical strength, high conductivity, attractive optical properties, chemical versatility, etc.). Among them, graphene and carbon nanotubes are the ones utilized in chemical analysis most frequently [43]. Nanomaterials fabricated from carbon include fullerenes, carbon nanotubes, graphene and its derivatives, graphene oxide, nanodiamonds, and quantum dots which are products of carbon. These materials are highly sought-after in many disciplines, including biological applications, thanks to their extraordinary thermal, mechanical, structural, electrical, optical, and chemical properties. Recently, emphasis has been on the imaging of cells and tissues, because of the delivery of therapeutic molecules

for the treatment of disease and tissue repair. Carbon-based nanomaterials are suitable as imaging agents for tumor diagnosis thanks to the wide range of one-photon characteristics, the ease with which they can be functionalized, and their biocompatibility. Deep tissue imaging is possible thanks to carbon-based nanomaterials' special two-photon fluorescence characteristics within the near-infrared region of wavelengths. The significant developments in carbon-based nanomaterials are discussed in the literary analysis by Patel et al. [44]. A carbon nanotube is a tube-like structure with a diameter in the nanometers. These nanotubes can single-walled or multiwalled. Single-walled carbon nanotubes are carbon allotropes having nanometer range diameters and a structure which is transitional between cages of fullerene and flat graphene. Carbon nanotubes (CNT) are also known as the generation of nanoprobes with important applications in biosensing. This may be attributed to their exceptional optical, mechanical, and electrical properties [45]. Because of their large aspect ratio, high conductivity, great chemical stability, and sensitivity, they are remarkably well suited for biosensing applications. The cornerstone of CNT-based biosensors is the immobilization of biomolecules on their surface, which enhances identification and the signal transduction process [46]. Based on their methods for identifying and transducing targets, CNT-based biosensors are primarily categorized into either electronic/electrochemical biosensors or optical biosensors. Due to the remarkable capability of CNTs to improve electron transport, they have been found to be appropriate for a combination of electrochemical and electronic biosensors [47].

2.2 Inorganic-based nanomaterials

Inorganic nanoparticles are reported as biocompatible, extremely stable, nontoxic, and hydrophilic in nature when compared with organic materials. Due to their biocompatibility and ease of control over the distribution of their size and shape, which can include spheres, nanorods, and cubes, among other shapes, gold nanoparticles have been extensively explored. Additionally, the addition of many polymers, antibodies, small-molecule therapies, and molecular probes can easily change the surface chemistry of AuNPs [48]. Iron-oxide nanoparticles (IONPs), another popular form of INP, have been employed extensively for medicinal and diagnostic purposes since the 1960s. Several IONPs have received FDA approval to date for use in therapeutic and imaging procedures. Magnetite (Fe_3O_4) nanoparticles exhibit their application in magnetic resonance imaging (MRI) due

to exceptionally low cytotoxicity, magnetic reactivity, and MRI contrast-enhancing capacity [49]. The incorporation of Ag nanoparticles into TiO_2-NTs has shown their used as Ti implants. The incorporation was done by a simple method of $AgNO_3$ immersion and UV irradiation. Ag nanoparticles adhere to the length of the inner surface of the nanotubes. The size and quantity of the Ag nanoparticles are controlled by changing the immersion time and concentration of $AgNO_3$ [50]. Another example is gold nanoparticles which can be used for coating samples for SEM analysis to improve the electron stream and thus obtain a high-quality image. Various synthetic methods can be adopted to prepare metal nanoparticles. These synthetic methods include chemical and electro/photochemical methods. In the chemical method, generally, metal ion precursor reduction is done in solution form with the help of reducing agents to obtain metal nanoparticles. Metal nanoparticles have the remarkable ability of adsorption of small molecules. Thus, metal nanoparticles can be used in a wide range of applications in areas such as biosensing, bioimaging, antimicrobial agents, waterproofing agents, biomolecular detection, and other environmental and bioanalytical applications [1,23,48].

2.3 Organic-based nanomaterials

Organic nanoparticles are materials with two dimensions or more with sizes ranging from 1 to 100 nm. Distinct size-dependent physio-chemical properties of organic nanoparticles lead to their usage in optical science, magnetism, catalysis, physics, and electrochemistry. The composition, size, and shape of a nanoparticle are also responsible for its specific properties. Organic nanomaterials consist of peptides, liposomes, proteins, micelles, and dendrimer-based material. A dendrimer is a highly branched manmade polymer (<15 nm) with a recognized layer structure of the central core, inner region, and different end groups confirming the character of the dendrimer. Organic-based nanomaterials such as liposomes, micelles, and polymer nanoparticles have been developed. Liposomes are a type of lipid-based nanomaterial that has an aqueous core surrounded by a phospholipid bilayer. As a result, this structure is amphiphilic and allows the formation of a thermodynamically stabilized vesicle [51]. Phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), and phosphatidylglycerol (PG) are some of the most common phospholipids found in liposomes. Additionally, stabilizers such as cholesterol are frequently included in liposomes to increase their stability. Liposomes have been

shown to improve the permeation of hydrophilic drugs, and protect peptides and other protein-based drugs from harsh conditions such as stomach acidity, and improve drug bioavailability [52].

2.4 Composite-based nanomaterials

Nanomaterials with a composite structure comprising of two or more nanoscale components provide unique physical and chemical properties to composite materials. Due to these unique properties of composite nanoparticles, they exhibit a wide range of applications. On the basis of their structural properties, composite nanoparticles can be categorized as (a) hybrid, (b) core/shell structured, and (c) multifunctional quantum nanoparticles [53]. A nano-reinforcement material disperses into the substrate and thus provides better hardness, tensile strength, optical properties, dielectric, mechanical, electrical, and thermal properties, and also resistance to heat, abrasion, and damage [54].

2.5 Polymer-based nanomaterials

Polymer nanoparticles are one kind of organic nanoparticle and the processing method applied for their preparation results in either nanocapsules or nanospheres. Nanospheres have a matrix system with a core—shell morphology. The active ingredient is generally trapped or encapsulated and surrounded by a polymeric shell [55]. Biocompatibility, drug protection, controlled release, and ease to form composites are a few advantages of polymer nanomaterials. The addition of nano-sized clays to polymeric products improves their mechanical, thermal, and other properties for use in diverse applications such as automotive parts, textiles, and packaging materials [56].

3. Synthesis and characterization

There are two synthetic approaches that are generally used for producing nanomaterials: (a) top-down approaches and (b) bottom-up approaches. The top-down approaches include sputtering, etching, ablation, mechanical edging, milling, etc. [57]. Mechanical milling can be used for the cost-effective production of nanomaterials and is very useful for nanocomposite production. The oxide- and carbide-reinforced aluminum, nickel, magnesium, and copper-based nanoalloys have been reported to be synthesized via a top-down approach. Carbon nanomaterials produced with the help of pearl milling have been found to be very useful in energy storage, environmental remediation, and energy conversion [58].

The bottom-up approach is another method for nanomaterial synthesis. Methods such as chemical vapor deposition (CVD), solvothermal, hydrothermal, precipitation, and sol–gel are a few excellent techniques for the synthesis of nanowires, nanotubes, nanorods, nanosheets, graphene, nanospheres, etc. [57,59–63].

Electrospinning is one of the methods for producing nanomaterials, particularly polymers [60]. Coaxial electrospinning is a kind of electrospinning consisting of two coaxial capillaries for preparing ultrathin fibers [60,61]. This method is also useful for producing different types of polymers like core–shell or hollow, and also for the synthesis of inorganic and organic composites as well as hybrid materials [55,61].

The application of nanomaterials in the textile industry to create smart and high-performance textiles essentially needs controlled size, shape, dispersion, and deposition on the textile substrate. Thus, the characterization of nanomaterials becomes an important factor. Techniques such as scanning electron microscopy (SEM), tunneling electron microscopy (TEM), atomic force microscopy (AFM), X-ray and neutron diffraction, X-ray scattering, X-ray photon spectroscopy, particle size analyzer, Raman, UV-vis, and FTIR spectroscopies, etc. are quite useful in determining the size, shape, morphology, and other critical properties [57,62,63].

4. Antimicrobial and antiviral potential of nanomaterials

Recently, it has been observed that there is increased resistance of bacteria to current antibiotics and antibacterials, leading to an urgent requirement for new antibacterial agents. Nanomaterials have been found to have antimicrobial and antiviral [64,65] potential, which may be attributed to their nanoscale and inflated surface area, high stability, sustainability, and heat resistance. Various types of metal-based nanomaterials with antimicrobial properties such as Cu, Zn, Ti, Mg, Ag, Au, etc. have already been reported [66]. Previous reports suggested that carbon-based nanomaterials (like SWCNTs, graphene oxide, and fullerene) and polymeric materials have potential antimicrobial properties [65,66].

This perspective of nanomaterials has attracted researchers to further explore their potency as antimicrobial and antiviral agents. Antimicrobial materials may be described by their activity against organisms, i.e., antibacterial potential and antifungal activity. Numerous antimicrobial materials may furthermore act against microscopic organisms and infections at the

same time. A few chemicals are additionally required to target a wide diversity of organisms and are ordinarily described as antimicrobial. In common open spaces such as restaurants or trains this type of cloth is greatly demanded, e.g., for towels cleaning cloths, shades, and carpet can be a source of infection. Nanoparticle-based coatings are widely used in authentic and counterfeit goods. Silver nanoparticles (AgNPs) exhibit activity toward a wide variety of microbes but not toward human cells. Silver (Ag) nanomaterials are well known for their established antimicrobial activity. Nanostructured inorganic/metal materials may be utilized for the development of antimicrobial textiles/fabrics.

To prevent the spread of viral diseases, recently, nanocomposites have been reported as effective antimicrobial filters for air purification. Nanomaterials have been used as antiviral agents. The antiviral potency of nanoparticles is due to the inhibition of viral replication [67]. The antiviral action of nanomaterials depends on the type as well as the form of the nanoparticles. Contamination of surfaces is majorly responsible for the spread of viral diseases. Thus, significant attention should be given to the development of antiviral and antibacterial surfaces [68]. using the surface properties of nanoparticles may potentially help in controlling viral spread, and these nanoparticles can be used as antiviral agents.

Nanoparticles have potent antimicrobial properties. When nanoparticles are exposed to bacterial cells, they can cause membrane damage due to nanoparticle adsorption, which is sometimes followed by cell penetration [69]. Adsorption of nanoparticles causes cell wall depolarization, which modifies the wall's normally negative charge and makes it more permeable. The combination of reactive oxygen species, gene regulatory alterations, cell wall permeability, and metabolite binding poses adaptation and survival obstacles, and the bacteria struggle to produce a barrier against all of the activities at the same time [70]. The toxicity is caused by this combination, and it is unlikely that a single component is responsible for bacterial killing. Despite the fact that these methods would be hazardous to human cells due to the closeness of the biomolecules, possible treatments for bacterial infections might be targeted focally by using particular ligands as well as bacterial cell receptors. Because multidrug-resistant bacteria are unlikely to be able to mount numerous protections at the same time, nanoparticles' multitarget activity would be excellent for treating and killing them [71]. The mechanism for antibacterial activity of nanoparticles is shown in Fig. 12.5.

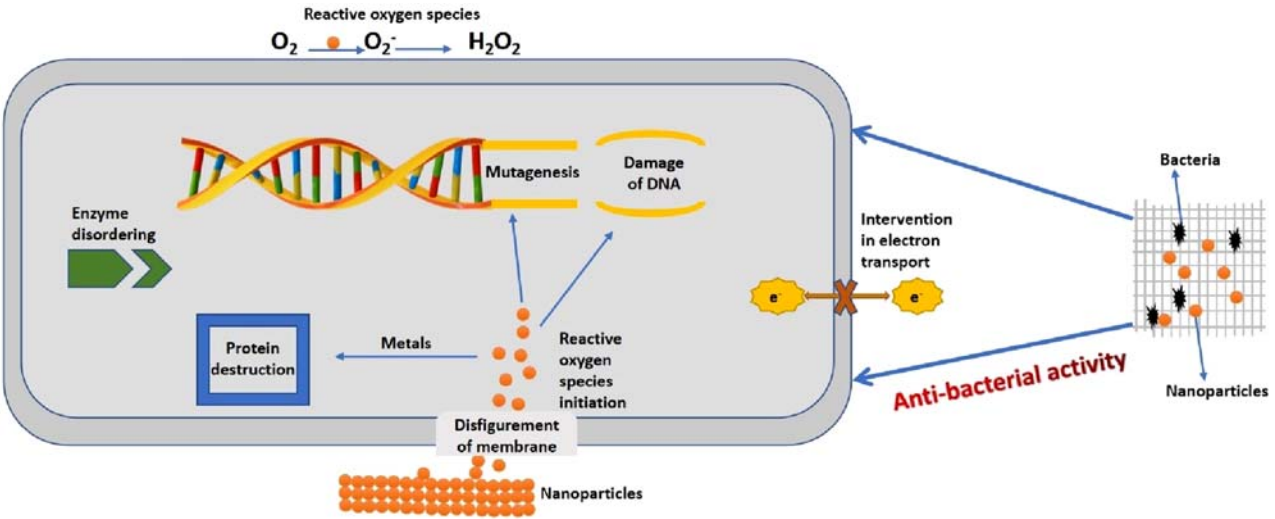

Figure 12.5 Mechanism for antibacterial activity of metal nanoparticles on fabrics.

Viral infectious spread is mostly due to the phases like surface attachment, penetration followed by replication, and then budding. The functionalized nanoparticles with antiviral potency are designed to inhibit one or more of these phases [72]. The majority of viral infections begin with host cell attachment, usually through affinity to a target acceptor protein. The nanoparticles can efficiently prevent adhesion to host cells and will be immune from infection. Functional nanoparticles can be employed as a broad-spectrum antiviral agent to inhibit the attachment stage of viral infection. The second method of virus suppression is to prevent virus penetration and entry into host cells by altering the surface of the cell membrane and protein architecture. Thus, creating barriers between viruses and host cells is an efficient strategy to combat viral infections. In the instance of entry of a virus into a cell, the third successful technique to inhibit the virus is to disrupt its replication, which is usually accomplished by decreasing the expression of particular enzymes that previously assisted in the multiplication of DNA or RNA of the virus. The final technique is to prevent viral replication and expel it from host cells [73]. A virus's offspring can be more deadly than its parent, so if functional nanoparticles inhibit the virus from budding and drastically reduce the number of progeny viruses, the toxicity will be considerably reduced. The mechanism for antiviral activity of nanoparticles is shown in Fig. 12.6.

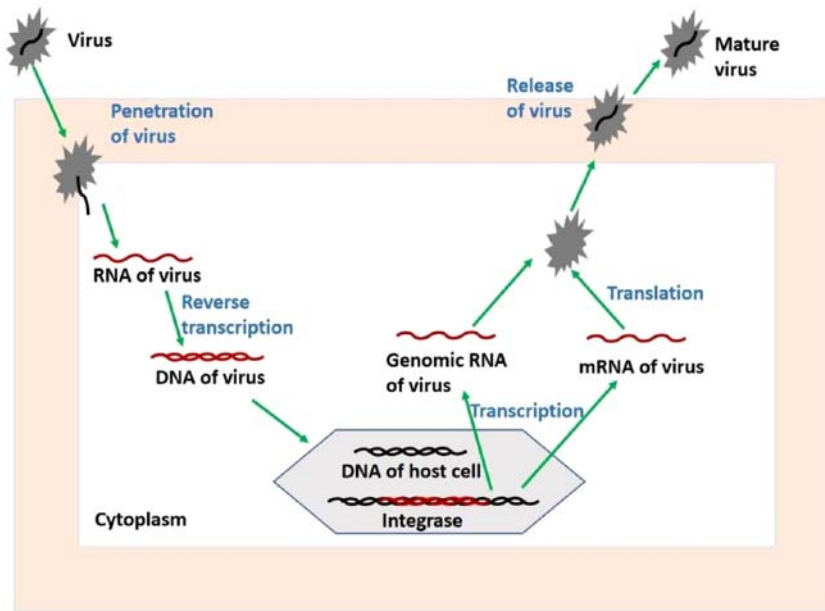

Figure 12.6 Mechanism for antiviral activity of nanoparticles.

5. Functionalization of nanomaterials

Nanoparticles show very limited applications because of certain drawbacks such as their toxicity and low biocompatibility, nonspecific characteristics, etc. [74]. To enhance their applicability in various areas, the surface of nanoparticles has to be modified in order to overcome these problems. The surface modification of nanomaterials is enabled by capping or adhering organic and inorganic materials on the nanomaterial surface via covalent interactions, electrostatic interactions, or secondary interactions such as van der Waals force, hydrogen bonds, dipole—diploe interactions, etc. [75]. To get the desired properties for nanomaterials, the material's surface can also be functionalized with the help of biomolecules, as shown in Fig. 12.7 (antibodies, nucleic acids, folic acid, peptides, plant extracts, bacteria, fungi, etc.) [76]. Functionalization results in overall increased efficiency, functionality, stability, physical properties, and biocompatibility [77].

Surface modification enables nanoparticles to play an important role for their utilization in the fields of medicine, the environment, and textiles [78]. The specific applicability of nanoparticles is decided by the functionalizing material, for example functionalization with antioxidants imparts anti-Alzheimer's, antitumor, antibacterial, and antidiabetic activities to nanoparticles. Magnetite functionalization with quercetin resulted in the synthesis of materials with antioxidant and antimicrobial properties. Thus, the rational selection of functionalizing biomolecules may be used for designing nanoparticles with increased antibacterial activity [79]. Additionally, functionalization led to improved attributes like printability, wetting, and adhesion [80].

6. Functionalized nanomaterials incorporation in textiles for antibacterial and antiviral properties

There are four main areas where nanotechnology exerts its applications in textiles: (a) nanofinishing, (b) nanocoatings, (c) nanofibers, and (d) nanocomposites [81]. This field is very new and growing rapidly, with the incorporation of Ag nanoparticles by some textile companies in their products such as socks and t-shirts in 2000. Ag nanoparticles have antimicrobial potential and thus inhibit bacterial growth on fabric. Incorporating nanoparticles into cloth may prevent odors caused by bacteria [82]. Nanomaterials such as carbon nanotubes, bio-based nanomaterials, metal nanoparticles (Ag/Au, TiO_2, ZnO, and CuO) have shown their use in

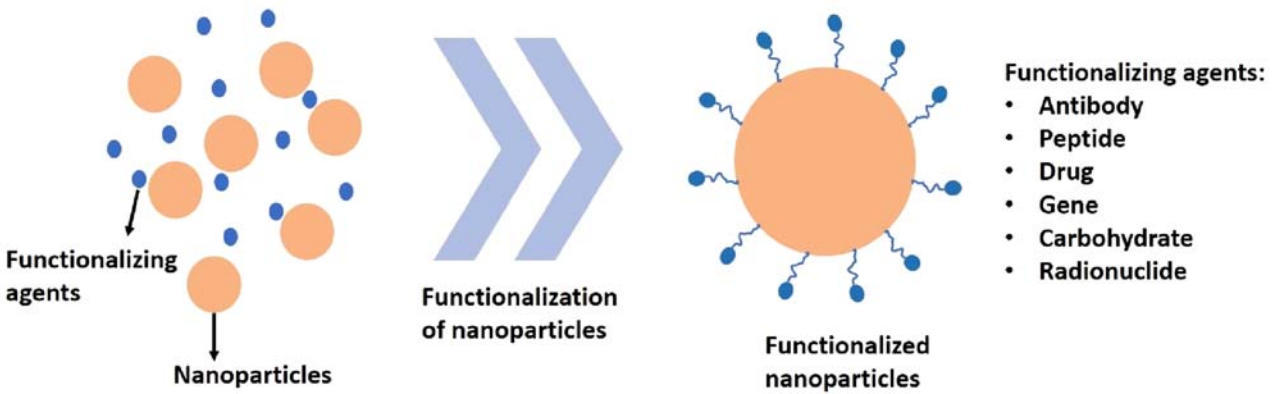

Figure 12.7 The functionalization of nanoparticles with the help of biomolecules.

textiles to enhance textile utility and properties like conductivity, hydrophobicity, antimicrobial activity, increased strength, self-cleaning, etc. The applications of nanotechnology in textiles deliver many desired functionalities to fabrics, as shown in Fig. 12.8.

Modifying of the surfaces of textiles by methods like plasma treatment, electrospinning, polymerization, nanotechnology, etc. has been well reported [83]. Turning the surface properties of nanoparticles may potentially help in controlling viral transduction, and thus these nanoparticles can be used as antiviral agents [84]. Surface and air contamination are more substantial for the spread of viral disease, which can be limited by the development of surfaces which have an antiviral and antibacterial nature. The use of nanoparticles of copper or their solutions (chloride, iodide, etc.) has been reported to have antiviral activity and thus found to be helpful for the development of PPE kits. The functionalized nanoparticles with antiviral drugs work as viral reproduction inhibitors and provide synergistic effects [85]. These nano antivirals are increasingly used for the production of efficient healthcare safety materials (masks, PPE kit). Surface-modified nanomaterials can also be used in coatings for hard surfaces and also as PPE modifiers for better protective action [86]. Nanomaterials with

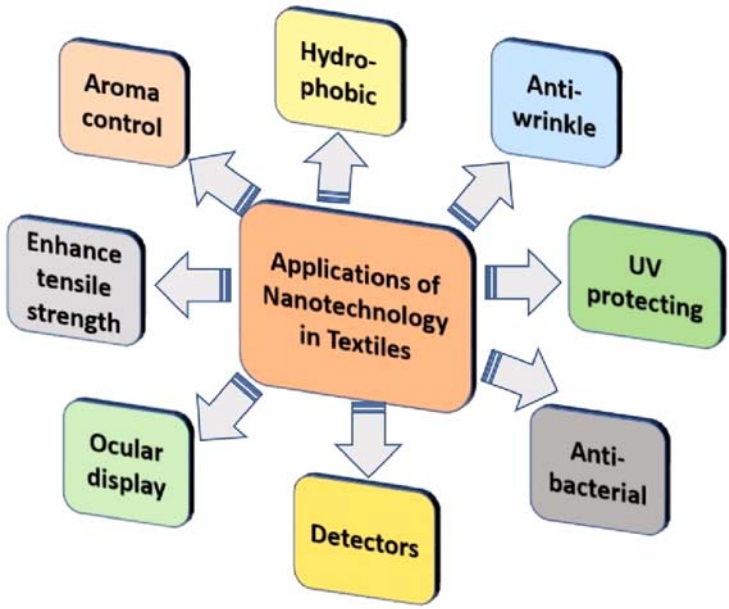

Figure 12.8 :The applications of nanotechnology in textiles.

Table 12.2 Textiles modified using nanoparticles for antimicrobial effects.

S. No.	Nanoparticle	Size (nanometers)	Fiber	References
1.	Cadmium oxide	32-41	Cotton	[88]
2.	Copper oxide	10-20	Cotton	[89]
3.	Titanium dioxide	15	Cotton	[90,91]
4.	Silver	2-6	Cotton	[92,93]
5.	Gold	12-40	Cotton	[94,95]

antimicrobial properties are also used in biomedical textiles [87]. Several types of nanomaterials having antimicrobial properties like copper, zinc, titanium, magnesium, zinc, etc. have been reported in the literature [57].

Table 12.2 summarizes textiles modified using nanoparticles for antimicrobial effects. These nanomaterials may be utilized for the development of antimicrobial and antiviral fabrics which can be achieved by simple coating of these nanomaterials on the fabric materials or they can be incorporated onto the polymer during synthesis to have antimicrobial and antiviral activity.

AgNPs can be applied to textiles by simple deposition or mixed with polymers that help fix it to textiles. Alternatively, AgNPs can be functionalized with a ligand that can enhance the binding to chemical groups present in cotton and wool. In a more direct approach, Lee et al. reported a method of forming a silver film on glass using the same principle and using ethanol as a solvent to grow AgNPs directly on the surface of cotton fibers [96].

Some of these significant qualities can be transferred to the final textile products by modifying textile materials with AuNPs. Heat treatment was used to modify cotton fabric with AuNPs produced in situ. After modification, cotton cloth was used to investigate AuNPs antibacterial properties [97]. The literature on textiles dyed with AuNPs focusing on antimicrobial assessment has been compiled in detail by Mehravaniin et al. [98]. Copper was embedded in a poly(vinyl methyl ketone) film and the antibacterial properties were reported. The coating on cotton and polyester with cationic copper provides antibacterial, antiviral, and antifungal properties [99]. Thus, it may be suggested that the fabrics can either be coated with these functionalized nanoparticles or they can be incorporated in situ into the fabric thread, as shown in Fig. 12.9.

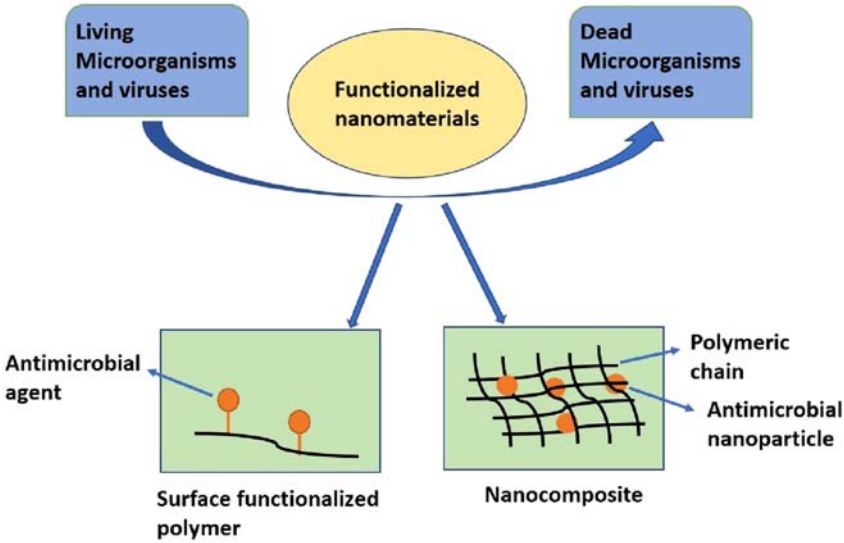

Figure 12.9 Different methods of incorporating nanoparticles in textiles.

7. Antimicrobial textiles and nanotechnology

Natural or synthetic textiles can be impregnated or modified in various ways via various types of nanocompounds. Among these are Ag NPs which exhibit high antimicrobial potential but with low toxicity for human cells [100,101]. The coating of these Ag NPs on fabrics provides long-term durability, self-cleaning property, enhanced dyeability, and antimicrobial activity [102].

A plasma-activated cellulose knitwear surface deposited with silver nanoparticles has been prepared which shows improved color performance and antimicrobial activity [103]. The radiochemical process has also been used for immobilizing silver nanoparticle fabrics for the preparation of antiviral textiles [104]. Cotton fabrics incorporated with silver nanoparticles with viable antimicrobial potential were found to be useful in wound-healing applications [105]. Silver nanoparticles with antiviral activity against COVID-19 virus SARS-CoV-2 have also been reported [106]. Antibacterial linen fabric coated with chitosan—silver nanoparticles has been prepared and reported [107]. Nanox company developed silver nanoparticle-incorporated fabric found to be active against SARS-CoV-2 virus [108].

Not only silver but also titanium, titanium oxide, zinc, zinc oxide, silica, gold, copper, and copper oxide applied to natural or synthetic textiles have been reported. Gold nanoparticles also have excellent antimicrobial properties which have been used by Wang et al. for the preparation of antibiofilm fabrics [109]. Functionalized CuONPs coated on textile materials exhibited antimicrobial activity through ROS generation [110]. Nylon 6 films immobilized with copper nanoparticle exhibited antibacterial potential [111].

Cellulose fibers impregnated with zinc oxide nanoparticles synthesized via white-rot fungus were found to be antimicrobial in nature [112].

Nanoparticles of zinc oxide capped with seaweed coated over the surface of cotton fabric via pad-dry-cure technique showed antibacterial activity [113]. Date seed extract-capped ZnONPs coated over the surface of cotton fabric demonstrated high antimicrobial activity as well as UV protective property [114]. ZnONPs cross-linked enzymatically have been coated sono-chemically on cotton fabrics. The coated fabric exhibited antibacterial properties and it retained its antibacterial activity after several times of washing with hot water [115]. Cotton fabric functionalized with amino-capped TiO_2 NPs exhibited effective activity against *S. aureus* and *E. coli* [116]. Selenium NPs-coated cotton fabric brooms have been prepared for cleaning purposes and showed antibacterial activity [117].

The nanocomposite of PVP—nanosilver deposited on polyamide 6,6 fabric was reported to show antimicrobial potential [118]. Biocomposite of Ag:ZnO nanoparticles/chitosan-coated textiles exhibited antimicrobial activity [119]. The polyethylene terephthalate/ZnO composite prepared by Hwang et al. showed antimicrobial and antiodor activity [120]. The hydrogel corn silk/ZnO nanocomposites incorporated on polyester fabric showed low toxicity and high antimicrobial activity [121].

A surface coated with nano-polysaccharides exhibited protection against coronavirus infections [122]. An oligochitosan/nano-silica-based nanohybrid material was found to be active against *Phytophthora infestans* fungus [123]. Wool fabrics treated with chitosan-based nanocomposites exhibited antimicrobial properties [124].

8. Major toxicity concerns

Nanomaterials that enter land can contaminate soil and migrate to the surface and groundwater. Particles contained in solid waste, sewage, direct discharges, or accidental spills can be carried into bodies of water by wind

and stormwater runoff [125]. The largest releases to the environment are from spills associated with transporting manufactured nanomaterials from one production site to another, intentional releases for environmental purposes, and wear and erosion from general use. It also can be caused by diffuse radiation [126]. The impact of the nanomaterial life cycle on the environment, humans, and animals has been discussed and reported [127].

The environmental impacts of nanotechnology may be divided into two aspects: the potential for nanotechnology innovations to improve the environment and also the new kinds of pollution that nanotechnology materials can cause when released into the environment. Engineered nanomaterials are so small in size that they can be exposed to airborne particles consisting of nanomaterials ranging from a few nanometers to a few microns in diameter [128]. Nanomaterials can aggregate into larger particles or longer fiber chains, altering their properties and potentially affecting indoor and outdoor environments and causing human exposure. There is also the possibility of intrusion. All toxic effects of nanomaterials are inherent in the substrate type, size, shape, and coating. Nanomaterials are observed to be quite environmentally friendly and less toxic if a biocompatible polymer coating is done over them such as coating carbon nanotubes by polymerization of dopamine or biodegradable polymeric coating on silver nanoparticles [129]. Adverse effects of nanomaterials on the lungs, immune, cerebrovascular, and central nervous systems have been investigated via toxicological studies [129,130]. Silver nanoparticles are also known to disrupt the blood–brain barrier, thus resulting in neurodegeneration [131]. Titanium dioxide nanoparticles were found to affect the central nervous and reproductive systems [132].

The very existence of nanomaterials (substances containing nanoparticles) is not a threat. Only certain aspects are generally dangerous, most notably, increased maneuverability and responsiveness. Only certain properties of certain nanoparticles are harmful to living organisms and the environment. In this case, it is called nano-pollution. Environmental impacts of nanotechnology include the potential environmental impacts of the employment of nanotechnology materials and devices. Since nanotechnology is an emerging field, the extent to which the commercial use of nanomaterials will affect living organisms and ecosystems remains a subject of debate [133]. The application of nanomaterials in the textile industry affects humans, animals, and the environment in four ways (shown in Fig. 12.10) [81]: (a) as the effluents and other wastes of these textile industries contain nanoparticles, which may contaminate soil, water

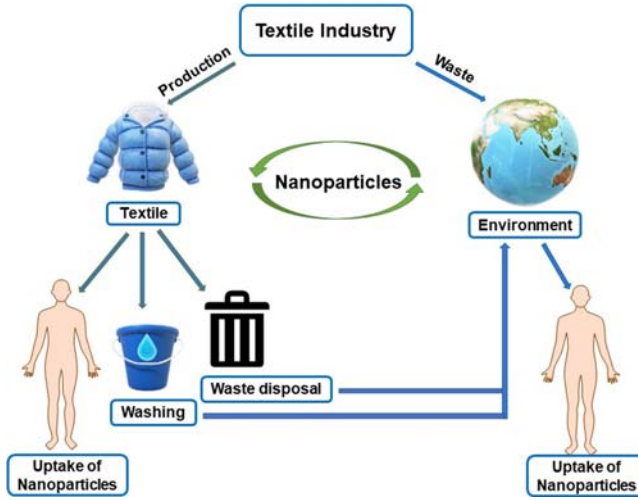

Figure 12.10 The discharge of nanoparticles (NPs) from textile materials and the textile industry into the surroundings and uptake by the human body.

sources, etc. thereby posing a threat to humans, animals, and the environment, (b) during use humans are in prolonged and direct contact with nanoparticles, thus there is a risk from toxic effects, (c) during use and washing nanoparticles are released into the environment and (d) finally, after use the textile product is disposed of, causing leaching of nanoparticles which is again a major concern as nanoparticles go into the environment and thus enter into human and animal bodies causing adverse effects on health and the environment. Uncertainty in shape, size, morphology, and chemical compositions of nanomaterials poses a threat to animals and the environment. Textile materials are directly in contact with human skin for a long time and thus their carcinogenicity and toxicity must be checked comprehensively [81].

9. Conclusions and future prospects

Nanoparticles are a promising new type of material for fiber and textile functionalization. They are one of the most beneficial additions that provide advantageous functionality to textile materials due to their remarkable qualities derived from their small size and large surface area. They are suitable for industrial applications due to their inexpensive cost, which is lower than that of other nanostructures. Alternative functionalization

procedures like corona treatment resulted in in situ nanoparticle production, which has effectively been used with excellent results. Additionally, electrospinning technology may be used to create unique nonwoven micro- and nanofabrics. There are some issues with their commercialization, and multiple substantial scientific research studies have reported their appropriateness for high-value functional textile applications. There is increased exposure to humans for nanoparticles through nanotextile materials, but this is not being accompanied by adequate awareness or/and restrictions set by safety regulations in terms of toxicological information. It is possible that this scenario will change in the near future. Modern science, particularly analytical chemistry, provides a wide range of techniques for monitoring nanoparticles in textiles and wastewaters. The application of nanoscience in the field of textiles has both advantages and disadvantages. Nanomaterials are currently found in a variety of commercial items, some of which are not labeled while others are, and there will undoubtedly be more to come. Nanotechnology not only enables the development of intelligent fabrics that are free of stains and wrinkles but also develops stronger, lighter, and more durable materials for making motorcycle helmets and sporting goods. It is important and necessary to carry out research in the concerned area to avoid risks to human health. Therefore, it is critical that the textile industry has sufficient knowledge of nanoparticles in order to make informed decisions.

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CHAPTER 13

Fabrication of functional nanoparticles onto textile surfaces with the use of metal (oxide) nanoparticles and biopolymers

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1. Introduction

In the period between 2015 and 2020, the market for functional textiles grew at a rate of 30% per year, demonstrating a significant increase in popularity across numerous industries. In particular, the sports, military, healthcare, fashion, and automotive industries have all made significant contributions to this development. There are numerous functional textiles available on the market with one or more of the following properties: electrically conductive, self-cleaning, wrinkle-resistant, antistatic, thermo-regulating, ultraviolet protective, sensing, windproof, heat-resistant, flame-retardant, odor control, oil/water repellent, and antimicrobial [1–3].

Nanotechnology has been extensively utilized in the fabrication of functional textiles and has the potential to transform clothing technology. Fabrics engineered with nanomaterials contribute to the development of textile-based nanoproducts, offering tailored physico-chemical properties without compromising the functionality and pliability of the substrates [4]. These textile-based nanoproducts are fabricated employing textiles made of nanofabrics or utilizing traditional textiles chemically modified with nanoparticles [5,6]. In particular, metal nanoparticles have been intensively investigated for textile functionalization owing to their unique biological, chemical, and physical characteristics [7,8]. Metal nanoparticles play a significant role in technological advances, as their exceptional surface properties allow them to be more effective than bulky traditional

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additives [9,10]. Numerous metal oxide and metal nanoparticles, including iron oxide/iron, cobalt, nickel, titanium oxide/titanium, zinc oxide/zinc, and copper oxide/copper, have been utilized [11].

Biopolymers are essential materials in fabric development as they can serve as building blocks of stabilizing components, coatings, or fibers [12]. Biopolymers have been extensively studied as renewable sources owing to their wide range of biological activities, biodegradability, and biocompatibility [13]. Hence, biopolymers have been extensively employed in material engineering, particularly in 3D printing, flexible electronics, controlled drug delivery, tissue engineering, and packaging systems [14]. Polysaccharides, which are organic macromolecular compounds constituted of monosaccharide molecules bound by glycosidic linkages to build polymer chains, are the most prevalent biopolymers [15]. Various polysaccharides are now derived from microbes, animals, and plants, including bacterial cellulose, pullulan, dextran, xanthan gum, chitosan, chitin, heparin, hyaluronic acid, carrageenan, fucoidan, agar, alginate, pectin, starch, and cellulose [16].

Hybrid textiles, which contain both inorganic and organic materials, are a developing and intriguing sector of the textile industry. There can be synergistic effects between the material components of hybrid textiles, which significantly improve their performance characteristics, functionality, and thus the end products. Multiple configurations are attainable, resulting in a wide range of novel fabrics with unique properties [17]. In particular, polysaccharides offer a number of advantages when integrated with diverse metal nanoparticles. Besides, there has been an increase in the use of metal nanoparticles and polysaccharide derivatives for the fabrication of hybrid materials over the past decade. Enhanced and novel functionalizations enable the emergence of applications in biomedical engineering that were previously unattainable. This chapter covers in detail hybrid fabrics containing metal nanoparticles and polysaccharides, with a special focus on the utility of polysaccharides in hybrid textiles. Regarding textile hybrid materials, polysaccharides have several potential applications: (1) to stabilize metal nanoparticles; (2) to act as a reducing agent for metal salts; (3) to enhance the functional characteristics of textiles; (4) to improve the adhesion of metal nanoparticles onto textiles; and (5) to serve as a binder in textile materials.

In general, metal ions attach to polysaccharides via noncovalent bonds. Once the metallic precursor is formed, it is reduced to the zero valent state, which triggers nucleation and nano-crystallization by merely modifying the

order of free energy. On the other hand, it is possible to stabilize metal nanoparticles as well as control their growth rate and morphology by increasing the temperature. The top-down synthesis of metal nanoparticles—polysaccharide composites is inferior to self-assembly synthesis because the precursors used in self-assembly synthesis are shrunk by chemical, thermal, or mechanical processes. These approaches may result in the unintended oxidation of nanoparticles, altering their chemical properties and/or surface physical properties. Moreover, the coordinated metal ion is not readily leached from stabilized metal nanoparticles in the absence of an external stimulus, such as a pH transition. In most cases, polysaccharides are pH sensitive, making them ideal for drug delivery and controlled release in polysaccharide-based nanocarrier system [18].

2. Biopolymers in the fabrication of metal nanoparticle functionalized fabrics

2.1 Chitosan

Chitosan is a linear polycationic biopolymer produced by deacetylating chitin to varying degrees [19]. Chitin, the primary component of chitosan, is typically found in bacteria, fungi, insects, shrimp, and crabs; as a result, chitosan has gained popularity among researchers. Chitosan is a fascinating polysaccharide owing to the presence of high levels of hydroxyl and amino groups, which provide intriguing physicochemical characteristics and highly reactive surfaces with enhanced chemical bonding capabilities. Despite its hydrophobic carbon backbone, the presence of NH_2 groups on the chain of chitosan is protonated in an acidic environment to form NH_3^+, making it water-soluble at a pH below 6.2. Chitosan is regarded as a biomolecule that is thermally stable, antibacterial, film-forming, antioxidant, biodegradable, biocompatible, and renewable [20].

Chitosan is commonly used in conjunction with metal nanoparticles in fabrics across a range of industries [21]. Besides, numerous fibers based on alginate, viscose, ramie, linen, aramid, polyethylene, polypropylene, polyester, polyamide, and cotton have been combined with metal nanoparticles such as Ce, Ni, Co, Fe, Ti, Zn, Cu, and Ag nanoparticles. These fabrics have been recommended for packaging, smart garments, wound dressings, controlled drug delivery, and tissue engineering. As a textile substrate, chitosan has been used to fabricate scaffolds, wearable electrodes, and catalysts for separating contaminants from water. Commercially, wet spinning and electrospinning processes are most commonly employed to develop

chitosan substrates for antimicrobial studies (Fig. 13.1) [22]. For instance, the electroless plating of silver nanoparticles on the surface of chitosan nanofiber can serve as novel textile electrodes for smart clothing [23]. The fabricated wearable retains its conductivity because the amino groups present in the chitosan biomolecule effectively interact with metal ions owing to their nitrogen atoms bearing lone pairs of electrons, making them

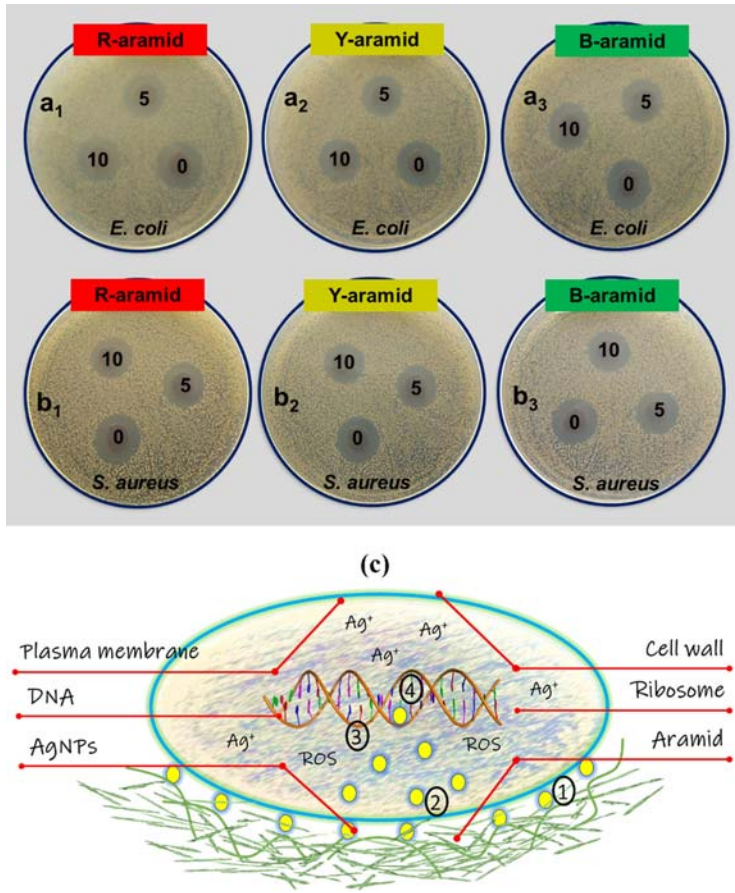

Figure 13.1 Antibacterial activity of silver nanoparticles deposited on aramid fabrics against (a1—a3) *E. coli* and (b1—b3) *S. aureus*. (The numbers included in the images indicate the number of washing executed before the test: 0—zero washing cycles, 5—five washing cycles, and 10—ten washing cycles). (c) Proposed mechanism of antibacterial action of silver nanoparticles deposited on aramid: ①, electrostatic attraction; ②, production of free radicals; ③, interaction with phosphorus-containing molecules; and ④, stopping DNA repetition.

highly conductive even after multiple washes. Furthermore, nanocomposites of titanium dioxide and chitosan with various metal ions, including Ni^{2+}, Ag^{+}, Co^{2+}, and Cu^{2+}, have been prepared to produce highly effective and easily recoverable catalysts via a wet spinning process [24]. Chitosan was chosen for this study because it contains reactive amino functional groups capable of absorbing metal ions through chemical and electrostatic interactions. Later, titanium dioxide nanoparticles were introduced to combat chitosan's poor mechanical strength and solubility in acidic media, as well as to enhance its chemical and mechanical properties. Using these metal nanoparticles, an increase in the catalytic efficiency for nitrophenol reduction was observed.

Electrospun nanofiber mats made from chitosan appear to hold great promise for the treatment of diabetic wounds, as they mimic the extracellular matrix and enhance wound healing, cell proliferation, and cell adhesion. The electrospun nanofiber mats showed antioxidant capacity as well as antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Escherichia coli*. In addition, in vivo studies validated the properties of electrospun nanofiber mats, indicating their potential use as a wound dressing [25].

It has been shown that the incorporation of chitosan enhances the washability of the treated nanocomposites, thereby ensuring long-lasting color stability and antimicrobial properties that endure after multiple washings. Recently, silver nanoparticles and chitosan-functionalized aramid fibers have been employed to induce thermal resistance, color resistance, and antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*. It is important to note that the antibacterial activity was retained even after multiple washes [22]. Besides, a woven cotton fabric modified with chitosan biopolymer has been fabricated by layer-by-layer coating to offer antimicrobial resistance without compromising the mechanical and physical attributes. Using chitosan agents containing silver nanoparticles and polystyrene sulfate as cationic and anionic auxiliaries, respectively, layer-by-layer coating was utilized to produce a novel textile [26]. Another study employed a pad-dry-cure technique to fabricate antibacterial cotton fabrics by employing carboxymethyl chitosan as a stabilizer and binder [27]. Herein, the existence of ester bonds and amine groups in the carboxymethyl chitosan facilitates the establishment of a coordination bond between the cellulose hydroxyl groups and the silver nanoparticles, resulting in the uniform distribution of silver nanoparticles on cotton fabric. Subsequently, the antibacterial characteristics of these materials were examined

against *Staphylococcus aureus* and *Escherichia coli*, and the results demonstrated a significant reduction in bacterial growth even after multiple washings.

Besides, chitosan has a positive effect on UV protection owing to its potential to develop films on textiles and enable greater adherence of metal nanoparticles to the fabric surface. Furthermore, the enhancement in flame-resistant attributes utilizing metal nanoparticles and chitosan can be ascribed to the abundance of nitrogen atoms in the amine and acetamide functional groups of chitosan structure and high thermal resistance property of metal nanoparticles [28]. Another efficient approach involves the incorporation of phosphorous molecules into chitosan to impart flame-retardant properties [29]. For this application, metal nanoparticles and phosphorous were chosen for their flame-retardant capabilities, whereas silver and chitosan were opted for because of their antibacterial properties.

Cotton fabrics are often treated with metal nanoparticles and chitosan through dipping and padding processes to develop textiles with antimicrobial properties. For instance, cotton fabric, chitosan, zinc-doped titanium dioxide nanoparticles, and polyvinyl alcohol have been used to develop an antimicrobial textile using the pad-dry-cure technique [30]. Herein, titanium dioxide enhanced the photocatalytic effect, leading to increased antimicrobial activity against *Aspergillus niger*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. Another study reported the utilization of *Psidium guava* leaf extract as a green reductant for the synthesis of zinc oxide nanoparticles, with the leaf extract being an environmentally friendly alternative to conventional reducing agents [31]. Later, the researchers modified cotton fabrics with biological polymers, including carboxymethyl cellulose, chitosan, and alginate, and found that the chitosan-zinc oxide composite was superior in terms of antimicrobial and UV protection properties. Besides, polyester material functionalized with cyclodextrin and chitosan and cross-linked with citric acid has been prepared using a pad-dry process [29]. The textiles were then treated with heat to facilitate the development of silver nanoparticles. Afterward, a layer-by-layer process was employed to deposit a multilayer of polyelectrolyte as a thin film on the surface of functionalized polyester material, providing high antibacterial resistance against *Escherichia coli* and *Staphylococcus aureus* [32].

Chitosan in nanocomposites serves as a stabilizing and reducing agent in the synthesis of metal nanoparticles, which is one of their primary functions. For instance, chitosan has been used as a stabilizing and reducing agent for the in situ synthesis of silver nanoparticle-functionalized polyamide fabrics.

Later, a ternary complex was formed by dispersing the chitosan solution over the surface of the silver nanoparticle-functionalized polyamide fabric. The chemical interaction between silver ions and the hydroxyl and amino groups of chitosan and polyamide facilitated the adsorption of silver nanoparticles. In addition, durability tests revealed that the bacterial counts were reduced by nearly 88% after 20 cycles of washing [33]. In another study, chitosan was used as a stabilizing and reducing agent to enhance the antibacterial properties of viscose fabric against *Escherichia coli* and *Staphylococcus aureus* by functionalizing silver nanoparticles on its surface [34].

2.2 Alginate

Alginates are colloidal polysaccharides derived from brown seaweeds, marine algae, and bacteria, including *Azotobacter* and *Pseudomonas* [35]. G (L-guluronic acid) and M (D-mannuronic acid) blocks are the basic building blocks for the synthesis of alginate polymers, which are associated together by α-(1,4) and β-(1,4) glycosidic linkages to form complex carbohydrates. However, depending on the extraction technique, certain copolymers may contain distinct blocks such as GM, GG, or MM [36]. They are commercially available in a variety of salts, including ammonium, potassium, or sodium, with varying distributions and molecular weights of the G and M blocks. The different types of salts modify the physicochemical characteristics of the polymer, including its sol—gel transformations, viscosity, and ability to absorb water. Furthermore, polymers with heterogenous GM molecular architecture are more soluble in water at acidic pH levels than those with MM or GG structures. Due to the fact that their characteristics are alterable based on their physical and chemical properties, alginates can be employed in a number of different applications, including the beverage, food, agriculture, biomedical, pharmaceutical, and textile industries [35]. Besides, alginates are nontoxic, biodegradable, and biocompatible, and are utilized as stabilizing, reducing, and thickening agents for the formation of ultra-thin films. In addition, alginates facilitate the development of coatings, scaffolds, fibers, or hydrogel beads after being cross-linked by divalent ions, forming a chelating complex within the polymeric chains of alginate, thereby producing a 3D network. This process of gelation is useful because it may be performed at a neutral pH and ambient temperature.

Typically, alginate is coupled with silver by the replacement of monovalent ions, including potassium or sodium ions [37]. Due to the

presence of multiple functional groups on its surface, alginate can also serve as a stabilizer and reducing agent, inhibiting the aggregation of silver nanoparticles during synthesis. Silver nanoparticles can be conjugated with alginate for use as a finishing/coating agent in textiles. In addition, silver nanoparticles can be integrated into the alginate fibers via electrospinning or wet spinning. For instance, the wet-spun alginate fibers implanted with silver nanoparticles exhibited highly efficient antimicrobial resistance to *Staphylococcus aureus* and *Escherichia coli* and were effective in eliminating cervical cancer cells [38]. Another study employed electrospinning to fabricate alginate nanofibers embedded with silver nanoparticles, with the silver nanoparticles being reduced in situ to produce an efficient humidity-sensing element capable of monitoring human breath [39]. In other studies, chitosan—silver nanocomposites coated on poly(ethylene terephthalate)-coupled alginate fibers synthesized by electrospinning have been employed as a composite membrane to form an ultra-thin film capable of purifying water (Fig. 13.2) [40]. The as-prepared composite materials exhibited good antimicrobial activity against tested microbes, including Gram-negative and Gram-positive bacteria. In addition, the incorporation of silver nanoparticles onto the surface of ramie, cotton, and silk textiles by the use of sodium alginate as a stabilizing agent and reducing agent for surface functionalization has been reported [41]. The purpose of this was to produce dyed fabrics with enhanced washability that were more effective than standard dyeing techniques. All of the textiles exhibited enhanced catalytic properties for reducing 4-nitrophenol, improved crease recovery angle, tensile properties, UV protection, and antimicrobial activity.

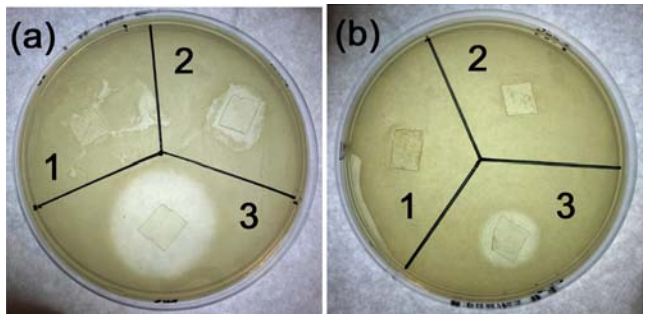

Figure 13.2 Antibacterial inhibition zones against (A) *E. coli* and (B) *S. aureus*. The numbers on the photos indicate Ga-CaA (1), CaA-CS (2), and CaA-AgNPs (3).

In addition to silver nanoparticles, copper, copper oxide, and silver nanoparticles can also be employed to endow textiles with antimicrobial activity and UV protection. As far as zinc oxide nanoparticles are concerned, alginate can be employed in the formation of zinc oxide nanoparticles as a functional layer on the surface of cotton fabrics. Later, a pad-dry-cure method can be used to form a matrix on the surface of functional cotton fabrics to enclose zinc oxide nanoparticles. Regarding studies performed with copper nanoparticles, sodium alginate can be utilized as an ion exchange material in the fabrication of composites with antibacterial properties in polyamide, polyester, and polypropylene nonwoven fabrics [42]. Each of the three textiles displayed high antimicrobial resistance against *Candida albicans*, *Staphylococcus aureus*, and *Escherichia coli*. Through testing, it has been estimated that polypropylene composites are not harmful to human keratinocyte cells. In contrast, polyester composites contained 30% more copper in their surface layers than polyamide composites, resulting in superior antifungal and antibacterial properties. In another study involving the functionalization of viscose fabrics with sodium alginate and copper nanoparticles, alginate-treated textiles exhibited superior antimicrobial resistance to Gram-negative cyanobacteria due to a 145% increase in the surface concentration of copper nanoparticles, thereby inhibiting the copper degradation and providing long-term antimicrobial protection against microbes even after 50 washings [43].

2.3 Starch

Starch is a polysaccharide that has significant potential for many industrial purposes owing to its unique physicochemical properties, including nontoxicity, biodegradability, biocompatibility, and film-forming ability. This polysaccharide is one of the most affordable renewable biopolymers. Further, starch is widely abundant and derived from numerous plant parts, including seeds, roots, and stalks. There are five principal sources of starch: potato, corn, rice, wheat, and cassava [38]. Chemically, starch is a polymer of glucose units bound together by glycosidic linkages. The two monomers that make up starch are amylopectin and amylose. Amylose is composed of a linear chain of glucose molecules and accounts for 30% of the amorphous form in starch grains. On the other hand, amylopectin is a highly branched polymer of α-D glucose that contains crystalline zones and comprises 85% of starch [35]. In addition to being a multifunctional polymer, starch is employed in a wide range of industrial products such as textiles,

pharmaceuticals, coatings, paints, adhesives, paper, and food. As far as the textile industry is concerned, starch is commonly employed as a sizing agent in fabrics owing to its excellent film attributes and good adhesion to electrospun fibers, preventing yarns from being mechanically abraded [44]. In addition to its use as a textile raw material, starch can also be used to develop functional textiles, particularly through the use of metal nanoparticles. When metal nanoparticles are synthesized in an environmentally friendly manner, starch can aid in heterogenous nucleation and function as a stabilizing agent, complexing agent, and surface-capping agent, thereby preventing aggregate formation [45]. For instance, starch has been utilized as a capping agent in the process of synthesizing zinc oxide nanoparticles on cotton fabrics (Fig. 13.3). The experimental findings demonstrated that starch influences the shape and size of nanoparticles. In the absence of starch, spherical nanoparticles with an average diameter of 52 nm were observed. However, upon addition of the capping agent, nanoparticles with a rod-like morphology with an average size of 88 nm were observed [46]. Furthermore, starch was responsible for the increase in water contact angle and nanoparticles' ability to withstand repeated washings. With regard to antibacterial properties, zinc oxide nanoparticles incorporated into cotton textiles had a similar antibacterial effect against *Escherichia coli* regardless of the presence or absence of starch. Besides, the synthesis of zinc oxide nanoparticles utilizing starch as a stabilizer and incorporation onto cloth face masks as an outer layer has been reported. The textile treated with zinc oxide nanoparticles and starch showed antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*, and the textile coating remained intact even after multiple launderings [35].

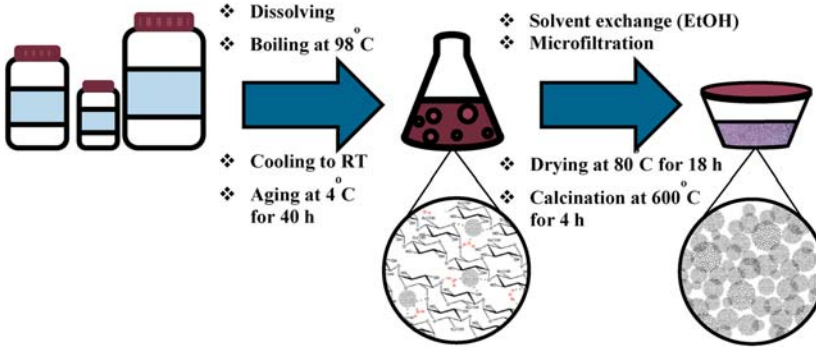

Figure 13.3 Typical solution—solid procedure utilized for preparation of nanosized ZnO and Au/ZnO.

Despite being a poor reducing agent, starch can act as a nucleation aid when combined with cellulose. A knitted antimicrobial fabric made of cellulose was developed by incorporating silver nanoparticles prepared with starch as a stabilizing and reducing agent into cellulose fibers. During autoclaving, the starch swells, making it easier for the silver ions to be reduced by the aldehyde terminal groups. The silver nanoparticles-infused fabric was antibacterial against *Escherichia coli* and *Staphylococcus aureus* and the coating was stable after multiple washings [47]. In addition, copper nanoparticles were also synthesized using starch as a reducing agent. Then the copper oxide nanoparticles were attached to cotton fabrics utilizing polysaccharide, sodium alginate and pad-dry-cure. Despite a significant reduction, fabrics treated with copper oxide retained antimicrobial activity against *Candida albicans*, *Bacillus subtilis*, *Pseudomonas fluorescens*, *Escherichia coli*, and *Staphylococcus aureus* and hydrophobicity after 20 washings [48]. Another study utilized manganese dioxide nanoparticles as a precursor and potassium permanganate as a cross-linker to fabricate hydrogel nanocomposite fabrics with antibacterial, photocatalytic, and biocompatible properties. In addition, starch was utilized as a reducing agent. Despite the high antifungal and antibacterial activity of hydrogel, the hydrogel nanocomposite textiles failed to achieve promising outcomes owing to the uneven distribution of hydrogel nanocomposite on the textile, inadequate loading, and poor absorption [49].

Despite their unique properties, nanoparticles used in textiles may not adhere well to the substrate, resulting in poor performance over time. In addition, since nanoparticles have yet to be fully studied for their environmental and health impacts, disposal, domestic washing, and excessive leaching during use can pose issues. For the immobilization of zinc oxide nanoparticles on the fabric surface, corn starch has been used to functionalize cotton fibers in order to improve their adhesion characteristics. Upon irradiating with ultrasound, zinc oxide nanoparticles were synthesized in situ. Furthermore, stabilizing zinc oxide nanoparticles by altering their shape and size during the process of surface functionalization using starch is another way to enhance the amount of zinc oxide nanoparticles incorporated into the cotton fabric. As a result, the leaching of zinc oxide from the surface of fabric can be reduced, resulting in improved antibacterial activity [50]. In addition to its hydrogel qualities, starch can also be used to develop flame retardants. For instance, incorporating cotton, silk, and starch as organic polymers that were combined with zinc oxide nanoparticles in situ led to the development of multifunctional polyester textiles [51].

The fabrics treated with zinc oxide nanoparticles exhibited photocatalytic and antimicrobial activity owing to the presence of zinc oxide nanoparticles, while starch gave the fabrics an antiflammability property. In addition, a layer-by-layer assembly of anionic and cationic species comprised of titanium dioxide clay—vermiculite and starch, respectively, has been formed on the cotton fabric in order to develop an efficient hybrid system with flame-retardant properties [52].

2.4 Cyclodextrins

Cyclodextrin is a kind of polysaccharide composed of 6, 7 or 8 α-(1,4)-linked α-D-glucopyranose units derived from enzymatic breakdown of starch. Cyclodextrins have a structure in the shape of a truncated circular cone with an outer hydrophilic surface and an inner hydrophobic cavity. As a result of the hydrophobic cavity inside the molecule, inclusion complexes can be formed with guest molecules, which remain bound together owing to hydrophobic and van der Waals forces. In the textile industry, β-cyclodextrins are most often used owing to their affordability, cavity size, ease of manufacture, and ready availability. On the other hand, in the dyeing process, cyclodextrins are utilized to spin fiber, encapsulate active substances including antimicrobial agents, drugs, and fragrances, and enhance dye adsorption [53]. For instance, it has been reported that nanocomposites of silver nanoparticles, cyclodextrin, and polyamidoamine incorporated into polyester fabric are capable of delivering drugs and acting as antibacterial agents. Herein, polyamidoamine was used to aminolyze polyester fabric, which gave rise to the formation of stable associations between silver—β-cyclodextrin nanocomposite and polyester fabric. Utilizing the aforementioned nanocomposite fabric, a drug release rate of 45% was obtained after 150 hours and 99%, 100%, and 100% reductions in microbial load were achieved for *Candida albicans*, *Staphylococcus aureus*, and *Escherichia coli*, respectively (Fig. 13.4) [54].

Another study reported the synthesis of silver nanoparticles on a nanocomposite of ketoconazole—β-cyclodextrin, which were then coated on cotton fabric to develop an antibacterial drug-delivery system. Herein, ketoconazole, an antifungal drug, and silver nanoparticles were added to cotton fabric to increase its antibacterial capabilities and regulate its release rate. However, when 2% of silver nanoparticles were introduced to the surface of cotton fabric, 100% of *Aspergillus niger* and *Candida albicans* were eliminated, while *Staphylococcus aureus* and *Escherichia coli* were reduced by

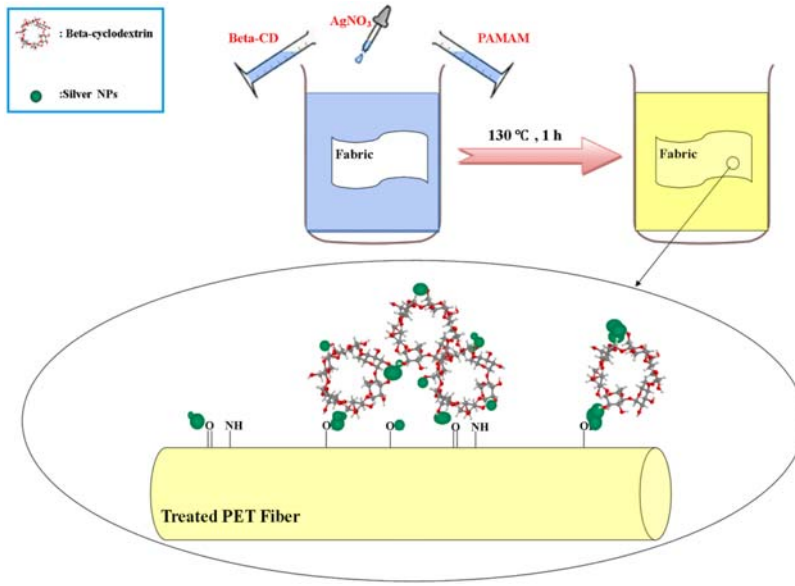

Figure 13.4 Mechanism of single-step in situ processing and loading of nanocomposites on the polyester fabric.

85% [55]. In addition, sulfated β-cyclodextrins and β-cyclodextrin have been used to host silver nanoparticles and form inclusion complexes in order to produce antimicrobial cotton fabrics. Furthermore, it was observed that the surface modification of fabric with silver nanoparticle—β-cyclodextrin composite and cross-linking with ethylenediaminetetraacetic acid was the most efficient. After 10 washing cycles, the fabric treated with ethylenediaminetetraacetic acid, silver nanoparticles, and β-cyclodextrin reduced *Escherichia coli* and *Staphylococcus aureus* by 77% and 95%, respectively. In addition, nanocomposites of β-cyclodextrin, titanium dioxide, and silver nanoparticles have also been synthesized and deposited onto cotton fabrics to produce self-cleaning fabrics. The proposed surface-functionalized cotton fabric exhibited potent antimicrobial activity against *Staphylococcus aureus* at 97% and remarkable dye degradability.

Innovative wound dressings have been developed using nonwoven polyethylene terephthalate impregnated with dual polysaccharides (cyclodextrins and chitosan), where the chitosan and cyclodextrins are cross-linked by citric acid using a pad-dry-cure method. After being functionalized with anionic polyethylene terephthalate fabrics, silver sulfate was added, and a polyelectrolyte multilayer comprising of cationic chitosan

and anionic, water-soluble polycyclodextrins was formed. In comparison with textiles functionalized with chitosan, poly-cyclodextrin-functionalized fabrics adsorb more silver ions, leading to higher bacterial (*Escherichia coli* and *Staphylococcus aureus*) reduction. In the polyethylene terephthalate-coated textiles, a substantial decrease in silver ion release was observed without affecting its antibacterial properties, resulting in a significant reduction in bacterial counts [55]. In addition, wound dressings containing both ibuprofen and silver nanoparticles to provide antibacterial and analgesic properties were fabricated using the same technique to develop a dual therapy. Later, ibuprofen lysinate was loaded onto nonwoven polyethylene terephthalate fabrics using a polyelectrolyte multilayer system. As a result, the as-fabricated surface-functionalized fabric showed excellent antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* [56].

Electrospinning is a dynamic and efficient method for producing dense and uniform nanofibers, resulting in nanomaterials with high porous qualities, a high length-to-width ratio, and high surface area-to-volume ratio. In another study, silver nanoparticles were electrospun with polyoxymethylene—cyclodextrin microfibers to form composite microfiber matrices. With the addition of cyclodextrins, the mean fiber diameter increases and the microfiber becomes less rough and porous [57].

2.5 Cellulose

The term nanocellulose refers to cellulose, a naturally occurring polysaccharide composed of long chains of sugar molecules with nanoscale dimensions [58]. Molecularly, β-(1—4) linked anhydro-D-glucose assembles to form nanocellulose, a polysaccharide; however, its degree of polymerization can vary by up to 20,000 based on the source of cellulose. Nanocellulose is found naturally in animals, algae, bacteria, and plants [59]. There are numerous types of nanocellulose, including bacterial nanocellulose, cellulose nanofibrils, and cellulose nanocrystals. Nanocrystals of cellulose with rod-shaped or needle-shaped morphologies are produced by chemical hydrolysis of plant-derived cellulose. The amorphous or disordered parts of cellulose are hydrolyzed by strong acids, while the crystalline sections of cellulose remain resistant to acid. The nanofibrils of cellulose are distinguished by their pliable, extended, cross-linked structure; to manufacture them, the starting material is purified in a way that enables disintegration prior to mechanical delamination [60]. Unlike other forms of nanocellulose, bacterial cellulose is derived primarily from bacteria in their natural state. Bacterial nanocellulose doesn't contain byproducts like hemicellulose,

pectin, or lignin. Rather, a sodium hydroxide mercerization treatment is adequate for eliminating medium culture components, bacterial cells, and other debris. The biological, physical, and chemical attributes of nanocellulose-based materials are particularly intriguing. The presence of hydroxyl groups enhances the adsorption of molecules, atoms, and ions onto nanocellulose-based materials, which have a high surface area and are chemically inert. Typically, nanocellulose is not only mechanically strong but also optically and chemically tailorable. In addition, nanocellulose is an abundant and environmentally friendly material that is relatively cheap to produce [59].

In textile finishing, the different types of cellulose are commonly utilized as stiffener, binder, reducing, and stabilizing agents to facilitate the inclusion of metal nanoparticles into the textile, allowing for the incorporation of special features into the textile. On the other hand, cellulose nanofibrils serve as a support for nanoparticles in wound dressings. For instance, the nanocomposites of aminated silver nanoparticles, gelatin, and cellulose nanofibrils formed a complex, interconnected polymeric network with enhanced self-recovery, mechanical, and antibacterial properties (Fig. 13.5) [61]. Compared to cellulose nanofibrils alone, the employed

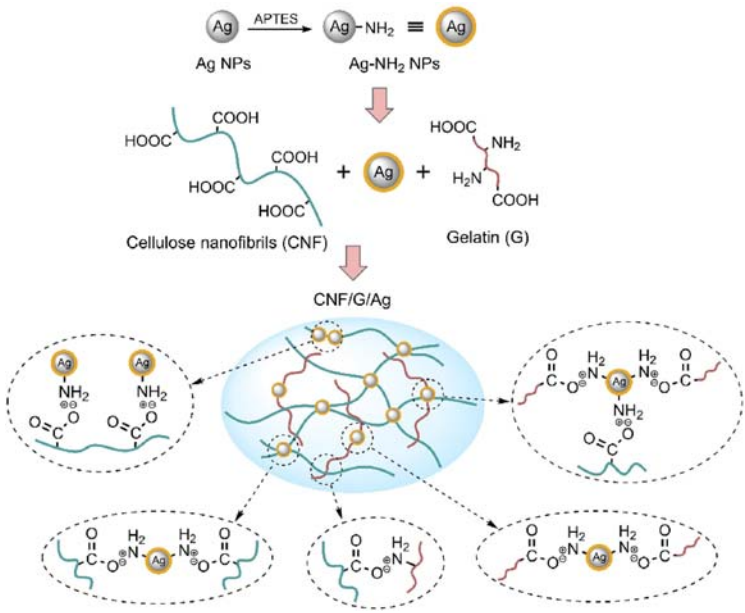

Figure 13.5 Schematic illustration of the prepared aminated silver nanoparticles ($Ag{-}NH_2$ NPs), CNF/G/Ag hydrogel dressing, and mechanisms of cross-linking reactions of multicomponents.

hydrogel, which is noncovalently cross-linked, has been shown to be effective in wound healing by preventing hemorrhage and controlling the evaporation of water, resulting in a reduction in wound size. Also, a high-quality cotton fabric imprinted with silver ink was shown in the application of cellulose nanofibrils to electronic textiles [62]. Herein, a coating of cellulose nanofibrils was applied, which caused the pigments to accumulate on the surface, making the printed circuits more conductive. Additionally, cellulose nanofibrils have been shown to be effective as stabilizing agent for zinc oxide nanoparticles. Cellulose nanofibrils are commonly employed in the finishing of UV-protective clothing owing to their effective shielding effect. Due to the high surface area of the cellulose nanofibrils, zinc oxide nanoparticles typically clump together after being embedded on the cotton fabric surface, despite the fact that they are a stabilizer and have a good shielding effect [59]. Carbonyl and hydroxyl groups on the surface of cellulose nanofibrils impart negative charges, which interact electrostatically with zinc to reduce nanoparticle agglomeration. Besides, since cotton fabric and cellulose nanofibrils are similar in structure, they can interact through intermolecular hydrogen interactions. As a result, zinc oxide nanoparticles are more likely to adhere to cotton fabrics, preventing nanoparticles from leaching out during washing.

In recent years, there has been an increase in the popularity of self-cleaning textiles, from the earliest highly hydrophobic materials to the most recent photoactive catalytic materials. The two basic mechanisms underlying photocatalytic activity are reduction and oxidation reactions that take place in the presence of light to break down dirt [63]. Titanium dioxide is regarded as one of the most effective metal oxide nanoparticles owing to its exceptional photoactive catalytic property and ability to degrade dye contaminants [64]. Despite the utility of nanoparticles in textile finishing, the polymer employed in the coatings demonstrated poor washing fastness. In order to address this issue, it has been demonstrated that viscose-derived cellulose is capable of coating cotton fabric with titanium dioxide nanoparticles, thereby enhancing its self-cleaning ability, hydrophobicity, and durability [65]. In another study, carboxymethylcellulose was employed to impart hydrophilic properties to the biopolymer by binding its carboxyl groups to the hydroxyl groups of glucose [66]. Besides, sodium has been added to carboxymethylcellulose to form a complex that acts as a reducing agent in the preparation of silver nanoparticles to enhance the antibacterial properties of cotton fabrics against *Candida albicans* and *Staphylococcus epidermidis* [66].

2.6 Other biopolymers

A variety of polysaccharides, including locust bean gum, k-carrageenan, pullulan, pectin, and hyaluronic acid, have been used in textiles to incorporate metal nanoparticles. These biopolymers, specifically locust bean gum, k-carrageenan, dextran, and pectin, were used to reduce and stabilize metal nanoparticles [67]. As a result of the above-mentioned properties exhibited by polysaccharides, chemical usage is limited, thereby reducing the environmental impact. As one of the most prevalent polysaccharides, pectin, a complex anionic heteropolysaccharide, is primarily composed of α-(1,4)-linked galacturonic acid homopolymer [68]. In addition, pectin is an integral component of plant cell walls and is therefore widely available. Owing to its biodegradability, biocompatibility, and sustainability, pectin has developed into a very intriguing biopolymer (Fig. 13.6) [69].

The process of electrospinning fibers from pectin is possible. Nevertheless, this approach is highly complex, time-consuming, and labor-intensive [70]. In order to achieve the desired functionality of electrospun composite textiles, pectin is often combined with electrospun fiber. Hyaluronic acid is a linear polysaccharide with repeating units of N-acetyl-glucosamine and glucuronic acid. Hyaluronic acid is highly prevalent in nature and can be found in all kinds of mammals. Nevertheless, *Pseudomonas* bacteria are also known to contain an abundance of hyaluronic acid. The highly hydrophilic nature of hyaluronic acid makes it easy to dissolve in water. Furthermore, its viscoelastic attributes are unique, showing a high water-retention capacity and it is therefore employed as a lubricant [71]. The abundance of hyaluronic acid in the extracellular matrix of mammals makes it an attractive material for the development of functional biomaterials with wound-healing capabilities. For instance, the formulation of electrospun nonwoven biomedical fabrics containing silver nanoparticles and hyaluronic acid has been reported. As part of the design of these textiles, hyaluronic acid was added to inhibit adhesion between cells

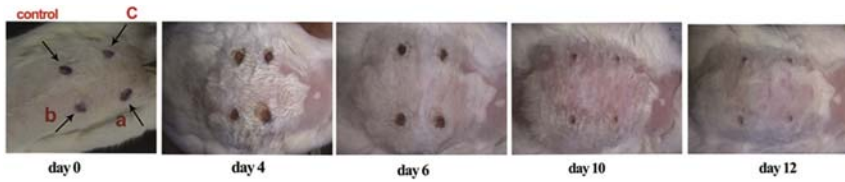

Figure 13.6 Trend of wound healing after 4, 6, 10, and 12 days in wounds covered by AgNPs/PVA/PVP/PEC/MF nanofibers containing 0.2%, 0.5%, and 0.7% wt.%, respectively, of AgNPs, against PVA/PVP/PEC/MF nanofibers as control.

and enhance cell regeneration. Despite being highly soluble, it took between 60 and 84 hours for 50% of the hyaluronic acid to be released from the textile [71]. These fabrics demonstrated anti-inflammatory properties, enhanced collagen formation, and prevented adhesion of cells in peritendinous and tendon regions.

3. Conclusions and future prospects

Polysaccharides offer a great deal of potential for developing distinctive, functional, and environmentally friendly textiles containing metal nanoparticles. Besides, combining metal nanoparticles and polysaccharides has broadened the horizons of textile functionalization, allowing for the emergence of stacking properties, new functions, and synergistic improvements. In textiles, polysaccharides substantially improve the washability, concentration, and activity of metal nanoparticles by reducing and stabilizing them. In addition, metal nanoparticle contamination of the environment can be prevented by lowering their concentration without affecting their enhanced washing fastness and antimicrobial activity, which should be emphasized greatly. Furthermore, polysaccharides should be studied for their long-term sustainability as well as their capability to reduce (or remove) toxic reduction chemicals. In conclusion, the interaction between metal nanoparticles and polysaccharides determines the most crucial characteristics of next-generation textiles.

Strategies that do not require covalent bonds, such as layer-by-layer deposition and heterocoagulation, have been demonstrated to be effective in the synthesis of highly tailored, shape- and size-specific structures. Nevertheless, noncovalent bonds can be destabilized under certain circumstances. In contrast, the covalent bonding between inorganic nanoparticles and polymers is a suitable alternative to the noncovalent attachment. The integration of inorganic nanoparticles with polymer chains, particularly in bioconjugation for bioengineering applications, has been the subject of extensive research. In contrast, very few studies have investigated the attachment of nanoparticles in hierarchical ways of various types. This is unquestionably an area that will be investigated in the near future, as it offers extremely intriguing opportunities for the synthesis of new materials through the assembly of multifunctional nanoparticles. It is still unclear how the surface functionalization of the nanoparticles affects the overall morphology of hybrids formed by polymerization with

surface-modified inorganic nanoparticles. A deeper comprehension would facilitate the development of new structures like patchy and Janus nanoparticles, which have gained popularity in the last few years. Although in situ precipitation methods offer the advantage of simplicity and a wide range of sizes, controlling the final morphologies remains difficult. Moreover, the fabrication of these types of system is conducted under favorable circumstances, thereby severely limiting the chemical compositions that can be obtained using these systems. It is recommended that further research be carried out to examine the techniques under extreme pressure and temperature. We believe that the synthesis of hybrid nanoparticles employing all in situ methods of preparation by simultaneously polymerizing and forming the inorganic component is an unexplored area that requires further investigation.

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SECTION 5

Functionalized nanoparticles-based antimicrobial coatings for biomedical applications

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CHAPTER 14

Drug delivery and functional nanoparticles

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1. Introduction

Nanotechnology is the science of developing and investigating materials at the nanometer scale. It is an interdisciplinary field constituting of chemistry, physics, biomedicine, and engineering. Strictly speaking, the description of manipulating materials at the nanoscale involves matters ranging from 1 to 100 nm, but biomedical researchers recognize it within a broader range (submicron scale). There have been remarkable developments in this field, where nanomaterials are being translated into biomedicine as drug-delivery systems for diagnostic and therapeutic applications.

The bioavailability of drugs depends on various factors such as the route of administration and solubility. Therefore, a drug with poor aqueous solubility will not be biologically and pharmaceutically advantageous [1]. On the other hand, one of the primary issues with a certain group of drugs, e.g. anticancer drugs, is the inability to target a specific tissue. Moreover, these drugs have high toxicity profiles. An ideal drug-delivery system, thus, should primarily be concerned with temporal delivery or controlled release of the drug, and its ability to specifically reach the target. Targeted drug delivery should provide an easy and efficient way to deliver the drug to its target cells or tissues without compromising on the drug's chemical activity, adequate loading, and controlled release [2]. When these two criteria are met, it will increase the efficacy of the drug and reduce its adverse effects [3,4].

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An optimal drug-delivery formulation, therefore, should be biocompatible, specific to the target site, avoid enzymatic degradation, have optimal drug loading and release, and be cost-effective. The nanoparticle (NP)-mediated drug-delivery systems have come as a boon in the past few decades, with their small size (measuring only up to hundreds of nm), unique and advantageous physicochemical characteristics, increased surface-to-volume ratio, and diverse therapeutic potential [5]. It is now possible to modulate the pharmacokinetic as well as pharmacodynamic properties of drugs to improve their therapeutic index [6]. NPs can navigate the systemic, microenvironmental, and cellular barriers to overcome patient heterogeneity [7] (Fig. 14.1). Moreover, cell surface-specific and organelle-specific targeting have promised a paradigm shift in cancer therapeutics [4]. More and more NP research is generating positive results in both in vitro and in vivo models [8].

NPs improve water solubility of the drug, enhance the intracellular uptake, preserve the metabolic stability, and diminish its cytotoxic effects, providing superior efficacy and lowered toxicity profiles [9]. However, these drug parameters further depend on a variety of extrinsic (e.g., renal clearance) and intrinsic factors (e.g., particle size, surface area, surface charge) [10],

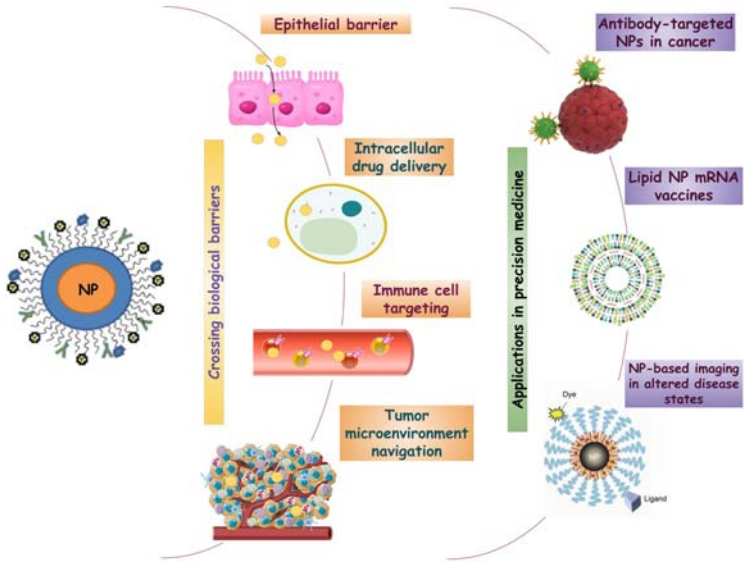

Figure 14.1 Nanoparticles (NPs) in overcoming biological barriers and their applications in precision medicine. NPs can improve drug delivery and enhance the performance of therapeutics, imaging, and vaccines.

depending on which most, if not all nanocarrier actions are associated with unwanted side effects that diminish their value in medicine. Notably, the half-life of NPs primarily depends on their interaction with the macrophages of the reticuloendothelial system [11]. To reduce clearance by macrophages, NPs can be coated with a hydrophilic layer, usually with polymers such as polyethylene glycol, a process known as PEGylation [12]. Overall, the modern NP systems fine-tune the physicochemical properties of NPs to alter their dimensions, composition (organic, inorganic, or hybrid systems), shapes (rod, multilamellar, spherical), and surface properties (coating processes, PEGylation, functional groups, surface charge). There is also a translational gap between the success of NPs in animal models and humans. The difference in functionality can be attributed to species differences and heterogeneity among patient populations, the latter of which is underexplored [13].

In this chapter, we focus on the advancements in NP-mediated drug-delivery systems and how they have facilitated improved treatment options for the individual. The mechanistic actions and clinical applications for each of the NPs have been discussed in the context of particular disease categories or organ systems. The obstacles in the development and marketing of nanotherapeutics have also been scrutinized.

2. Classification

NPs are categorized into organic (polymer-based) and inorganic (and metallic) (Fig. 14.2). The organic nanoparticles include liposomes, polymer-based micelles, dendrimers, and solid lipid NPs, while the inorganic group can be classified into gold NPs, silica, carbon nanotubes, magnetic, and quantum dots.

3. Organic

Organic NPs are carbon-based NPs characterized by their colloidal stability and high biocompatibility, allowing them to incorporate a wide combination of different drugs [14]. They can further be subdivided into amphiphilic systems and synthetic methods. The newer generation of carriers is often constituted from suitable combinations of both of these methods (the supramolecular approach) [15].

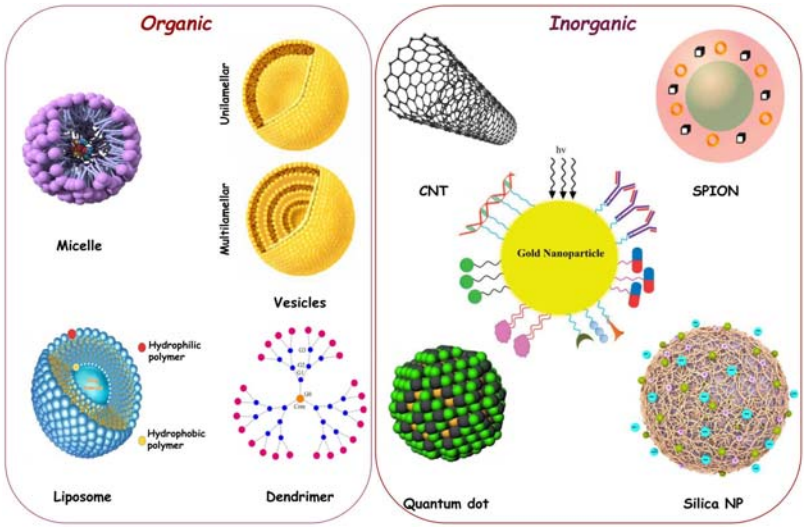

Figure 14.2 Classification of nanoparticles (NPs). Organic NPs include micelles, vesicles, liposomes and dendrimers. Inorganic NPs include carbon nanotubes (CNT), superparamagnetic iron oxide nanoparticles (SPION), gold NPs, quantum dots, and silica NPs.

3.1 Amphiphilic nanocarriers (from self-assembly processes)

These nanocarriers are assembled from basic building blocks of polymer by virtue of noncovalent bonding, including steric hindrance, hydrophobic effect, van der Waals interaction, and solvation [15,16]. Being amphiphilic, they possess a charged or uncharged hydrophilic portion that interacts favorably with surrounding water, and a hydrophobic part made up of hydrocarbon chains, which minimizes the interaction with water. These two processes work simultaneously to cause a microphase separation and aggregate formation above the concentration when micelles start forming, also known as the critical micelle concentration (CMC) [17]. The critical packing factor parameter can be varied to manipulate the nanocarrier architecture into the desired shape, e.g. spherical ($C_{pp} \leq 1/3$), cylindrical ($1/3 \leq C_{pp} \leq 1/2$), vesicular ($1/2 \leq C_{pp} \leq 1$), lamellar ($C_{pp} = 1$), or inverted phase ($C_{pp} > 1$) [17]. As vehicles, micelles and liposomes are the basis of many of the existing targeted or combination therapies involving functionalization [2,15].

3.2 Micelles and vesicles (from polymer-based amphiphiles)

By modulating the weight fraction (Fw) of the hydrophilic block, various amphiphilic nanocarriers of different shapes and morphologies can be obtained, e.g., spherical micelles (Fw = 55−70%), spherical vesicles (Fw = 45−55%), and vesicles (Fw = 20−40%). Micelles have gained much popularity in drug-delivery applications [18], as their hydrophobic core can incorporate the lipophilic active compounds or drugs. This creates a favorable microenvironment that enhances the solubility and improves the bioavailability of the drug. The hydrophilic shell, on the other hand, provides the stabilizing interface with the aqueous medium, inhibiting aggregation and undesired reactions with other molecules, and enhances the colloidal stability. Vesicles have a characteristic bilayer structure. They are prepared from polymerosomes (amphiphilic polymers). Their aqueous interior core encapsulates hydrophilic molecules and integrates lipophilic molecules internalized within the bilayer membrane.

When the polymer concentration is greater than the CMC, the hydrophobic shell could be modulated to enhance the colloidal stability, which in turn will result in a longer circulation time in the body for the drug-loaded micelles. For nanoscaled micelles (size <200 nm), nonselective uptake by the reticuloendothelial system is reduced, resulting in increased permeability and retention, especially for solid tumor tissue sites (known as 'passive targeting') [18].

The controlled release of drugs is of pivotal importance in drug delivery. Many polymers have shown promise in applications with a high degree of control. Natural polymers such as dextran, heparin, chitosan, and hyaluronan have been widely investigated [19]. However, synthetic polymers as the building blocks for NP delivery platforms have been gaining attention recently. Polycarbonates, polyesters, polypeptides, and polyamides constitute the most widely utilized synthetic polymers. Among these, saturated poly(α-hydroxy esters) (including poly(lactic acid) and poly(lactic-co-glycolide), because of their low toxicity and immunogenicity, excellent safety profile, and good biocompatibility, have been most employed for targeted drug delivery [20−23].

3.3 Liposomal nanocarriers

Polymer-based NPs as drug-delivery systems are widely used for cell and animal model experiments. However, lipid-based systems are still dominant over the market as far as clinical applications are concerned. Indeed, these

lipid-based (natural or synthetic) vesicles provide a versatile platform for enhanced drug delivery [24,25]. They may be classified into small unilamellar vesicles (size <100 nm), large unilamellar vesicles (100−1000 nm), or giant unilamellar vesicles (>1 μm). They may also have concentric bilayer surfaces—known as multilamellar vesicles [26]. In the case of solid lipid nanoparticles, the (lipophilic) drug compound is contained inside a solid hydrophobic lipid matrix, coated by a phospholipid monolayer to stabilize with the surrounding aqueous environment [27].

Liposomal formulations are advantageous, because they self-assemble and control the colloidal stability around the diseased tissue microenvironment [26−29]. Moreover, due to the wide availability of the base compounds, these molecules are easy to manufacture, and more efficient at controlled drug release. It is worth noting that the inclusion of the drug (or any macromolecule) can strongly influence the lipid bilayer structure in the nanocarriers, while the final morphology would be determined by interactions with other compounds, and the size and charge of the molecule [27,30]. However, by encapsulating the active compound, the liposomal bilayer provides it with additional protection against drug degradation. All these factors contribute to the improved therapeutic efficacy of the carriers.

Liposomal nanocarriers are extensively used in cancer therapeutics. Their low toxicity profile, biocompatibility, ease of size modulation, and intermediate solubility (hydrophilic/hydrophobic) make them excellent candidates [31] (Table 14.1). As lipids are degraded mainly in the gastrointestinal tract, the liposomal formulations for cancer therapy are primarily administered intravenously [32,33]. Anticancer drugs that have been most extensively investigated for clinical use in cancer therapeutics are doxorubicin, paclitaxel, cisplatin, and vincristine [34,35].

As mentioned above, hydrophilic polymer moieties (natural or synthetic) may be attached to the lipid NPs to improve their circulation. Such conjugation (most commonly PEGylation) creates a highly hydrated surface, which inhibits hydrophobic or electrostatic interactions, and reduces the liposomal uptake process by the macrophages. This process allows the carrier to overcome the immune mechanisms, and improves the half-life, biocompatibility, and toxicity profile [50,51]. Therefore, PEGylated liposomes are "stealth liposomes" that can escape opsonization and phagocytosis [25]. Another advantage of PEGylation is the prevention of biofilm formation. The interaction between nanocarriers and biological tissues results in protein adsorption at the carrier surface, which may initiate cellular attachment, microbial colonization, and ultimately biomaterial failure [37].

Table 14.1 Advantages and disadvantages of functionalized nanoparticles in drug-delivery systems.

Types of nanoparticles	Advantages	Disadvantages	References
Organic			
Lipid-based formulations	Biodegradability Biocompatibility Low toxicity Intermediate solubility Increased permeability and tissue retention	Moderate loading capacity Rapid clearance Short shelf-life	[18,31,36]
Polymer-based	Biodegradability Ease of size modulation Prevention of biofilm formation	Metabolism and elimination routes yet to be elucidated for many polymer-based NPs Tissue accumulation	[31,37,38]
Dendrimers	In vitro transfer of genetic material Nucleic acid-based therapeutics Low immunogenicity	Cytotoxicity Nondegradability	[39–41]
Inorganic			
Carbon nanotubes	High surface functionalization Efficient drug loading	Latent toxicity Nondegradability Hydrophobicity	[42,43]

Continued

Table 14.1 Advantages and disadvantages of functionalized nanoparticles in drug-delivery systems.—cont'd

Types of nanoparticles	Advantages	Disadvantages	References
Mesoporous silica	Large surface area for drug loading Controllable porous structure	Low stability Rapid elimination	[44,45]
Gold	Ultra-small size and distinct, tuneable conformations Excellent optical properties	Potential cytotoxicity Nondegradability	[41,46]
Quantum dots	Photoluminescence Diverse synthetic methods	Toxicity Nonspecific tissue damage	[47,48]
Iron oxide	Tuneable pore size and functionalization Large surface area	Oxidative stress Poor dispersion Effect on iron homeostasis	[41,49]

Indeed, studies have found that PEGylated liposomes have a lower volume of distribution, lower plasma clearance, and minimal interactions with nondiseased targets [25,52]. However, we need to be careful as excessive PEGylation can diminish cellular uptake—undesirable for cancer treatment—and hence, a balance needs to be achieved with hindered protein adsorption and cellular uptake by cancer cells [53]. Furthermore, incorporating ligands, e.g. peptides, aptamers, and monoclonal antibodies, improves tissue specificity during sustained release of the drug [54,55]. The modification of functional groups in antibodies can be used for targeted therapy by conjugating them to the liposomal surface (immunoliposomes) [56]. Liposomes targeting epidermal growth factor receptor (EGFR), conjugated with thiolated antibody, showed more efficient transfer of siRNA in mice compared to nontargeted liposomes. Lung metastasis was also suppressed [57]. Paclitaxel liposomes with mitochondrial targeting were effective in drug-resistant A549 cells [58], implying its possible efficacy in multidrug-resistant cancer. Liposomes functionalized with anti-CA-IX antibody were more efficacious in lung cancer in mouse models [59].

The drug-release process from NP carriers can also be stimulated externally by light [60], heat [61], magnetic field [62], and ultrasound [63], or internally by enzymes [64], pH [65], or redox [66]. Moreover, liposomes can multitask with simultaneously carrying out active targeting and diagnostic endeavours [55].

Overall, liposome-mediated drug delivery produces fewer side effects than nonliposomal anticancer formulations, and presents an efficacious approach toward targeting diseased tissues.

3.4 Dendrimers

Dendrimers are characterized as NPs having polymeric concentric branching attached to a central core through covalent bonding. The concentric layers end in a number of external surface functional groups [67]. They are the products of a stepwise synthesis sequence tailor-made for the desired molecular design. Dendrimers are highly characterized for conjugating chemical species onto the surface, which makes them great candidates for the transfer of genetic material in vitro [39,68,69]. The temperature and pH of the solution can affect the structure of dendrimers [70], whereas the drug-delivery process is affected by electrostatic forces. Dendrimers can be useful in increasing the solubility and bioavailability of

hydrophobic drugs by trapping them in their intramolecular cavity or conjugating them to the surface functional groups.

The combination of bioactive ligands with dendrimers has emerged as a new field, where dendrimer conjugates containing peptides or polysaccharides can be used as antimicrobials. Dendrimers also enhance the solubility and stability of compounds, making them beneficial in nucleic acid-based therapies [40,71]. As nucleic acids readily form complexes with positively charged surfaces, dendrimers are also promising carriers in gene therapy. These compounds are then endocytosed and enzymatically degraded. In this way, the targeting genes are released [72].

More studies are required to shed light upon the structure—function relationship of dendrimer-ligands and the interactive role of conjugation in targeted drug delivery and release.

4. Inorganic NPs

Inorganic NPs have been in use recently for the development of drug carriers. They are constituted of a core (an inorganic component, e.g. gold, iron oxide) and a shell (organic polymers), the latter for either shielding the core from physicochemical interactions with the external environment or for conjugation purposes [73,74]. Because inorganic NPs generate imaging contrast by computed tomography (CT), magnetic resonance (MR), or positron emission tomography (PET), they can be employed for diagnostic imaging of a particular diseased region [75]. Nevertheless, due to high toxicity and limited success so far, they are not widely used.

4.1 Carbon nanotubes (CNTs)

CNTs are composed of graphene sheet(s) rolled up into a cylindrical tube-like shape. They can be single-walled (0.4—2 nm for outer diameter) or multiwalled (2—100 nm outer diameter) [76,77]. Being from the fullerene family of compounds, CNTs possess some unique physical and biological properties, including a high aspect ratio (length:diameter = 200:1), high mechanical strength, ultralight weight, and high thermal and electrical conductivity [76,77]. A high propensity for surface modifications makes them promising candidates as drug carriers. They can be spherical, ellipsoid, or take other forms, but what is unique is their high penetrating ability (due to the nano-needle shape) which, combined with high surface functionalization, high conductivity, and intrinsic stability, makes them one of the most investigated nanocarriers in therapeutics [42,78].

Cancer chemotherapeutic agents can be attached to the surface of CNTs (noncovalent bonding) or encapsulated inside the inner cavity [75]. Drugs such as methotrexate, doxorubicin, and cisplatin can be delivered in a target-specific manner through surface functionalization [79]. They have also shown the potential to carry plasmid DNA, siRNA, and aptamers [77]. CNTs are also good candidates for the early diagnosis of cancers. Due to their strong absorption in the near-infrared region, they can be used in photothermal ablation therapy [80].

The primary drawbacks for CNTs are cytotoxicity, non-biodegradability, and poor solubility. However, the latter can be bypassed through surface functionalization. PEGylation can be employed for this purpose and also to lower the toxicity.

4.2 Gold

Gold NPs have been extensively investigated in the areas of diagnostics as well as therapeutics [81,82]. A gold atom constitutes the core that is surrounded by negative surface charge conjugated to ligands for active targeting. In biomedicine, gold NPs are primarily prepared through the colloidal synthesis method, which allows strong modulation of the optical and electrical properties. Gold NPs can be of varied shapes, such as nanorod, nanosphere, nanoshell, and nanocage, and sizes (1−100 nm) [82,83]. Their surface negative charge allows for functionalization of a wide range of biomolecules (drugs including antibiotics, proteins, nucleic acids) and targeting ligands. In human cell lines, gold NPs have shown their nontoxicity, and in vivo, their biocompatibility and degradability have been investigated with good results [46,84].

An interesting facet about gold NPs is their surface plasmon resonance effect, caused by the light-induced collective electron oscillation on the NP surface. By changing the shape of the NP, light absorption and scattering can be controlled at the desired wavelength. This property can be used to maintain the colloidal stability of gold NPs and kill cancer cells [85]. These nanocarriers have shown promise in various biomedical applications, such as tumor imaging, biosensors, and multimodal drug-delivery systems [46,82]. To increase the efficiency of the cellular uptake, cations such as quaternary ammonium can be utilized alongside a thinner, more hydrophilic coating to enhance favorable electrostatic interactions [86,87]. Cellular affinity ligands also have been investigated, which, through intracellular triggered release, enhanced the therapeutic effect in chemoresistant cancer cells [88]. On the

diagnostic side, a DNAzyme-based metal sensor has been developed for intracellular metal ion detection [89].

4.3 Iron oxide

Iron oxide NPs, namely Fe_2O_3 and Fe_3O_4, have been investigated in drug delivery with positive results [49,90]. This is achieved due to the superparamagnetic effect, i.e. the magnetization of NPs at sizes 10–20 nm. An external, high-gradient magnetic field can be used to concentrate the NPs at a specific diseased site [49,90,91]. As with many other forms of NPs, surface functionalization hinders aggregation, protects from oxidative damage, and avoids nonspecific binding through targeted ligands. Various biomolecules such as antibodies, peptides, and anticancer drugs may be used to target specific receptors overexpressed in cancer cells [92]. For example, surface-conjugated iron oxide NPs bound to methotrexate increased the drug uptake in cancer cells [91].

However, iron oxide carriers have limited biomedical applications due to their possible effects on iron homeostasis, regulation of gene expression, oxidative stress, and altered cellular response [49].

4.4 Quantum dots (QDs)

These are fluorescent semiconducting inorganic nanocarriers, which are constituted of group II and group VI elements of the periodic table (e.g., CdS, ZnS, CdTe). The synthesis of QDs are either by a top-down approach (e.g., X-ray lithography, ion implantation) or a bottom-up approach (chemical reduction and self-assembly) [47,93]. QDs are usually composed of a semiconductor nanocore (diameter 2–10 nm) surrounded by another semiconductor, encapsulated by a cap. The most commonly investigated QD has CdSe as the core and ZnS in the outer shell. Their unique optical properties make them possible candidates for real-time imaging during drug delivery and drug release [47,85,93]. In fact, since they offer near-infrared emission spectrum (>650 nm), and high quantum yield and resistance to photobleaching, they are preferred over organic fluorophores. QDs are part of the new class of biosensors for cancer theranostics [47,93].

Toxicity is main concern with QDs due to the involvement of heavy metal ions. Surface functionalization with biocompatible molecules can help reduce the toxicity. Further, PEGylation can help increase the permeability and retention of the drug in specific tumor sites [53]. Active

targeting of tumor sites using peptides or monoclonal antibodies can help develop theranostic platforms [94].

4.5 Silica

Due to their simplistic synthesis process and porous architecture, they are a popular option as nanocarriers [95,96]. They have a large surface area, high loading capacity, physicochemical stability, and narrow, controllable pore distribution. They can carry a large amount of anticancer drugs to target specific tissues [44]. Anticancer drugs such as methotrexate, paclitaxel, and doxorubicin have been successfully delivered using mesoporous silica NPs. PEGylation can be done to increase bioavailability and distribution [97,98]. Several physical (magnetic stimuli, light, temperature) and chemical factors (pH, enzymes) can be utilized to induce controlled drug release using silica NPs [99,100]. They are at once suitable as biosensors, targeted drug-delivery systems, and in diagnosis. Hu and colleagues [99] showed that silica NPs tagged with metalloproteinase-2 (MMP2)-activated fluorescent imaging peptides enhanced tumor targeting in cells through receptor-mediated endocytosis. Applications in the clinical side still remain distant, although silica NPs are definitely promising tools.

5. Applications

Targeted delivery comprises of (1) accumulation of the drug in the desirable site and (2) tissue-specific direction of the compound. To achieve this, the loaded compound must be retained in the circulation for the desirable period of time, should evade the reticuloendothelial system, release the drug in a controlled manner, and specifically target the cell/tissue [101]. Targeted delivery of NPs has been widely studied in cancer. In fact, one-fifth of the NPs already in use clinically are part of anticancer therapeutics.

5.1 Cancer

One of the major causes of mortality around the globe, cancer has been a major hurdle to overcome in clinics. Chemotherapeutics suffer from various drawbacks such as low tissue specificity, low water solubility, and dose-dependent toxicity [102]. Another major challenge is multidrug resistance—resistance to multiple drugs—which can be inherent or acquired. The ATP-dependent efflux transporters are mainly responsible for this phenomenon [103,104]. NP-mediated delivery systems have been able

to overcome these limitations to a great extent by increasing target specificity and controlled drug delivery [105]. Moreover, drug conjugates can facilitate targeted drug delivery and decrease systemic drug toxicity [106].

Two major mechanisms are utilized in the delivery of antitumor drugs—active targeting and passive targeting [107]. In active targeting, the targeted cells are recognized selectively through surface-conjugated ligands or stimuli-based carriers [108,109]. The most commonly used FDA-approved formulations are drug combinations with polymeric NPs. Doxil (PEGylated liposomal formulation of doxorubicin) has been able to extend the circulation time and reduce immune interactions. Doxil also has a lower cardiotoxic effect [110]. Vincristine sulfate (Marqibo), made of cholesterol and sphingomyelin, improves the circulation time and expedites dose intensification compared to the standard drug [111]. Several other liposomal formulations are under clinical trial [112,113]. Lipoplatin (cisplatin), a combination of soy phosphatidylcholine, cholesterol, dipalmitoylphosphatidyl glycerol, and methoxy-PEG-distearoyl phosphatidylethanolamine has shown less nephrotoxicity. It has been declared as an orphan drug in breast cancer, advanced gastric cancer, and pancreatic adenocarcinoma by the European Medicines Agency [114–116]. A covalently conjugated Maytansine derivative DM1 to trastuzumab (Kadcyla) is approved for $Her2^{+}$ breast cancer [117,118]. The DM1, after internalization, triggers apoptosis. Other FDA-approved therapeutic NPs include Abraxane (paclitaxel) and Rapamune (rapamycin), both of which have lower side effects [119].

Passive targeting, on the other hand, is dependent on the distinctive features of the tumor compared to normal tissue, which helps in accumulating the therapeutic agent in the tumor.

5.2 Infectious diseases

Resistance to antimicrobials results in increased dose and frequency, which causes increased toxicity and side effects. Many pathogens also stay dormant inside the cell, where the drug cannot reach or act [120]. These limitations can be overcome by NPs. Polymeric, nonpolymeric, and liposomal delivery systems improve the activity of antimicrobials [121]. Lipoquin is a ciprofloxacin formulation that has a sustained release of 24 h, reducing the side effects of the drug [122]. Similarly, the antifungal liposomal preparation Ambisome (Amphotericin B) reduces drug toxicity, allowing it to be used in immunocompromised individuals, e.g. HIV patients [123,124]. NPs are utilized in viral infections as well. Virosomal vaccines can carry viral

adjuvants, e.g. protein fractions, viral glycoproteins, etc. Currently, Inflexal V (for hepatitis A) and Epaxal (for influenza) are in use for therapy [125]. In vaccine formulations, it creates a safer vaccine profile and long-lasting immune response. Medical devices can also be coated with antimicrobial nanodevices to prevent biofilm formation, e.g. silver NPs for central venous catheters [126,127]. Further applications in diagnostics and medical devices include Endorem, Silverline, and Verigene [34,128,129]. Table 14.2 summarizes the utility of functionalized NPs in infectious diseases.

5.3 Cardiovascular diseases

For cardiovascular disorders, NP-mediated drug delivery primarily involves increased bioavailability and targeted delivery for vascular restenosis. Liposomal preparation (cholesterol and phosphatidylcholine) of the drug sirolimus (mTOR inhibitor) coated with chitosan significantly inhibits vascular restenosis [140]. Carvedilol is widely used for myocardial infarction, hypertension, congestive heart failure, and post-MI left myocardial dysfunction. Niosome-based NP formulation of carvedilol increased the plasma concentration by almost twofold compared to the free drug. Therefore, it increases the bioavailability as well as the therapeutic effect [141]. Similarly, a resveratrol nano-formulation of liposomes and solid lipid NPs increases oral bioavailability and controlled release [142]. Hypoxia-mediated injury in myocardial infarction can be overcome by angiogenic therapy with vascular endothelial growth factor (VEGF). Poly(lactic-co-glycolic acid) (PLGA) NPs loaded with sustained-release VEGF improved vasculogenesis and cardiac tissue remodeling in ischemia—reperfusion injury [143]. Magneto-fluorescent NPs and ligand-binding polymeric micelle formulations are targeted nano-delivery systems that can be used in visualizing and treating lesions in atherosclerosis [144].

5.4 Ocular diseases

Several ocular barriers make the eye impermeable to many therapeutic agents, e.g. the corneal epithelium, muco-aqueous tear layer, and the blood—retina barrier [145]. Miotics, cycloplegics, antiinflammatory agents, antimicrobials, and surgical adjuvants are some of the modalities improved with NPs. The advantages include targeted delivery, enhanced bioavailability to the eye, and lowered irritation [146]. Again, liposomes and nanopolymers are the most widely used delivery systems, which are capable of targeting the specific compartment in the eye and enhancing corneal

Table 14.2 Functionalized nanoparticles and some of their applications in infectious diseases.

NP-delivery system	Drug/method	Application	Study group/ experimental model	Author, year
Liposome	Ciprofloxacin	Intranasal preparation for *B. anthracis* treatment and PEP	In vivo	Stratilo et al. 2020 [122]
Liposome	Amphotericin B	Invasive aspergillosis	Clinical	Cornely et al. 2007 [124]
Magnetic NP (FePt)	Vancomycin	Vancomycin-resistant enterococci and *S. aureus*	In vitro	Gu et al. 2003 [130]
Liposome	Polymyxin B	*P. aeruginosa*	In vitro	Alipour et al. 2008 [131]
Polyacrylate glyco-NPs	Ciprofloxacin and β-lactam	*S. aureus* and *B. anthracis*	In vitro	Abeylath et al. 2008 [132]
Liposome	Amphotericin B	Visceral leishmaniasis	Clinical	Sundar et al. 2010 [133]
Functionalized carbon nanotubes	Amphotericin B	*L. donovani*	In vitro and in vivo	Prajapati et al. 2011 [134]
Gold NPs	CRISPR-mediated RNA biosensor	POCT for SARS-CoV-2 detection	Clinical	Lopez-Valls et al. 2022 [135]
Gold NPs	β-Lactam antibiotics	Detection of bacterial contaminants (*S. aureus*, *P. aeruginosa*, *E. coli*)	In vitro	Elliott et al. 2021 [136]

Gold NPs	Conjugation of V3 peptide of HIV-1 gp120	Synthetic HIV vaccine candidate	In vivo	Gianvincenzo et al. 2015 [137]
Gold NPs with nanorods	Glycoprotein antigen of RSV	Immune activation of primary T cells	In vitro	Stone et al. 2013 [138]
Gold NPs	Imipenem/cilastatin	Induction of M2 macrophage polarization	In vivo	Taratummarat et al. 2018 [139]

NPs, nanoparticles; PEP, postexposure prophylaxis; POCT, point-of-care testing; RSV, respiratory syncytial virus.

permeability [145,147]. Pranoprofen, as a formulation of PLGA, enhances the ophthalmic delivery and antiinflammatory effect of the drug [148]. Diclofenac, cefuroxime, and dexamethasone are other drugs which have their ocular bioavailability increased as chitosan-based polymeric NP encapsulations [149]. These drugs are protected by the NPs from metabolic degradation [150]. A lipid-based formulation of brimonidine has been successfully used to treat glaucoma [151]. PLGA-based or PEGylated sustained-release preparations of dexamethasone and curcumin can prevent corneal graft rejections [152,153].

5.5 Autoimmune diseases

Recently, the interaction between NPs and the immune system has gained much attention. Developing NPs that can interact with the different cellular components of the immune system can be beneficial in autoimmune disorders, and inflammatory diseases in general. Several nano-delivery strategies to combat constituents of the innate as well as the adaptive immune system to treat various conditions are summarized in Table 14.3.

Drug-delivery NPs for autoimmune disorders primarily have applications in rheumatoid arthritis (RA) and acquired immunodeficiency syndrome (AIDS). For RA, the repetitive long-term treatment causes systemic adverse effects. NP systems can directly target the synovial membrane, i.e. the inflamed tissue, and reduce the systemic side effects [173]. The PEGylated nanoformulation of Certolizumabpegol (CZP), a TNF-α inhibitor, has an increased half-life of 14 days and showed promising results in clinical trials of RA patients [174]. Water-soluble C60 fullerenes showed reduced synovitis and lessened bone resorption and destruction in RA treatment in mice models [175]. Current nano-delivery systems also provide enhanced target specificity and sustained release of anti-HIV drugs, which limit the systemic side effects [176]. For example, poly(propyleneimine) dendrimer-loaded efavirenz functionalized with Tuftsin recognizes mononuclear phagocytes and increases drug uptake specifically in infected macrophages [177].

5.6 Pulmonary medicine

There is a lack of effective treatment for restoring pulmonary function in diseases such as asthma, chronic obstructive pulmonary disease, cystic fibrosis, and pulmonary tuberculosis. Traditional therapy involves inhalers,

Table 14.3 Nano-delivery strategies against the immune system in inflammatory conditions.

NPs/carriers	Drugs/functional molecules	Component of the immune system	Application	Disease model	Author, year
PLG	—	Monocytes and neutrophils	Autoimmune encephalomyelitis	In vivo	Saito et al. 2019 [154]
PLG	Neutrophil membrane coating	Neutrophil	Rheumatoid arthritis prophylaxis	In vivo	Zhang et al. 2018 [155]
Liposome	Clodronate	$CD68^+$ macrophage	Rheumatoid arthritis	In vivo	Zhang et al. 2019 [156]
Dendrimer (folate-targeted)	Methotrexate	Macrophage	Rheumatoid arthritis	In vitro and in vivo	Thomas et al. [157]
PEI	Catalase	Macrophage	Parkinson's disease	In vivo	Brynskikh et al. 2010 [158]
SPIO	—	Monocyte	MRI-cell tracking for inflammatory cells	In vitro, in vivo, and clinical	Richards et al. 2012 [159]
PLG	—	Macrophage	Spinal cord injury	In vivo	Park et al. 2019 [156]
Hyaluronic acid-PEI	MicroRNA-223	Macrophage	Lipopolysaccharide-induced inflammation	In vitro and in vivo	Tran et al. 2016 [160]
α-gal	—	Macrophage	Diabetic wound healing	In vivo	Kaymakcalan et al. 2020 [161]

Continued

Table 14.3 Nano-delivery strategies against the immune system in inflammatory conditions.—cont'd

NPs/carriers	Drugs/functional molecules	Component of the immune system	Application	Disease model	Author, year
EGFP-EGF1-conjugated PLG	CCR2-shRNA	Macrophage	Atherosclerosis	In vitro	Wu et al. 2020 [162]
PLG	Myelin antigen	Th1, Th17 lymphocytes	Autoimmune encephalomyelitis	In vivo	Hunter et al. 2014 [163]
Dextran-coated or PEGylated iron oxide	Peptides-MHCII	Treg cells	Autoimmune encephalomyelitis, nonobese diabetes	In vitro and in vivo	Clemente-Cesares et al. 2016 [164]
Curcumin	—	Treg cells	Dextran sulfate sodium-induced colitis	In vivo	Ohno et al. 2017 [165]
Gold NPs	Methotrexate	γδ T cells, $CD4^+$ T cells, and neutrophils	Psoriasis	In vivo	Ozcan et al. 2020 [166]
PEGylated PLG	Eggmanone	$CD4^+$ T cells	Rheumatic autoimmune disease	In vitro	Haycook et al. 2020 [167]
Liposome	CD22	Citrulline-specific B-cells	Rheumatoid arthritis	In vitro and in vivo	Bednar et al. 2019 [168]
Iron oxide	Ocrelizumab	B cells	Multiple sclerosis	In vivo	Carnasciali et al. 2021 [169]
PLG	Metformin	IL1β and TNF-α	Periodontitis	In vivo	Pereira et al. 2018 [170]

Silk fibroin	—	IL1β	Experimental colitis	In vitro and in vivo	Rodriguez-Nogales et al. 2016 [171]
Polydopamine poly(ethylene glycol)	DNase-1	cfDNA	SARS-CoV-2	In vivo and clinical	Lee et al. 2021 [172]

CCR2, chemokine (C-C motif) receptor 2; cfDNA, cell-free deoxyribonucleic acid; PEI, polyethylenimine; PLG, poly(lactic-co-glycolate); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SPIO, superparamagnetic iron oxide; TNF-α, tumor necrosis factor alpha.

where the active drug molecules are released in aerosol form. They are limited by high lung toxicity, aerosol sizes (e.g., particles >5 μm settle in the upper respiratory tract) and decreased efficiency. NP-based formulations increase bioavailability and controlled release and decrease drug dosage and frequency. Natural (chitosan, alginate, gelatin) as well as synthetic (PLGA, PEG) polymers are used in the development of nanoformulations [178,179]. Polyamidoamine dendrimers used as nanocarriers showed promise as part of vibrating-mesh nebulization of beclomethasone dipropionate [180]. Moreover, polystyrene or silver-based engineered NPs can be utilized for pulmonary immune homeostasis and vaccine delivery [181].

5.7 Neurodegenerative disorders

The blood–brain barrier (BBB) with its specialized properties allows selective entry of circulatory drugs into the central nervous system. Therefore, usually a high drug dosage is necessary for neurodegenerative diseases, which also leads to increased systemic adverse effects. NP-based approaches build upon targeted delivery after the drug crosses the BBB [182,183].

For Alzheimer's disease, treatment options include cholinesterase inhibitors and N-methyl-d-aspartate (NMDA) receptor antagonists. The NP-based formulations (polymeric, quantum dots, liposomal) enable higher passage of the drug through the BBB [184–187]. Neuroprotective compounds such as metal chelators and antiamyloid NMDA antagonists have been attempted by nanocarriers to reduce Aβ aggregates [188]. Targeted delivery of dopamine using liposomal or polymeric NPs improves sustained release and reduces adverse effects for several drugs such as bromocriptine and ropinirole for Parkinson's disease [189–191]. Another approach in Parkinson's disease is using PEGylated liposomes for hindering neuronal death [192,193]. These liposomal systems loaded with glial cell-derived neurotrophic factor increase dopamine levels by decreasing the loss of dopaminergic neurons [193,194]. Therapeutic nanosystems for the incorporation of genomic material to overexpress desired proteins or inhibit deleterious gene expression have been attempted with success in striatal cells and grafted animal models [195,196].

A few approaches have been reported in the literature for amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS). MS is a debilitating disease, and severely affects its sufferers' quality of life [197]. Recently, a nanoformulation of pomegranate seed oil was investigated in a randomized

control trial involving 30 MS patients, and it was observed to have a stabilizing effect on cognitive disability [198]. Riluzole, an approved drug for ALS, can be used with a solid lipid—NP formulation to decrease biodistribution in organs other than the brain and increase drug delivery to the CNS [199]. ABS-75 (water-soluble fullerene derivative) attached to an NMDA receptor-antagonist demonstrated neuroprotective effect in an in vivo model [200]. Glatiramer acetate (Glatopa), an FDA-approved therapeutic peptide composed of l-lysine, l-alanine, l-glutamic acid, and l-tyrosine suppressed inflammatory responses by modulating T-cell populations [201].

Brain-derived neurotrophic factor (BDNF) has been extensively documented to have neuroprotective effects. Clathrin triskelia-conjugated BDNF, delivered intranasally, has recently been shown to have cognitive-enhancing effects in learning and memory deficits, and a reduced toxicity profile [202].

5.8 Regenerative medicine

Both synthetic (e.g., PGLA) and natural polymers (e.g., collagen, chitosan, gelatin) as well as nonpolymeric NPs (e.g., silica-based, calcium phosphate-based) have been used as nano-delivery systems for bone regenerative therapy [203—205]. NP-based growth factors can be a strategy for osteoblastic stimulation [206—208]. Several types of metallic NPs have been in use for the delivery of bisphosphonate drugs, which promote osteoclastic apoptosis [209]. Equivabone is an NP-based osteoinductive bone graft substitute approved by the FDA [210]. Therapeutic NPs loaded with antiinflammatory agents for bone tissue could benefit the healing of large wounds [211].

6. Challenges and future perspectives

NPs and nano-delivery systems have shown excellent promise, and in many cases, diverse applicability that could revolutionize therapeutics as we know it. However, the design of effective nanotherapeutics still remains a roadblock in many cases. Only a handful of formulations enter clinical trials, and even fewer enter the market. The related challenges can be broadly classified into three domains: (1) physicochemical properties of the nanomaterials, (2) toxicity and regulatory measures, including intellectual property, and (3) large-scale production.

The bioavailability, compatibility, and toxicity profile of the drug-delivery system depend primarily on the physicochemical properties of the NPs [212]. Therefore, the NPs must be synthesized and characterized carefully. Additionally, the stability of the molecule also has an effect on its pharmacokinetics [213]. The second and perhaps the most important challenge is to assess and minimize the toxicity of NPs in the human system. Through the interaction with other biological molecules, nanocarriers may result in unwanted toxicity [214]. In fact, "nano-toxicology" has become a branch in itself, to deal with this issue in particular.

Last but not least is the commercialization of nanomedicine. Several key factors, including translational barriers from in vitro or in vivo studies to clinics, large-scale production, batch variability, and high production costs are only some of the challenges. A well-designed manufacturing process where the clinical benefit outweighs the costs is the need of the day. Furthermore, the absence of any specific regulatory guidelines for nano-drugs means unnecessary delays and long-winding roads before the drug can be brought to the market (Fig. 14.3). Thus, on the one hand, effective design and developmental strategies need to be put in place along with a case-based approach to reveal the benefits and drawbacks of each nano-formulation. On the other hand, a comprehensive set of regulatory guidelines must be created to better evaluate and approve newer nanotherapeutics.

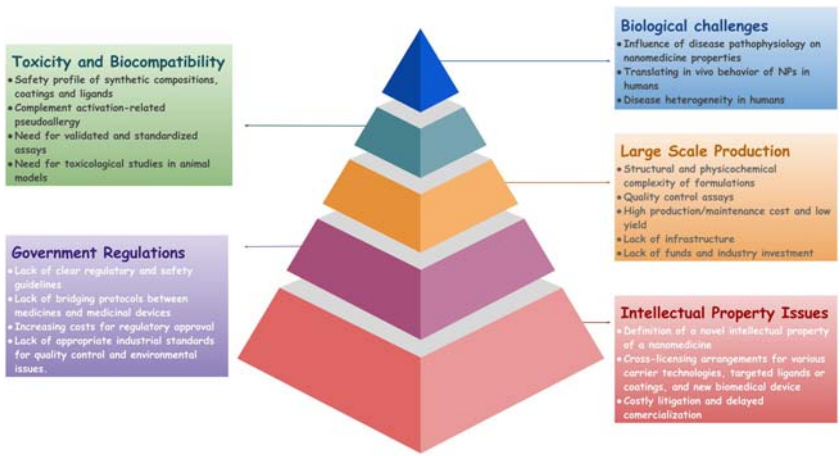

Figure 14.3 Challenges and roadblocks in the development and marketing of nanotherapeutics.

7. Conclusions

NPs have shown tremendous potential to be a major player in diagnostics and therapeutics. They could facilitate personalized and precision medicine in the near future, depending on the individual disease profile of the patient, including molecular pathway activation, genetic variability, and receptor expression. The physicochemical properties of the nano-delivery carriers can also be tailor-made according to disease preponderance. Overall, NPs can revolutionize the way we treat patients. However, much remains to be addressed in terms of manufacturing, cost-benefit, and regulatory protocols. From the design of the formulation to marketing of the compound, complexities need to be reduced, and methods need to be streamlined.

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CHAPTER 15

Applications of functionalized nanoparticles in tissue engineering

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1. Introduction

Nanomaterials were defined by the European Commission (EC) in 2011 as a natural, incidental, or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate, and where one or more external dimensions are in the size range 1−100 nm for 50% or more of the particles in the number size distribution [1]. Nanomaterials have unique physical, chemical, and biological qualities that distinguish them from other types of materials. They are small, have high surface energy, magnetic effects, a large surface area, and so on (biocompatibility, low immunogenicity, biodegradability, etc.). In terms of their structure and morphology, nanomaterials can be divided into three categories: zero-dimensional (nanoparticles) [2], one-dimensional (nanowires) [3], and two-dimensional (nanolayers) nanomaterials [4], all of which are in all directions, two axes, or one axis, and are smaller than 100 nm in any direction, respectively [5]. Due to their distinct characteristics and small size, nanomaterials can replicate elements present in the natural nanoscale extracellular matrix and transfer biologically active chemicals straight into cells.

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Nanoparticles (NPs) are microscopic particles that are capable of passing between cells and aiding in the absorption of proteins into the body. Based on the qualities listed above, production and use of nanomaterials with natural properties or those functionalized with other essential qualities are possible in several applications such as bioengineering, tissue engineering [6], gene therapy [7], drug delivery [8], bioimaging [9], and many more.

Tissue engineering is a novel discipline of bioengineering that brings together engineering, cell biology, and material science techniques and concepts to create tissue succedaneum that looks and functions like real tissues [10]. The National Science Foundation (NSF) defines "tissue engineering" as "the application of the fundamentals and methodologies of engineering and life sciences to comprehend the structural relationship among normal and mammalian tissues essentially, and the development of biological alternatives to reinstate, sustain, or enhance tissue function." There are a variety of biomaterials (especially ceramics, polymers, and inorganic compounds), bioactive substances, and cells combined during tissue engineering to develop and/or activate differentiation signals and induce tissue regeneration at a damaged region. For tissue engineering nanomaterials, biodegradability, biocompatibility, biointegration, simplicity of fabrication, and low production costs are crucial conditions for their utilization [11].

The benefits of nanoparticles in TE lie in their high surface area to volume ratios and small size, as compared to small proteins and peptides. They can effectively pass through membranes and facilitate cellular uptake. Furthermore, in the case of nanoparticles, the size and surface finish can be tailored to the intended use without being limited to a given size. Nanoparticles can also mimic the natural nanoscale components of the tissues' extracellular matrix (ECM).

From one perspective, nanostructures can be deemed as an essential part of our body, where the components of tissues and organs, like ECM and cells, organize different atoms, molecules, as well as nano-, micro-, and macrostructures in a hierarchy. On the contrary, many foreign nanoparticles enter our body, usually with the air we breathe in or through our mouth and topical routes, and depending on the toxicity or nature of the particles, these may or may not be harmful to the body. The third source of nanoparticles in our body may be the release or secretion of urea from biomedical implants and prostheses implanted in our bodies. As reported in several studies [12,13], a number of metal nanoparticles such as Sb, Ta, Cr,

Cr, Co, Fe, Ni, Ag, Mo, and Sc [13] have been found in tissues adjacent to and outside the implantation site after bioremediation of the body. Hip prosthesis patients had higher levels of metallic elements in the brain and lungs, while arthroplasty patients had higher levels of Mo, Co, and Cr ions in the hair [14].

This chapter focuses on the fabrication and bioactivity of nanomaterials used in tissue engineering, their implications in bone, skin, nerve, and dental tissue engineering, as well as drug administration and delivery of therapeutic agents.

2. Application of FNPs

2.1 Dental tissue engineering

Nanoparticle applications in dental tissue engineering have gained increased attention since the start of the 21st century. As age increases, the incidence and risk of periodontal disease and other associated diseases like rheumatoid arthritis [15], diabetes [16], and cardiovascular disease [17] increase gradually. Because of the deterioration of periodontal tissue and the impairment of self-healing in persons suffering from periodontal diseases, efficient therapies are necessary to repair damaged tissues and restore the natural shape and function in those who suffer from these conditions. Over the last several years, the development of various metal and polymer nanoparticles has offered significant assistance in the treatment of periodontal disorders [18]. Nanomaterials are used in the dental field for a variety of reasons, including (1) antimicrobial drugs for the treatment of oral infections, (2) nanofillers for enhancing or mending the mechanical characteristics and physiological functions of periodontal materials, (3) implants with fresh coatings, and (4) personal care items such as toothpaste.

Poly(lactic-co-glycolic acid) (PLGA) has outstanding mechanical qualities, a variable degradation rate, and excellent biocompatibility made from polylactic acid (PLA) and polyhydro acetic acid (an aliphatic polyester). Furthermore, due to its biocompatibility, it has been employed in periodontal disease therapy research [19]. In the field of dental bioengineering, current research concentrating on the implications of PLGA-based composites is focused on alveolar bone growth, tissue regeneration guidance, bacterial infection prevention, and periodontal medicament administration. Reis et al. [20] created a bilayer biomaterial based on PLGA for use in periodontal regeneration. Compared to the control group, the

PLGA-based biomaterial significantly increased the quantity and thickness of bone trabecular cells. Furthermore, only the PLGA-based biomaterial group demonstrated the formation of new cementum and bone. The findings revealed that the PLGA-based bilayer biomaterial was more effective in promoting periodontal regeneration than previously documented flexible membranes in the laboratory.

In recent years, nanoparticles of silica, chitosan, and poly(caprolactone) (PCL), among other materials, have been employed in dental tissue engineering [21]. A nondestructive technique was devised by Boguslavsky et al. [22] for grafting monodisperse silica nanoparticles with diameters less than 30 nm onto the surfaces of polystyrene, polyvinyl chloride, and polyethylene polymers. Compared to the absence of silica NPs, the presence of silica NPs resulted in 1.6−2.7 times increased roughness on the surface. The experimental findings showed that bacterial attachments were dramatically decreased following grafting with silica NPs, suggesting that the inclusion of silica NPs inhibited bacterial biofilm development. Bacteria could not cling to the polymer film grafted with silica NPs, irrespective of the kind of polymer. As a result, NPs do not promote bacterial adherence, thus preventing or delaying bacterial development. Furthermore, because of its biocompatibility and biodegradability, chitosan is widely used in periodontal tissue healing. Using human mandibular bone marrow mesenchymal stem cells (MSCs) inoculated on composite scaffolds made of chitosan and inorganic bovine bone, Zang et al. [23] investigated the therapeutic influence of periodontal disorders. Their findings revealed that the chitosan-based scaffold had high biocompatibility and boosted the compressive effect of the material used in the experiment. MSCs also produce fibrous cementum, periodontal ligament, and woven/brittle bone on the chitosan-based scaffold, suggesting that they have a healing impact on the periodontal tissues. As a result of its superior biodegradability and biocompatibility, and enhanced permeability and retention (EPR) effect, the FDA has approved PCL for clinical use in dental tissue engineering. Xi et al. [24] developed a PCL-based dual corona vesicle biofilm to treat periodontitis. In their research, they observed that PCL-based biofilms have exceptional biocompatibility and antibacterial properties. The ciprofloxacin hydrochloride-loaded dual corona vesicle system was shown to be effective in destroying biofilms formed by *Escherichia coli* and *Staphylococcus aureus* strains to destabilize plaque, making it a critical component of periodontitis treatment and research. Because of its biodegradability and reductive properties, polydopamine is also used to treat periodontal disorders. Bao

et al. developed a high-performance platform based on polydopamine that may be employed as a reactive oxygen species (ROS) executioner in treating periodontal disease induced by oxidative stress in mice. The in vivo experiment revealed that polydopamine-based NPs could scavenge a wide range of ROS and prevent ROS-induced inflammation. Also proven was the remarkable efficiency of polydopamine-based NPs in eliminating ROS and reducing periodontal inflammation while having no adverse side effects in in vitro studies [25].

Metal nanoparticles have been acknowledged in dental tissue engineering due to their unique antibacterial characteristics and customizability. Antibacterial metals such as Ag, Au, TiO_2, and ZnO are typical examples, and their antibacterial characteristics can be enhanced by property functionalization. Furthermore, the materials' size and form may contribute to their bactericidal action. According to studies, NPs with particle sizes smaller than 10 nm have more significant bactericidal activity, and triangular NPs had superior bactericidal effects than needle-shaped or circular NPs [26]. Holden et al. [27] used an electric current displacement technique to create Ag/Au alloy bimetallic NPs to evaluate the antibacterial properties of Ag/Au alloy bimetallic NPs in periodontitis. According to the results of in vivo experiments, these nanoparticles with high biocompatibility reduced the survival of P83 plankton by inhibiting the antimicrobial property of *Porphyromonas gingivalis* W83, which was found to be a critical pathogenic agent in the establishment of periodontal disease. Additionally, hydrogen oxide can simulate the oxidative stress environment associated with periodontal disease. When hydrogen peroxide is added, the antimicrobial effect is amplified.

Zhang et al. [28] created a light-activated nano-antibacterial scaffold based on gold nanocages. It is intended to regulate antibiotic release while integrating the antibacterial effects of chemotherapeutics and phototherapy. It demonstrated favorable antibacterial properties both in vivo and in vitro, which was ascribed to the formulation's synergistic antibacterial action mediated by the gold nanocages-based nanoplatform. Table 15.1 presents a summary of some of the important nanomaterials being used in dentistry and applications.

2.2 Neural tissue engineering

The central nervous system (CNS) and the peripheral nervous system (PNS) are the two most essential components of the nervous system.

Table 15.1 Summary of diverse nanomaterials currently being used for tissue engineering in dentistry.

Nanomaterials	Applications	References
Amorphous calcium phosphate NPs	Mouthwashes, toothpastes, and prevention of caries and periodontitis	[29]
Bioactive peptide amphiphile nanofiber	Regeneration of enamel	[30]
Calcium carbonate ($CaCO_3$) NPs	Mouthwashes, toothpastes, and prevention of caries and periodontitis	[31]
Carbon nanotubes	Repair and regeneration of bone	[32]
Nanohydroxyapatite and chitosan composite membrane	Repair and regeneration of periodontal tissue	[33]
Gold (Au) NPs	Diagnosis of oral diseases (malignant and premalignant)	[34]
Polyamide 66 GBR and nano-hydroxyapatite membrane	Repair and regeneration of periodontal tissue	[35]
Nano hydroxyapatite	Repair and regeneration of periodontal tissue	[36]
Nanofibrous poly(DL-lactide-co-glycolide) membrane	Repair and regeneration of periodontal tissue	[37]
Semiconductor nanocrystals	Diagnosis of oral diseases (malignant and premalignant)	[38]
Silver oxide NPs	Mouthwashes, toothpastes, and prevention of caries and periodontitis	[39,40]

Although both the brain and spinal cord are part of the central nervous system, the peripheral nervous system (PNS) comprises two types of neurons, namely motor and sensory neurons. Because the CNS and PNS lack regeneration capability, they frequently exhibit long-term functional

abnormalities due to illness or accidental damage [41]. With the rapid aging of the population, the prevalence of neurological illnesses is rising, posing a severe danger to human health [42]. At the moment, the most common clinical therapies for neurological illnesses are surgical sutures, allografts, and autologous transplantation, all of which are used to aid the healing of the wounded nerve [43]. Even though the illness can be cured to some extent, there are still several drawbacks, including immunological rejection, frequent operations, and poor treatment outcomes.

The advancement of nerve tissue engineering offers promise for neurological disorder treatment. Designing a suitable nanomaterial to manage the ECM microenvironment and cell behaviors, speeding up neuron regeneration, is one of the most common alternative approaches for mending nerve abnormalities. In the field of brain tissue engineering, a variety of polymers have been tested, with promising findings in areas such as neurite outgrowth, cell differentiation, and neural gap bridging in human neural stem cells [44]. Hydrogels, polymer scaffolds, nanoparticles (NPs), and nerve conduits are now often utilized in the area of brain tissue engineering, with the Food and Drug Administration regulating them in the United States. Whichever material is used, it must possess the following characteristics: biodegradability, permittivity, biocompatibility, permeability or porosity, resistance to infection, and superior mechanical properties.

The only natural biopolymer is collagen, which has been approved for use in clinical research for the restoration of peripheral nerve. Collagen, the fundamental structural component of connective tissue, may be found in various human tissues and is responsible for the body's stability and structure [45]. NeuraGen89 [46] and Neuromaix [47] are two collagen-based nerve guide therapies that are being developed for the restoration of peripheral nerve function. According to preliminary findings, researchers have discovered that collagen-based neural conduits may be used to repair small nerve gaps in monkeys [48]. Additionally, collagen, in conjunction with other compounds, to varying degrees, has been shown to boost the rehabilitation of the sciatic nerve in rodent and canine models of the disease [49]. It should be stressed that the collagen source should be given more substantial attention since various collagen sources may have varying effects, and the kind of collagen used will influence how the collagen is applied.

Hydrolyzing collagen in an acidic or alkaline solution that results in the formation of gelatin. In part, because it varies from collagen in several characteristics such as cost, hypotoxicity, biodegradability, and availability,

it has been employed in various applications, including tissue scaffolding and drug administration. Furthermore, when chemically modified, gelatin has the capacity to influence cell adhesion and proliferation and may be employed as a tissue engineering implant material [50]. For example, electrospinning can improve the dynamic and biological characteristics of gelatin-based scaffolds used in brain tissue engineering applications [51]. On the other hand, functional approaches may be able to increase the advantages of gelatin-based nanoparticles in the context of brain tissue engineering.

Additionally, Kriebel et al. [52] synthesized gelatin with collagen and PCL to a composite substance used to link the sciatic nerve of mice to the rest of their bodies. Gelatin may also be combined with PLA and electrospun to speed up axon development and differentiation into neurons of the neuronal motor lineage, which is also a possibility [53]. Gelatin NPs have been transformed into polymer scaffolds for brain tissue engineering in recent years, with the biocompatibility of the scaffolds being improved due to the transformation. Uncoated platforms were shown to have lower viable cell counts than gelatin NP-coated cellulose acetate/PLA scaffolds, and sciatic nerve injury treatment was facilitated by their employment as neural guide conduits, both in vivo and in vitro [54].

Other protein components utilized in nerve tissue creation include keratin, silk, and elastin. Elastin is a structural component of the ECM that has mechanical stiffness, self-assembly capabilities, long-term resilience, and biological function; as a result, elastin-based compounds are essential in tissue rejuvenation because they provide elasticity to organs and tissues, which is essential for organ and tissue regeneration. Because of their biocompatibility and durability, elastin-like polypeptides are more often utilized in neurological tissue engineering than elastin, which is routinely used to treat central nervous system illnesses [55]. Keratin polypeptide can produce suitable substrates and fold in a biologically active manner. Because of their biological characteristics, keratin-functionalized nanomaterials enhance cellular proliferation and adhesion, and their diverse amino acid structures may be readily modified to adapt to particular tissues [56]. Previous tissue engineering investigations showed that electrospun polyvinyl alcohol/keratin nanofiber scaffolding allows glial cells to connect, grow, and survive in vitro when used as a scaffold [57].

Silk is a vital fibrous structural protein generated by silkworms and spiders with high elasticity, excellent biocompatibility, tunable

biodegradability, antibacterial potential, and low immunogenicity [58]. As a result of silk's multifunctional qualities, it has been used to create biomimetic structures such as nanofibers, hydrogel scaffolds, films, and nanoparticles, among others. Silk-based hydrogels are frequently employed in creating nerve tissue as biomaterials because of their better structural integrity and capacity to produce axon bundles [58]. It has also been discovered that silk hydrogels may aid in neural tissue development and regeneration. The biocompatibility and low in vitro toxicity of silk fibroin should make it an excellent candidate for use in tissue engineering to treat injury to the central nervous system.

For the development of brain tissue engineering approaches, carbon-based nanomaterials are also crucial. Nanomaterials based on carbon have recently shown significant promise for interfacing with neurons and other brain tissue [59]. Carbon-based nanomaterials such as graphene (G), fullerenes, and carbon nanotubes, to name a few, are excellent examples. It has been shown that electrical stimulation may help in the regeneration of neurons. G-based materials' excellent electrical conductivity, flexibility, and high mechanical strength are ideal for brain tissue engineering. Neurodegenerative disorders benefit from the increased proliferation and differentiation of neurons that G-based materials facilitate [60]. A scaffold for brain tissue regeneration was created by combining functional GO nanosheets and nanofibers. The physicochemical and biological characteristics of the scaffold were adjusted, and the survival of neural stem cells was significantly increased [61]. Carbon nanotubes, which have an appearance similar to neurites, are among the most sought-after materials in the field of brain tissue engineering. It has been shown that a carbon nanotube with dendrites of identical size has better promise in the treatment of neuropathy and nerve tissue damage than other materials for exploring, repairing, and activating neural networks. Carbon nanotubes containing dendrites of comparable size are more effective in repairing and reactivating neural networks than conventional carbon nanotubes, which have been proven to be less effective at repairing neuropathy and nerve tissue damage [62].

Several polymers, such as chitosan, alginate, polyethylene glycol (PEG), and others, are being used to research nerve-related disorders. They have been intensively investigated in nerve tissue engineering, with promising experimental results.

2.3 Bone tissue engineering

Bone marrow tissue engineering is primarily used to repair irreversible injuries requiring adjuvant treatment. Nanomaterial-based implants are often used in this procedure. Bone tissue scaffolds, physicomechanical procedures, and biological strategies are now being used as treatment options [63]. Bone tissue engineering research has lately centered on developing 3D scaffolds that naturally support, strengthen, and organize bone tissue regeneration rather than on developing artificial scaffolds. For the same reasons, naturally degradable nanoparticles are often utilized in bone tissue engineering because of their outstanding biocompatibility and biosafety and because they encourage the formation of bone minerals. Their intrinsic degradability also enables them to be easily converted for in vivo usage after surgical implantation and without a second procedure to remove them, hence reducing the pain experienced by patients. Scaffold materials in bone tissue engineering are widespread because they provide mechanical support for wounded areas while also creating optimal bone repair conditions [64]. The success of a bone tissue engineering construct depends on the presence of surface features that encourage cell adhesion, differentiation, and proliferation.

Furthermore, the scaffold's permeability, bio-conduction, biocompatibility, and absorbability should be considered simultaneously. A polymer-based scaffold, for example, has been widely accepted as one of the sustainable materials for bone tissue scaffolds with low tensile qualities. Nevertheless, adding nanoparticles as fillers (chitosan-based nanomaterials, ceramic nanomaterials, materials based on carbon, and metal-based NPs, for example) can significantly improve the mechanical characteristics of the stent [65]. Moreover, incorporating functionalized methods on specific nanomaterials can modulate cell-signaling pathways, modify protein adherence to the scaffold, and boost mechanical qualities.

The FDA has recognized chitosan in several pharmaceutical compositions as a natural biopolymer with biocompatibility and biodegradability [66]. Additionally, throughout the last few decades, chitosan has played a significant role in advancing bone tissue engineering techniques. Chesnutt et al. [67] created a microsphere-based chitosan/nanocrystalline calcium phosphate scaffold to help patients who have lost bone due to illness or trauma. The mechanical characteristics and porosity of such a composite scaffold might be ideal for the development of new bone tissue. Moreover, chitosan-based porous structures can enhance bone conduction.

Because hydroxyapatite NPs constitute the primary inorganic ingredient of bone tissue, they have piqued the attention of researchers in the field of bone tissue engineering. Researchers have developed a biomimetic nanocomposite nanofiber scaffold made of chitosan and hydroxyapatite (nHAp/CTS) to evaluate the effect of bone marrow mesenchymal stem cell (BMSC) growth on nHAp/CTS for bone regeneration and to investigate the molecular mechanisms both in vivo and in vitro. Their research observed that the nHAp/CTS scaffold might promote the replication of BMSCs and the integrin-BMP/Smad signaling pathway in BMSCs. Because the chitosan/hydroxyapatite composite can promote osteoclast development in osteoblasts, it has been proposed for use in bone tissue engineering applications. The impact of hydroxyapatite NPs on composite nanofiber/chitosan scaffolds was examined [68]. It has been shown that hydroxyapatite stimulates cell adhesion and the BMP/Smad signaling pathway in bone marrow MSCs, resulting in enhanced cell proliferation and bone repair. They surpass organic polymer nanoparticles when it comes to stimulating bone's natural inorganic transition, making them a promising biomaterial for scaffold techniques in the future. Additionally, hydroxyapatite may be coupled with PCL, PLGA, PEG, whitlockite nanoparticles, and other organic polymers that have shown promise in treating osteoporosis and other bone disorders (Fig. 15.1) [69].

Moreover, bioactive glass–ceramic nanoparticles (nBGC) are making strides in bone tissue engineering since their composition is more closely related to bone than metal nanoparticles. Using electrospinning bioactive glass/polyvinyl alcohol and silk fibroin, Singh and Pramanik [70] demonstrated that a double-layer scaffold could be constructed, which aided in the differentiation and proliferation of bone marrow MSCs. Furthermore,

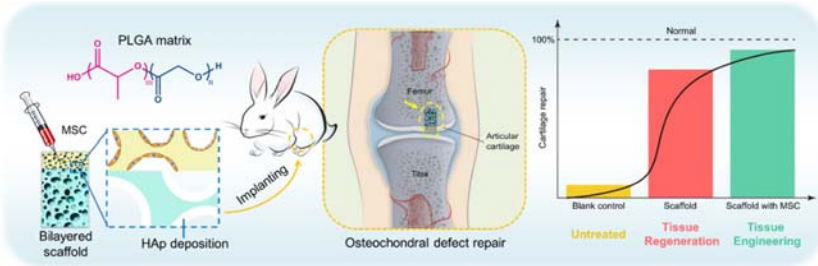

Figure 15.1 Representation of bone regeneration through hydroxyapatite-based scaffold. *(Reprinted with permission from Ref. [69]. Copyright (2018) American Chemical Society.)*

MSCs from the bone marrow promote the production of new bone, whereas MSCs from the umbilical cord promote neovascularization. Collagen, alginate, cross-linked dextran, PCL, PCL−chitosan (PCL−CHI), PLGA, fibrin, and other materials have also been utilized to make bone tissue engineering scaffolds in conjunction with bioactive glass.

Carbon-based nanomaterials are categorized according to their dimensions: 0D carbon dots, fullerene, nanodiamonds, 1D carbon nanotubes, 2D graphene, and 3D graphite are all examples of 0D carbon nanomaterials. These materials have various surface functionalities, a large surface area, are biocompatible, have outstanding mechanical strength, and are readily accessible on the commercial market. Bone tissue engineering scaffolds, in general, are composed of carbon-based materials and serve as a template for bone stem cell formation as well as for amplification, revival, adhesion, and differentiation [71]. Because of its low metal impurity level, extended length and breadth, and easy purification technique, G material may be prioritized in this regard. It is more hydrophilic than pure G because of the oxygen in the mixture. Because of this, it dissolves more readily in water and organic solvents, and other solutions [72]. A composite scaffold for bone replacement was developed by Kumar et al. [73], which was composed of polyethyleneimine (PEI) and GO (PEI/GO). Throughout the tests, it was discovered that PEI/GO boosted the proliferation of human bone marrow MSCs and the formation of focal adhesion complexes in these cells, and the differentiation of osteoblasts. It increased mineralization by around 50% and almost quadrupled alkaline phosphatase activity alone. According to their findings, using a PEI/GO polymer composite to replace absorbable bioactive components in orthopedic devices and stabilize fractures is possible. Carbon nanotubes exhibit exceptional mechanical tensile strength, maximum electrical conductivity, and maximum current transmittance due to their mechanically enhanced properties, and thus appear to be the most attractive component for improving the physical properties of nanocomposite scaffolds. It has been widely employed in bone tissue engineering to include a variety of carbon-based nanomaterials with varying degrees of biological activity [71].

Au, Ag, and titanium oxide have recently been used in the manufacture of bone tissue. Because metal NPs have outstanding mechanical qualities, many researchers have employed silver NPs for implantation for bone tissue engineering via improving osteogenic properties. Pauksch et al. [74] investigated the biocompatibility and osteogenic capability of silver nanoparticles stabilized with polyoxyethylene sorbitol monolaurate (Tween 20)

and polyoxyethylene glycerol trioleate (PGT). When silver nanoparticles were added to the culture system of osteoblasts and MSCs, the researchers saw an increase in the cells' absorption capacity without seeing any harmful consequences. This highlights how silver nanoparticles may be used in bone tissue engineering applications.

Furthermore, gold nanoparticles have high potential for boosting cell differentiation [75]. The size of gold nanoparticles might directly impact the meaningful interaction between cells and materials. A recent study found that gold nanoparticles with fewer than 20 nm have a favorable osteogenic influence on primary osteoblasts, but that gold nanoparticles with a diameter of 30–50 nm or more have a significant impact on human adipose-derived stem cells [76]. Using titanium dioxide nanoparticles in combination with a range of polymers, it may be possible to develop superior scaffolds to examine bone development efficiency.

3. Skin tissue engineering

In the wound-healing process, the following events occur: hemostasis, inflammation, proliferation, and remodeling/maturation [77]. Acute and chronic wounds are two types of skin wounds, based on how long they take to heal. Chronic wounds heal more slowly than acute ones. Acute wounds are defined by rupture or perforation of the epidermis, which heals rapidly. Chronic wounds are notoriously difficult to heal quickly due to their common association with diabetes and obesity. Angiogenesis is a crucial step in the healing of a wound. The vascular system may supply appropriate blood flow, nutrients, and oxygen, but it can also protect the body from infection. However, it also hastens wound healing and the creation of granulation tissue's basis [78]. On the other hand, chronic wound creation is caused by aberrant blood vessel formation, which delays healing.

Consequently, while treating skin wounds, it is necessary to consider both skin tissue regeneration and vascular regeneration. There are several therapeutic options for accelerating the healing process of chronic wounds for various skin injuries, such as hyperbaric oxygen therapy, local oxygen treatment, negative-pressure wound therapy, ozone therapy, etc. [79]. Commonly, autologous transplantation is used to treat large-area skin injuries. In essence, full-thickness skin is removed from other acceptable portions of the donor, stretched, and implanted into the wound. However, the donor site and the damaged region limit this method. Another viable

method is explored here by using autologous cell-based treatment. These fused cells are utilized for wound healing when they have grown sufficiently in vitro; however, several factors substantially influence the success rate, the length of the treatment cycle, and the cost. Nanomaterials are currently being used in skin tissue engineering to improve the effectiveness of the wound-healing process while also increasing the safety and proliferation of the cells [80]. As a barrier layer for regenerating keratinocytes, biomaterials should stick tightly to the lower dermis, remodel blood vessels in the injured area, and offer elastic structural support for the skin.

Chitosan is a biodegradable polycation polysaccharide and nontoxic substance that may be degraded in vivo by lysozyme to yield nontoxic amino sugars. It is notable for skin applications due to its high cell adhesiveness and biocompatibility properties. The chitosan possesses a positive charge, and it links to the negatively charged bacterial membrane, causing agglutination and, eventually, leakage of the cell components. Furthermore, chitosan can bind to metals, therefore inhibiting the action of particular enzymes. For example, the HemCon® bandage, commercially available and created initially as a hemostatic dressing, has shown good performance in various possible skincare uses [81]. The keratin−chitosan composite film also improved keratin's tensile strength, antimicrobial properties, and fibroblast adhesion.

Recent research has focused on nanocellulose, a novel nanomaterial made entirely of cellulose-based nanoscale structures. The capacity of nanocellulose-based nanomaterials to absorb exudate from wounds and remove bandages more effectively than standard wound dressing materials makes them popular in biomedical applications (such as gauze). As Fu et al. [82] demonstrated, compared to standard wound dressings, nanocellulose created by bacteria gave superior wound care advantages, including faster healing, less inflammation, and a product with low toxicity. Additionally, it assisted in accelerating tissue regeneration and the formation of capillary networks in wounds. According to the current study, nanocellulose dressings have a bright future in treating chronic ulcers of the lower limbs. Due to its exceptional adhesion to the wounded region (due to its flexibility) and capacity to maintain water balance, the nanocellulose-based film is also being utilized to enhance wound healing in severe burns therapy.

Additionally, in previous research, nanocellulose has been demonstrated to reduce inflammatory reactions during skin healing. In order to combat multidrug-resistant bacteria and enhance wound healing, Xi et al. [83] created a photoluminescent, elastomeric hybrid composite. The polypeptide-based

nanocellulose composite's biomimetic elastomeric nature and potent antibacterial effect were notable. In vivo, it was shown that the nanocellulose composite approach effectively suppressed MDR bacteria-induced wound infection while also significantly improving skin regeneration. Nanocellulose may also be used to accelerate skin tissue repair when combined with nanocomposite materials such as chitosan, polyethylene glycol, polyvinyl alcohol, alginate, and gelatin.

Generating suitable nanocarriers for gene delivery may effectively shelter molecules from nucleases and control gene expression, therefore boosting revascularization and the overall outcome. A team of researchers created PLGA nanoparticles containing the vascular endothelial growth factor (VEGF) interceptor plasmid pFlt23K to treat neovascular disorders. They were efficient in altering gene expression (and decreasing epithelial cell production of VEGF), implying the possibility of using gene therapy to treat traumatic disorders [84]. It has been shown that cultivating stem cells that express high amounts of vascular endothelial growth factor and undergo transitory modification promotes skin regeneration and angiogenesis (especially after transplantation) [85]. It has been shown that biodegradable nanoparticles successfully deliver the epidermal growth factor gene to human MSCs and cells produced from embryonic stem cells. Transplantation of VEGF-expressing stem cells onto nanostructured scaffolds resulted in a 2–4-fold increase in angiogenesis compared to control cells. It demonstrates the therapeutic potential of stem cells modified using biodegradable nanoparticles for tissue regeneration [86].

4. Drug delivery

Tissue engineering makes use of cells, biomaterials, and bioactive substances, which may be utilized alone or in combination, to create, repair, and replace tissues and organs. However, cell survival is poor in the first few days after transplantation, and combining cells with growth factors or drugs to increase cell survival has also been shown to be unsuccessful [87]. To improve the dependability and effectiveness of tissue engineering, it is vital to develop an efficient drug-delivery system capable of guiding functional tissue regeneration in situ while causing minimal injury to the surrounding tissue. New techniques for drug delivery are currently being developed. However, it remains challenging due to a lack of biological barriers, resulting in suboptimal drug-delivery effectiveness and bioavailability in vivo. Biomaterials, including vaccines, medicines, enzymes, peptides, and

antibodies, boost the delivery effectiveness of various therapeutic molecules by loading or co-conjugation techniques. Although tremendous progress has been achieved, there are still obstacles to improving delivery efficiency and therapeutic disease effects. Dendrimers, liposomes, lipid NPs, polymeric nanospheres, micelles, and inorganic nanomaterials are among the materials now available in the developing field of nanomaterial-based medication delivery. A variety of biomaterials are now being researched to trigger drug release in the presence of certain environmental stimuli (for example, enzymes, temperature, pH, pressure, glucose, etc.) [88]. Examples of nanocarriers, such as polymeric micelles and dendrimers, are used to demonstrate how nanocarriers may be used for drug delivery and disease treatment in tissue engineering.

Self-assembly and emulsion evaporation processes are often used to create polymer micelles. Micelle nanosystems are favorable to successful medication administration for illness treatment due to their unique physical and chemical features. Notably, the essential micelle concentration value is also essential in delivering polymer micelles. Micelles with a smaller value of micelle concentration have better pharmacokinetic stability [89]. Prior studies have shown improved tumor endocytosis and penetration for anticancer drugs when loaded with the immunological checkpoint IDO inhibitor NLG919, allowing for redox/pH cascade-responsive drug delivery. The micelle could cross biological barriers, stimulate the anticancer immune response, and limit tumor formation, metastasis, and recurrence in in vivo and in vitro experiments by decreasing tumor cell proliferation and migration [90]. The researchers also developed a micelle-based drug-delivery system with dual targeting capabilities (mitochondria and cells), which improved drug distribution at the cell and subcellular levels, resulting in higher antitumor effectiveness. The FA receptor-mediated method enhanced the micelle's endocytosis by tumor cells. In both animal and laboratory trials, it was shown that the polymeric micelle drug-delivery strategy might increase targeted delivery efficiency and combinational anticancer effectiveness, while producing a minimal amount of adverse effects [91].

Dendrimers have several benefits, including highly branching multivalent characteristics, increased solubility, and decreased drug toxicity [88]. The dendrimer's terminal group is bonded to the drug by covalent attachment, hydrogen bonding, or electrostatic interaction with the inner cavity. All provide unique options for interaction with guest molecules, leading to significantly increased drug loading content and effective disease

treatment. It has already been claimed that there is a strong relationship between packing trends and algebra: the more dendrimers formed, the more functional groups there are, and hence the more significant the area for drug loading [92]. The covalent binding of guest molecules to dendrimer surface groups may also be advantageous when creating dendrimer–drug conjugates. According to Wang et al. [93], a dendrimer–camptothecin (CPT) combination was developed to treat pancreatic ductal adenocarcinoma. The combination consisted of dendrimers containing camptothecin and polyamidoamine (PAMAM) dendrimers linked together by a ROS-sensitive linker and modified on the surface with glutathione for the treatment of pancreatic ductal adenocarcinoma (PDA). With the CPT conjugation, drug conjugates were transferred from one cell to another, penetration properties inside the tumor parenchyma were improved, and anticancer activity was shown in both in vivo and in vitro trials with outstanding results. Li et al. [94] developed stimuli-responsive clustered NPs for anticancer therapy by chemically attaching modified cisplatin to dendrimers. The NPs were concentrated more in tumor locations and released medicines, effectively inhibiting tumor development.

Many alternative nanoparticles, including organic polymers, metal-based nanomaterials, and carbon-based nanomaterials, have excellent characteristics and efficiency for drug administration and disease treatment. These materials can load and transport drugs to treat tumors and other disorders [88].

5. Constructing 3D tissues

Nanotechnology can open new doors in the field of tissue engineering. Nanoscale structures may regulate cellular processes, including segregation, adhesion, and propagation. As a result of their unique magnetic and optical properties, nanomaterials are ideal agents for monitoring cellular activity in vivo after transplantation. The development of 3D tissue-engineered scaffolds for the vascular system, skin, bone, and other tissues has already begun; in addition, nanostructures have been revealed to influence the differentiation, adhesion, and proliferation of primordial stem cells. Because of their exceptional magnetic properties and odd size, magnetic nanoparticles (MNPs) have lately piqued the public's curiosity due to their current popularity [95]. At ambient temperature or biological temperatures,

MNPs are smaller (20–300 nm) and have magnetic orientations that allow thermal changes.

5.1 Skin

The formation of keratinocyte sheets with five or more cellular layers established their potential for enhancement and transplantation. Keratinocytes that had been magnetically labeled were seeded in an ultralow attachment well that included a hydrogel layer that had been covalently connected to the plate and a neodymium magnet below the plate. In the absence of a magnet or MCLs, keratinocytes failed to adhere to the culture surface of the cell culture [96]. In addition, it was observed that the sheets of undifferentiated keratinocytes may be helpful in healing wounds in the future. Further research revealed that when the five-layered sheets were cultured in a high-calcium medium, they stratified into 10-layered epidermal sheets that grew and were far more robust. Additionally, the magnetic force aided recovery by allowing the magnetite cationic liposomes (MCLs) labeled sheets to float to the culture surface and stick to the hydrophilic poly(vinylidene fluoride)-treated membrane above a cylindrical magnet.

5.2 Skeletal muscle

Magnetic force scaffolds of free multilayered skeletal muscle cells were produced by depositing myoblast C2C12 cells on ultra-low attachment plates and placing a magnet underneath the plates. Consistent cell aggregation resulted in thick, robust, and multilayered sheets. However, the cells solidified into minute aggregates when the magnet was removed [96]. The method was modified to manufacture three-dimensional string-like tissues that resemble bundles of skeletal muscle fibers. The magnetic field gradient led the cells to aggregate into string-like lines, adjusted in width and thickness. Various unique methods for producing skeletal muscle tissues have been developed. Saxena et al. [97] used myoblasts placed on synthetic biodegradable polymers to create vascularized skeletal muscle designs. Another group achieved self-assembled 3D myoblast cell production on a silicon surface [98]. Moon et al. [99] enhanced skeletal muscle contractile force output using collagen-based acellular tissue scaffolds. Akiyama et al. [100] and Sato et al. [101] developed magnetic force-based tissue engineering (Mag-TE). A magnetic field and MNP-labeled cells were used to

create tissue. They also showed that they could build denser synthetic skeletal muscle tissue structures by employing Mag-TE.

5.3 Liver

Mag-TE has recently shown potential as a cell sheet for hepatic tissue engineering. The magnetic force has been shown to facilitate close and intimate cell interaction in the liver, resulting in the deposition of an ECM and cytokines between cell layers, improving liver function. Cocultures of Mag-TE with hepatocytes and endothelial cells were performed. MCLs were utilized to mark human aortic endothelial cells (HAECs) layered with rat liver cells. Multilayers of HAECs grew and remained uniformly connected to the hepatocyte layer where magnets were implanted. Multilayer cocultures maintained an enhanced level of albumin secretion for at least 8 days after being established [102]. In another work, HepG2 (a hepatocyte model) and NIH/3T3 (a stromal fibroblast model) cells were magnetically tagged and employed as models. The cells were planted in ultra-low attachment wells that included a magnet to prevent them from adhering to one another. A sheet-like structure formed due to the cells' attraction to the lower magnet. When the magnet was withdrawn from the cell sheets, they separated and disengaged without being disrupted in any way [103].

6. Nanoparticles in biomolecular detection

In tissue engineering, biomolecular sensing and biosensors are gaining fast traction [104]. Biosensors are biological devices that use physiochemical sensing to detect changes in molecules. Several biosensors, including electrochemical, optical, magnetic, and acoustic, have been used to detect functioning protein molecules, glucose, and harmful bacteria in tissue engineering [105]. The growing use of nanoparticles in biomolecular detection is the most significant advancement. Due to their high reactivity and exceptional chemical characteristics, nanoparticles have been employed in biosensors for protein, DNA, and nucleic acid detection, among other uses [106]. The expanding importance of biosensors in tissue engineering and the increasing significance of nanoparticle applications in biomolecular sensors demonstrate nanoparticles' promise. Researchers aim to implant intelligent nanoscale biosensors into scaffolds, cell sheets, or other relevant places to monitor synthetic tissue formation after transplantation and grafting. Changing immune cell adhesion and survival, including

nanomaterials in 3D-designed tissues, may also reduce inflammatory reactions to transplanted synthetic tissues.

6.1 Optical detection

The most often used nanoparticles for biosensors include semiconductor quantum dots (QDs), graphene nanoparticles (GNPs), and silica nanoparticles (SNPs). Optical sensors and optical imaging are two applications in which nanoparticles have been utilized as biosensors [106]. Quantum dots were used because of their exceptional stability, brightness, and long-lasting luminescence, all of which were previously mentioned [107]. Goldman et al. [108] used light quantum dots to detect proteins in immunoassays. In research done by Sharon et al. [109] QDs were also used to detect DNA in the presence of other molecules. In this study, the hemin structure in CdSe and ZnS quantum dots was used to develop innovative optical sensing technologies for use in various applications. Ding et al. [110] created carbon quantum dots in response to the toxicity of heavy quantum dots in in vivo applications. These quantum dots have been employed for molecular identification and have been proven to have negligible cytotoxicity. Due to their customizable strength and power, bandwidth, and frequency, metal nanoparticles are employed in optical detection. Metal nanoparticles are ideal for optical applications because of their properties ascribed to the collective oscillation mode. Newman et al. [111] created GNP-based optical sensors with silica microparticles that were employed to detect organophosphate compounds in their investigation.

6.2 Electrical detection

Nanoparticles are currently being used as electrical detectors for DNA molecules, which detect the presence of DNA molecules using electric impulses. The activity of DNA is transferred to electrical impulses using nanoparticles as intermediates [112]. Park et al. [113] devised a high-accuracy electrical DNA detection technique based on the binding of oligonucleotides to GNPs. Noor et al. [114] also used GNPs for the detection of DNA. DNA was placed on a silicon chip between gold nanoelectrodes and monitored in their work. The GNPs were identified to increase the conductivity between the electrodes, resulting in an improved DNA identification technique. Electrical detection has also been done with MNPs and carbon nanotubes (CNTs). One experiment included

encapsulating MNPs in CNTs [115]. Electrical and magnetic characteristics were improved as a result of this research.

6.3 Electrochemical detection

Electrochemical sensors for element identification combine the selective detection of biological components with the sensitivity of electrical sensors to provide more accurate identification of the element. The sensors provide an electrical signal by chemically reacting with the analyte due to its larger surface area, higher chemical convenience, and improved electrical conductivity [116]. GNPs were utilized by Wang et al. [117] to improve antigen immobilization. According to the study's findings, the inclusion of GNPs increased the detection of antigens and antibodies. GNPs have also been employed as DNA detection electrochemical sensors. Research by Li et al. [118] is one such example in which electrochemical sensors were employed to a variety of nanoparticles in addition to GNPs. Cui et al. [119] employed CdTe nanoparticles in a study to construct a twofold immunosensor that functions as both an electrochemical sensor and a fluorescent label. GNPs were also used to encapsulate the chip on which the sensor was created, which was a first for the industry. In another research, silver nanoparticles functionalized with oligonucleotides were created and used to detect DNA [120]. Although silver nanoparticles have been proved to have excellent properties, they have not yet been put to full use.

A sensor designed for an orthopedic hip implant is another example of electrochemical detection. Anodizing the titanium implant initially resulted in the formation of nanotubes, which was then further developed via the use of chemical vapor deposition [121]. Cell adhesion resistance is monitored by the CNTs, which may then transmit that information through radio frequency to a hand-held device. Remotely, the CNTs can also be used to deliver bone growth hormones, antiinflammatory medicines, or antibiotics to where they are needed, to make sure the implant will work. Electrochemical sensing of biological events in medical devices may be the future of nanomaterials in medical devices because they can detect biological events in real time based on the individual's response to the implant to make it more likely that the implant will work.

7. Challenges and future perspectives

Nanoparticles have increased biocompatibility and may have their surfaces changed using well-established techniques, making them appropriate for a

broad variety of biomedical applications. Additionally, nanoparticles have improved the electrical connection between decellularized cells and the growth rates of a range of different tissues. Additionally, the usefulness of nanoparticles in preventing bacterial growth has been examined, with encouraging results. We have examined the use of many nanomaterials in various typical tissue engineering applications in this chapter. Nanomaterial discoveries and tissue engineering applications are critical for the healing and regeneration of damaged or diseased tissue. Many researchers are seeking to create new biomaterials concerning current nanotechnology by combining a range of nanomaterials.

In various applications, NPs are used in concentrations below the threshold concentration that are considered harmless. However, nanoparticles are known to accumulate in the body over long periods of time. When these nanoparticles are utilized in tissue engineering to replace injured organs, concerns about implant sensitivity, the resulting immunological response, possible toxicity, effect on reproduction, and even embryonic development must be carefully evaluated.

Furthermore, despite the fact that there are numerous products on the market that include NPs/nanomaterials, there remain gaps in scientific and methodological knowledge about the specific risks associated with nanomaterials. The discovery of novel nanomaterials represents an incredible possibility for tissue engineering, which must meet both patient expectations and therapeutic needs. Even though nanoparticles have unquestionable medicinal benefits, the use of these artificial nanomaterials has substantial health consequences. This risk must be minimized following the precautionary principle during the development, testing, and therapeutic use of these materials.

As far as we know, there are currently no international standards for nanotechnology-related risk assessment, comprising of specific data obligations and testing methodologies. Assessing the risks associated with nanomaterials is complicated and costly. Manufacturers are currently doing their best to evaluate the safety of their NP-based products and implement necessary safety measures (self-regulation). So far, NP-specific regulations are not available, for example, standards for data requirements for chemical reporting and classification and labeling requirements for safety data sheets have not yet been widely prepared and adopted. Therefore, precautions must therefore be taken when using nanoparticles where there is a possibility of chronic bioaccumulation. There is still a long way to go in biosafety, nanomaterial use, and stability. We anticipate that the

development of rationally planned nanotechnologies will overcome the majority of the challenges faced in present tissue engineering in the future.

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CHAPTER 16

Medical applications of functional antimicrobial nanoparticles

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1. Introduction

The concept of multidrug-resistant organisms (MDROs) has led the way toward the medical use of nanoparticles. Infections caused by MDROs are difficult to treat [1] and they generate adverse effects, therefore nanoparticles are used to manage such infections [2,3] as they can overcome enzyme inactivation, low cell permeability, high efflux, etc. Additionally, they can synergistically act against MDROs by prohibiting the formation of biofilm [4]. The broad-spectrum antibacterial activity of nanoparticles is expressed by the varied physical structure of nanoparticles, such as in graphene oxide nanoparticles. Several features of nanoparticles make them stand out from several antibiotics: (1) the greater contact area with the target organism due to the large surface area to volume ratio; (2) theirs nanosize enables them to interact with bacterial cells for the regulation of cell membrane penetration and interference with the cell's molecular pathways [5–7]; and (3) they can easily conjugate with different compounds to enhance the inhibitory effects of antibiotics as in the case of gold nanoparticles which lower the minimum inhibitory concentrations against bacteria by conjugating with ampicillin or streptomycin [8]. These properties show that the combination of antibiotics and NPs can overcome the complex antimicrobial resistance more effectively [9].

Combating *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumonia*, *Acinetobacter baumannii*, and many others through NPs requires their combination with—silver (Ag), gold (Au), zinc (Zn), copper (Cu), magnesium (Mg), selenium (Se), cadmium (Cd), etc. [7]. Among these, silver

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nanoparticles are used more frequently as they possess multiple mechanism of antibacterial action, high biocompatibility, and ease to of use [10,11]. Also, metallic NPs release toxic ions and inflammatory cytokines, generating reactive oxygen species (ROS), which causes immunotoxicity, cytotoxicity, and genotoxicity in healthy as well as infected cells, making it extra powerful against infection [12,13]. In the biomedical sector, the biocompatibility and safety of zinc oxide nanoparticles makes them the best tool to be used on human skin as an appropriate additive for cosmetics and fabrics [14].

In addition to the positive aspects of nanoparticles, their negative side also persists which requires attention as it is not been fully understood so far. The toxicity of NPs is affected by multiple factors, including shape, size, surface charge, composition, and stability of the particles. Toxicity is also dependent on the dose of nanoparticles injected, route of administration of the particles into the body, and the tissue to be targeted. Therefore, before the administration of nanoparticles the above-stated characteristics should be considered for their safe and effective use [15]. Recent nanoparticles studies have prompted their importance in the biomedical sector, and in this chapter we identify various antimicrobial nanoparticles and their relevance in the health sector to promote human welfare. In Table 16.1 examples of functionalized nanoparticles and their biomedical importance are listed.

2. Synthesis of nanoparticles

Nanoparticles can be synthesized in three ways which are represented in Fig. 16.1. The time- and space-consuming physical method employs high temperatures and so can generate harmful environmental effects. As the temperature depends on the size and concentration of nanoparticles, the physical method is also proportional to these attributes. The uniformity of the distribution of NPs also affects the physical method but in a positive way [34].

Chemical methods work best for the synthesis of silver nanoparticles with the help of organic and inorganic reducing agents and a metal precursor, a reducing agent, and a capping/stabilizing agent. The process starts with (a) nucleation of metal ions an (b) agglomeration into oligomeric clusters. The different chemical methods are—microemulsion method, UV-initiated photo-reduction, photo-induced reduction, electrochemical synthetic method, and irradiation method [35]. As compared with the physical method, the chemical method has a higher yield.

Table 16.1 Examples of different functionalized nanoparticles with their biomedical importance.

Nanoparticles	Functionalized or conjugated with	Biomedical importance
AuNPs	Citraconic amide	Photoacoustic imaging agent that responds to the microenvironment of cancer [16].
	RNA aptamer	In vitro targeted imaging and therapy [17]
	PEG	CT scan imaging [18]
	Pyridines	In buffered aqueous conditions, it can be employed for direct colorimetric detection of the nerve agent simulant DCNP [19].
	Hyaluronic acid	Site-specific delivery of hydrophobic drugs [20]
AgNPs	Chitosan	Antimicrobial activity [21].
	Tryptophan	Enhanced photobleaching [22]
Liposomes	DNA aptamer	Anticancer drug delivery [23].
	Folate	Anticancer targeting [24].
Carbon nanostructures	PEG 1500, tyrosine	Fluorescence imaging
Iron oxide NPs	Silica	MRI
Hydrogel	Peptide CREKA	Cancer cell targeting [25]
Polylactic-co-glycolic acid (PLGA) NPs	PEG	Can improve delivery of drugs [26]
Polydopamine NPs	Glucose	Antitumor drug delivery [27]
Zinc oxide NPs	Aloe vera (ALE)	Antimicrobial and antibiofilm activities [28].
	PEG	Antitumor activity against human breast cancer cells [29].

Continued

Table 16.1 Examples of different functionalized nanoparticles with their biomedical importance.—cont'd

Nanoparticles	Functionalized or conjugated with	Biomedical importance
	Folic acid	Targeted cancer cell imaging [30]
Albumin NPs	Peptide PEG Folic acid	Drug delivery [31]. Drug delivery [32] Anticancer studies [33]

The natural, eco-friendly methods always gained popularity over the years, so the biological method of synthesis that employs the use of bacteria, fungi, and plants has gained increased attention over the other two methods such as in the case of the production of silver nanoparticles from *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Acinetobacter* species, *Lactobacillus* species, *Klebsiella pneumonia*, and *Enterobacter cloacae* [36–38]. Several plants are also used for the biosynthesis of NPs as their extracts are rich in phytochemicals and enzymes which facilitate the reduction of silver ions into nano-sized materials, for example polyphenols, flavonoids, and phenolic biomolecules extracted from *Camella sinensis* (green tea) and black tea leaf extracts that reduce and stabilize silver ions and AgNPs [39]. The biological method has an advantage over the other two in that it is highly stable. Synthesis at the laboratory scale uses different techniques, as represented in Fig. 16.2.

3. Antimicrobial activity of nanoparticles

The antimicrobial activity of NPs in many drug-delivery processes to tissues is a significant challenge in medical sciences, with several factors associated with it including the concentration of drug candidates and NP size specificity to the target tissue. Silver nanoparticles (AgNPs) inhibit Gram-negative and Gram-positive bacteria, and also exhibit antiviral and antifungal properties. They are used for coating of medical devices, in disinfection of medical devices, in home appliances, and in water purification [40]. In addition, they are used in the production of antimicrobial textiles [41], in the coating of refrigerators and food containers, and in nanosensors, biological labels, and optical data storage [42,43]. Zinc nanoparticles (ZnONPs) have high photo-catalytic activity and antimicrobial activity (due to which they are highly preferred in the food industry

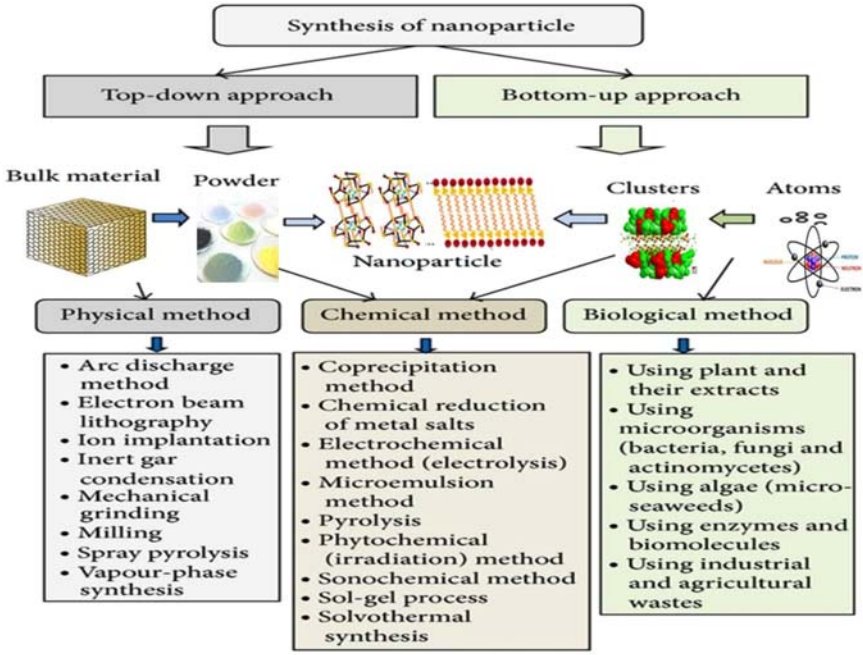

Figure 16.1 Methods for the synthesis of NPs [102].

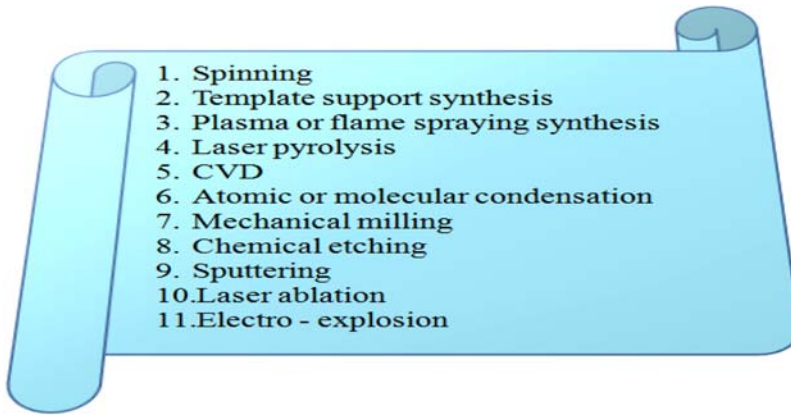

Figure 16.2 Synthesis methods of nanoparticles.

for the preservation of color and prevention of spoilage). They are also used in antibacterial creams, lotions, ointments, deodorants, and in self-cleaning glass and ceramics [44,45]. Titanium nanoparticles (TiO_2NPs) possess antimicrobial and antibiofilm activity against bacteria, fungi, parasites, and

viruses. Due to the photocatalytic activity and quantum size effect they are widely used in air purification, water purification, and in antimicrobial coating on biomedical devices [46]. By analyzing their microbicidal property, the FDA has approved their use in food, drugs, and cosmetics. Copper nanoparticles (CuNPs) are used in coating of medical devices due to their antimicrobicidal property against meticillin-resistant *S. aureus* (MRSA), *Bacillus subtilis*, *S. choleraesuis*, *P. aeruginosa*, and *Candida albicans* [47,48]. Gold nanoparticles (AuNPs) exhibit a unique photo-thermal property which increases its strong antibacterial and anticancerous activities. They are effective as a potent gene-delivery system in cancer therapy [49]. Carbon-based nanomaterials like fullerene, carbon nanotubes, graphene, and diamond-like carbon exhibit antibacterial properties and are therefore used in medical sciences [50].

4. Physicochemical properties of nanoparticles

The properties of NPs make them to stand out from the crowd of different types of particles. The various properties of NPs include:

I. Electronic and optical properties:

These interdependent properties can be explained through an example of noble metal NPs which exhibit a strong UV-visible extinction band and size-dependent optical properties due to the presence of freely transportable free electrons on the surface of NPs which rather than scattering sets into a standing resonance condition which leads to localized surface plasma resonance (LSPR) [51].

II. Size and surface area properties:

These attributes play a major role as they affect the interaction of NPs with the biological system. By decreasing the size of NPs, the surface area increases exponentially relative to the volume, which increases the reactivity [52]. The in vitro cytotoxicity of NPs of varying size employs different cell types, culture conditions, and exposure times [53,54].

III. Magnetic property:

Catalysis (heterogeneous and homogeneous), biomedicine, magnetic fluids, magnetic resonance imaging (MRI), and other techniques reflect the magnetic properties of NPs which work at a size smaller than the critical value [55,56]. The uneven electronic distribution generates the magnetic behavior of NPs, which can be altered by certain

synthetic methods such as solvothermal, coprecipitation, microemulsion, thermal decomposition, flame spray synthesis, etc. [57,58].

IV. Mechanical property:

The mechanical parameters such as elastic modulus, hardness, stress and strain, adhesion, surface coating, coagulation, lubrication, and fabrication are studied for a better understanding of the mechanical properties of NPs [106].

V. Thermal property:

Metal NPs show a higher thermal conductivity than other types of materials. Recently, the combination of NPs and nanofluids has been more commonly used as the nanofluids (fluids containing suspended solid particles) exhibit superior properties to conventional fluids, for example, nanofluids consisting of copper oxide or aluminum oxide nanoparticles in water or ethylene exhibit advanced thermal conductivity [103].

5. Biomedical applications of nanoparticles

The advances made in the development of nanotechnology therapeutics for a variety of medicinal applications have contributed to better treatment strategies, and nanocomposites in particular, have been widely employed in medication delivery and cancer hyperthermia therapy. Recent uses of magnetic nanoparticles, on the other hand, show that they can help reduce implantation infections and promote wound healing [59]. The five primary elements of bioimaging, biosensor, targeted drug delivery, genetic material interaction, and direct DNA delivery are used to classify distinct types of core/shell nanoparticles [60]. In Fig. 16.3 applications of nanoparticles in biomedicine are provided, indicating the multiple roles of nanoparticles.

The production of artificial nanoparticles has resulted in recent developments in nanotechnology. Metallic nanoparticles have been successfully utilized for biological applications, and gold nanoparticles (AuNPs) stand out among them. Spherical and gold nanorods (AuNRs) have received a lot of interest because of their unique characteristics, such as electro-optic, digital, physical, and chemical, and surface plasmon resonance (SPR), which can be changed by altering particle characteristics such as shape, size, aspect ratio, or environment; and their ease of synthesis and functionalization properties have led to a variety of implementations in biomedical science, including sensing, targeted drug delivery, imaging, photothermal and photodynamic therapy, and modulation of two or more

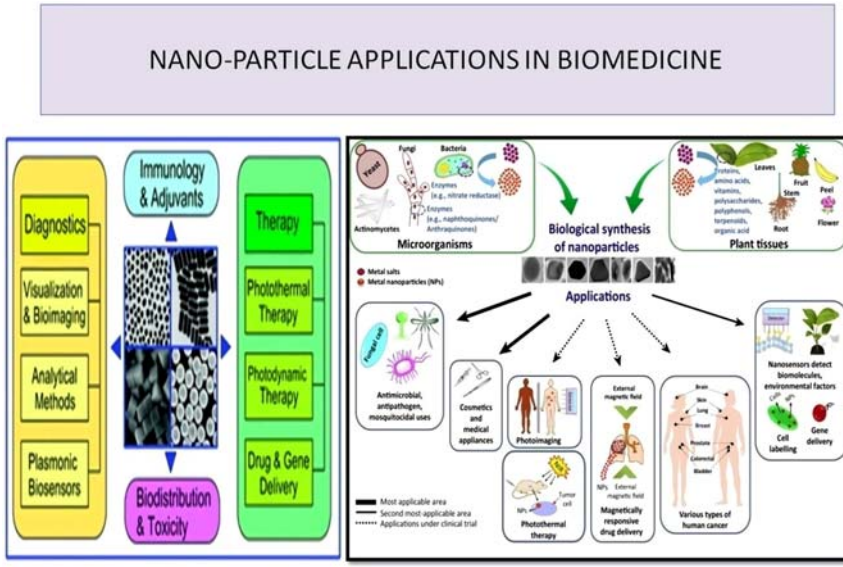

Figure 16.3 Applications of nanoparticles in biomedicine field [61].

parameters [62]. Fe—Pt nanoparticles have been found to reduce T2 relaxation durations in MRI imaging and to function as effective drug carriers for targeted medication administration. More studies are needed to see if magnetic hyperthermia can be used. Because of their unique qualities, such as biocompatibility, chemical stability, and photocatalytic capabilities, TiO_2 nanoparticles are increasingly being used in drug delivery, bio-imaging, photoablation treatment, and biosensors. TiO_2 nanoparticles have been found to be effective drug-delivery nanocarriers [63]. The latest technologies of bioinformatics and nanomedicine-assisted drug delivery have the potential for better therapeutic treatment of various pathogens like dengue virus [107], SARS-CoV2 [64], human cytomegalovirus [65], *Candida* fungus [66], and canine circovirus [67]. In Table 16.2 different types of medicinal applications of nanoparticles are described.

6. Modes of green synthesis of nanoparticles

Synthesis using enzymes: Enzymes are preferred for green synthesis because of their well-defined structure and availability in a pure state. For example, during the synthesis of NPs, AgNPs were assembled using an enzyme-induced emergence on strong substrates [68]. Agro-waste such as *Cocos*

Table 16.2 Nanoparticle types and modernization in design and medicinal applications.

S. no.	Type of NPs	Modernization in design	Cargo molecule	Medical applications	Diagnosis
1	Lipid nanoparticles	Charge dependent, surface modification, shape modification, and size modification	Nucleic acids: RNA, DNA, proteins	Therapy for cancer and autoimmune conditions, pulmonary diseases	Cancer diagnosis with ^{64}Cu
2	Polymeric nanoparticles	Responsivity, surface modification	Dyes, drugs, small nucleic acids	Variety of cancers, cystic fibrosis, osteoblastoma	Cancer diagnosis with ^{64}Cu and fluorescent dyes
3	Inorganic nanoparticles	Surface modification and responsivity	Photosensitizer, protein, nucleic acids, antibodies	Breast cancer, lung carcinoma, mitochondrial dysfunction, neurological disorders	Alzheimer's disease, anemia, tuberculosis, and cancer diagnosis with carrier molecules such as beta amyloid peptide, heat shock proteins, iron, and thrombin

nucifera coir, maize cobs, fruit seeds and peels, wheat and rice bran, palm oil, and others can also be used to produce NPs. These substances contain biomolecules such as flavonoids, phenolic acids, and proteins, which might function as a reductive agent in the creation of NPs [69].

Synthesis using vitamins: Vitamin B2 (as a reducing and capping agent) can be used to create a green mixture of Ag and palladium nanospheres, nanowires, and nanorods. For the manufacture of nanowires and nanorods, vitamin B2 is utilized as a reducing agent. This is a novel method in the field of green nanotechnology, since it proposes the use of natural agents in the progress of the field, such as their effect on various tumor cells [70]. Similarly, ascorbic acid is utilized as a capping and reducing agent, while chitosan is employed as a stabilizing agent in NP synthesis. Because chitosan bonds with metal ions, the concentration of NPs is exactly proportional to the chitosan concentration used [71].

Bio-based synthesis: This overcomes the chemical approach by being highly stable, well defined, and environmentally friendly.

Bacteria and actinomycetes: This was demonstrated by Simon Silver, who proposed that a certain gene is essential for Ag bacterial resistance, and that these bacteria may be used instead of Ag in the event of a burn to reduce the risk of Ag toxicity [72]. Since then silver nanocrystals of different compositions have been successfully synthesized by *Pseudomonas stutzeri* AG259 [73].

Yeasts and fungi: The metabolic mechanism of *F. oxysporum* changed silver nitrate into Ag oxide, resulting in well-dispersed NPs. When Ag particles were introduced to *F. oxysporum*, nitrate reductase was released, resulting in the formation of very functional AgNPs in solution. *Trichoderma viride* and *Fusarium oxysporum* were used in the formation of stable NPs [74].

Algae: *L. majuscule*, *S. subsalsa*, *R. hieroglyphics*, *C. vulgaris*, *C. prolifera*, *P. pavonica*, *S. platensis*, and *S. fluitans* are examples of cyanobacteria and eukaryotic green development genera that may be exploited as cost-effective materials for bio-recovery of metals from liquids [75].

7. Characterization of nanoparticles

Following the synthesis of NPs, multiple spectroscopic methodologies should be used to investigate the morphology and other conformational subtle components. UV-vis absorption spectroscopy, X-ray diffraction (XRD), Fourier transmission infrared (FTIR) spectroscopy, dynamic light scattering (DLS), energy dispersive X-ray examination (EDAX), scanning

electron microscopy (SEM), transmission electron microscopy (TEM), and other systems are some of the most common.

UV-visible spectroscopy: Because of the consolidated electronic fluctuation of a conduction band on the surface of metal NPs in resonance with incident light, the configuration of NPs from the UV-visible spectroscopy technique may be examined owing to the surface plasmon resonance assimilation band. Subhapriya and Gomathipriya described the bio-reduction of Ag nitrate to Ag NPs, which they measured using UV-visible spectroscopy on occasion [104].

FT-IR: FTIR spectroscopy is used to investigate the properties of functional groups or metabolites located on the surface of NPs, which may be responsible for NP reduction and stability, as well as information on capping and stabilization [76].

High-resonance SEM: The new era of high-resolution SEM (HRSEM) allows for measurements greater than 1 nm, paving the way for TEM measurements. It is possible to break down partnerships using this method, such as the adsorption and uptake of metallic NPs by cells. The shape and size distribution of NPs are clarified using TEM and SEM. AgNPs are spherical and monodispersed, according to the TEM data.

XRD spectroscopy: X-ray diffractograms of nanomaterials provide a wealth of information, ranging from phase formation to crystallite estimation, cross-section strain, to crystallographic introduction. XRD is noncontact and nondestructive, making it perfect for in situ research [77].

8. Nanoparticles for drug delivery

The emergence of nanoparticles as reliable drug-delivery devices has advanced dramatically over the last decade. The many types of nanoparticles now being researched for use as drug-delivery systems are as follows:

- Polymeric biodegradable nanoparticles that include nanospheres and nanocapsules
- Ceramic nanoparticles
- Polymeric micelles
- Dendrimers
- Liposomes.

Specific biological molecules such as antibodies, enzymes, hormones, and pharmaceutical medications can be structurally connected to make

these nanoparticles work as effective drug-delivery devices [78]. In Fig. 16.4 cancer drug insertion to the target site is shown to indicate how nanoparticles adsorb drug candidates and release drugs to cancerous sites by utilizing leaky blood vasculature channels between endothelial cells.

Polymeric biodegradable nanoparticles: These are colloidal solid particles made up of macromolecular compounds with sizes ranging from 10 to 1000 nm. These nanoparticles can be either nanospheres or nanocapsules, depending on the technique of manufacture. For the encapsulated drug, these two nanostructures have radically distinct properties and release characteristics [78]. By hydrolysis, these drug deliverers are reduced into biologically acceptable compounds, allowing the encapsulated medication to reach the target tissues. Collagen gels are more appealing for therapeutic applications because they can act as a "kennel" to retain cells or as gene-delivery complexes, which are significantly larger than drugs and therapeutic proteins.

Ceramic nanoparticles: Calcium phosphate, silica, alumina, and titanium are all used to make ceramic nanoparticles. These nanoparticles offer a number of benefits, including simplified preparation, excellent biocompatibility, ultra-small size (less than 50 nm), and high mechanical strength. They successfully protect doped drug molecules from denaturation due to

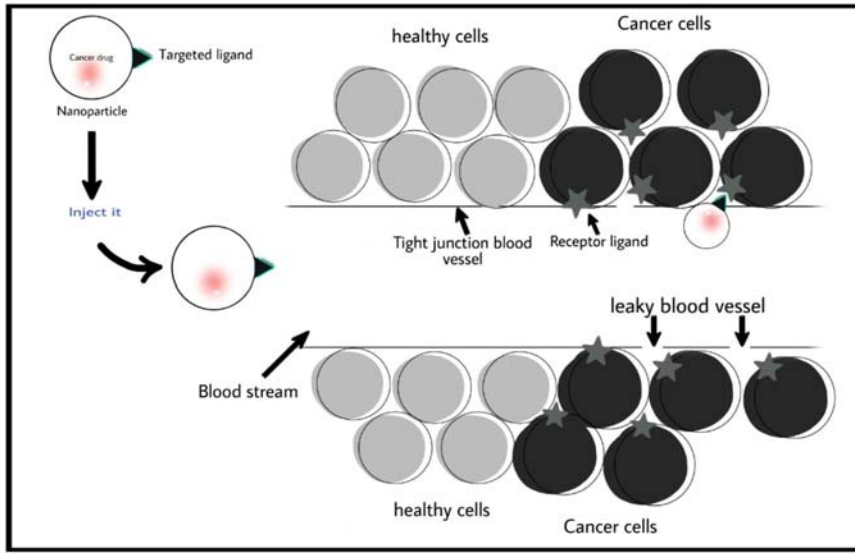

Figure 16.4 Nanoparticle-guided drug delivery using common leaky channels in body vasculature for cancer treatment.

external pH and temperature fluctuations. To target them to specific areas, their surfaces may be readily changed with various functional groups and coupled with a range of ligands or monoclonal antibodies. The size, shape, and porosity of these nanoparticles may all be customized. Changes in the outdoor landscape have no effect on the swelling or porosity of a ceramic nanoparticle. Insulin administration through parenteral injection has been explored using self-assembling ceramic nanoparticles [79].

Polymeric micelles: These are supramolecular structures that self-assemble in an aqueous media and are made up of cross-linked mixtures of hydrophilic and hydrophobic ligands. These copolymers have a diameter of only a few tens of nanometers, making them perfect for encapsulating a single drug molecule [80]. Because of their small size, these drug carriers are able to bypass renal excretion and the reticuloendothelial system (RES), boosting tumor cell absorption. While administering the drug, their hydrophilic outer shell isolates the core and its components from the adjacent aqueous medium in the patient's body.

Dendrimers: These monomers are made up of a succession of branches that surround an inner core [81]. Dendrimers are simple to make down to the nanoscale scale. They also feature a unique globular form with interior holes where medication molecules may be securely stored while being protected by the hydrophobic external surface. Drug molecules can also be connected to the outside of the cell. Divergent synthesis (bottom-up technique) or convergent synthesis (top-down approach) can be used to build them from the core to the periphery (top-down approach).

Liposomes: These are small spherical vesicles produced from harmless phospholipids and cholesterol found in nature. Liposomes are potential drug-delivery vehicles due to their size, biocompatibility, hydrophobicity, and simplicity of manufacture. To improve the circulation time in the bloodstream, polyethylene glycol units (PEG) can be attached to their surfaces. To increase target selectivity, liposomes can be coupled with ligands or antibodies [82].

9. Nanoparticles for cellular labeling

The use of nanoparticles to detect stem cells is gaining popularity. Indeed, they may provide a tool for stem cell research to carry out long-term noninvasive imaging of grafted cells in vivo to track their viability, movement, differentiation, and regenerative potential [83]. Nanoparticles have multiple applications in the medical sector (Fig. 16.5), such as in

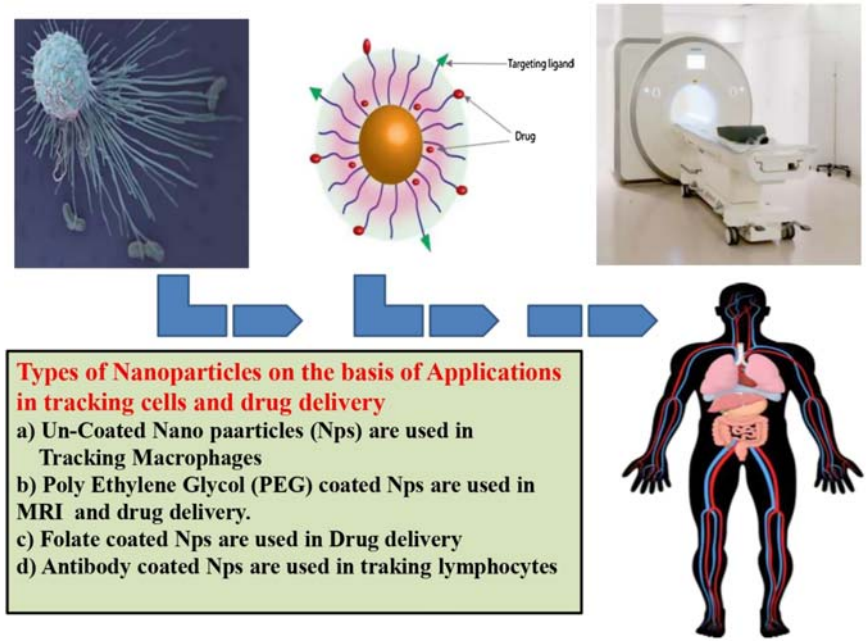

Figure 16.5 Nanoparticles in tracking cells, MRI detection, and drug delivery.

tracking various cells on the basis of affinity, MRI detection, and in drug delivery. Nanoparticles have several applications in stem cell biology, including (1) noninvasive monitoring of stem cells and progenitor cells engrafted in vivo, (2) subcellular delivery of DNA, RNAi, proteins, peptides, and minor drugs for stem cell differentiation or survival, and (3) biosensing of stem cell physiological status [84]. The majority of labeling solutions employ one of two approaches:

⇒ adhering magnetic nanoparticles to the stem cell's cellular surface
⇒ Internalization of the particles

SPIONs with suitable surface architecture and conjugated targeting ligands/proteins have gained a lot of interest in the last decade for biomedical applications, compared with all other forms of nanoparticles [85,86]. SPIONs have been identified as a suitable contrast agent option for MRI methods due to their unique magnetic characteristics [87,88]. One of the oldest applications for magnetic nanoparticles is the fabrication of ferrofluids; however, new and promising biocompatibility applications are being investigated, such as using Fe_3O_4 for contrast enhancement in MRI, drug/gene delivery, molecular/cellular tracking, magnetic separation techniques

(e.g., rapid DNA sequencing), magnetotransfections, and ultrasensitive diagnostic assays [89,90].

10. Nanoparticles in imaging

To improve the fluorescent markers used in diagnostic imaging processes, quantum dot technology and magnetic nanoparticles can be utilized. Current fluorescent imaging techniques have significant drawbacks, including the necessity for color-matched lasers, fluorescence bleaching, and the inability to discriminate between various dyes. Fluorescent quantum dots can be used to circumvent these drawbacks. Quantum dots are crystalline aggregates of nanocrystals with a few hundred atoms that are covered with a different substance on the outside [91]. Magnetic nanoparticles (ferrofluids containing iron oxide nanoparticles) have been studied for use in colon cancer imaging and therapy. The tumor cells were discovered to have a stronger affinity for these iron oxide nanoparticles than normal cells [105].

In vivo SERS imaging: The creation of safe and effective SERS nanoparticles for in vivo studies is a critical milestone in the therapeutic advancement of the technology. SERS stands for "Selective Entropy Reduction Strategy." The use of ultrahigh sensitivity, multipurpose, and bioadaptable SERS nanoparticles for in vivo bioimaging is becoming more common as nanotechnology advances. The detection of SERS was split into two categories: direct analysis and indirect analysis. Direct detection, also known as label-free SERS detection, uses SERS-active nanocrystals as SERS substrates to capture biological component information (such as proteins, DNA, and lipids). This approach is quite good at recognizing unsaturated bonds and aromatic ring structures, but it has limited sensitivity when it comes to identifying other groups. SERS nanotags are used in indirect detection to specifically distinguish the target species, which is very useful in a diverse biological environment. SERS nanotags are generally made up of SERS-active nanoparticles as the SERS substrates, which are then coated with Raman reporter compounds for detection using the spectrum.

Biosensor imaging: In the realm of medical sciences, improving biosensor performance is necessary to promote human health and extend the human life span. Various life-threatening disorders, such as cancer, HIV and viral infections, and bacterial infections, should be recognized sooner rather than later in order to properly treat diseases. Probes, DNA, proteins, and

antibodies or enzyme secretion are all used to identify these disorders. Nanoparticle-conjugated probes have been shown to improve target detection. Ag nanoparticles, like other nanoparticles, are active in the field of biosensors; probe-conjugated nanoparticles have demonstrated high-efficiency biomolecule detection. Surface plasmon resonance, Raman spectroscopy, ELISA, waveguide, and electrochemical detection all use Ag nanoparticle-conjugated biomolecules, which have exceptional stability and sensitivity toward target molecular validation.

11. Nanoparticles in veterinary medicine

When compared to their bulk counterparts, metal/metal oxides and their nanostructured materials such as zinc, silver, selenium, copper—chitosan nanocomposite, and other nanomaterials have significant fungicidal activity. These antifungal nanoparticles may be classified into several types based on their chemical composition and shape.

12. Nanoparticlemediated immunotoxicity

There has been a boom in the usage of different nanomaterials outlined in the preceding sections for a wide variety of therapeutic applications since the emergence of nanomedicine. Although nanoparticles' large payload, low dose, and targeting ability make them appealing options for cancer treatment, immunotoxicity remains an important clinical issue. When utilized in vivo, NP and biological agent interactions play a critical role in nanoparticles' fate in terms of successful delivery, clearance, and accumulation, especially for systemic administration of medicines. Nanoparticles are recognized by immune systems based on their surface qualities and compositional characteristics. As a result, these characteristics can be used as handles to modulate interactions between nanoparticles and the immune system. When NPs come into contact with biofluids for the first time, they are exposed to a variety of proteins, resulting in a crown effect known as the protein corona particle. Although additional biomolecules such as DNA, RNA, and ribose simple sugars interact with NPs, these have received little attention in the literature and subsequent scientific studies. As diverse biochemical changes modify the bioactivity of NPs, their interactions with plasma proteins and some biosubstances alter their destiny. Unwanted associations between the immune system and nanoparticles have been observed frequently as a result of immunostimulation or

immunosuppression, which can lead to inflammatory or autoimmune illnesses, increasing the risk of infection in the receptor's body. Immune recognition may be circumvented in a variety of ways, the most common of which is the use of a polymeric material to produce a hydrophilic environment. Antibody creation, on the other hand, cannot be ruled out. Antigen-presenting cells, on the other hand, are directly stimulated to induce the appropriate immune response, or antigen is supplied to the relevant cellular compartment by targeting procedures.

Nanoparticles have been used to decrease immune activity in a variety of ways, including inhaling carbon nanotubes (CNTs) to restrict B-cell function. Alveolar macrophages release the cytokine-transforming growth factor (TGF-α), which is a key component of the reported immunosuppressive process.

The induction of the response by nanoparticles, on the other hand, can improve the effectiveness of nanomedicine supplied via cutaneous or intradermal methods. Several systems have been shown to increase the antigenicity of conjugated mild antigens and so act as adjuvants, and created nanosystems have also demonstrated intrinsic antigenic characteristics. Nanoparticles trigger the complement system in a variety of ways, and this activation may be controlled by altering their physicochemical features. Mast cells are involved in the biological processes that occur after nanoparticle exposure and can start contributing to inflammation and the harmful effects of certain nanoparticles.

13. Importance of nanoparticles in immunological consideration

The destiny of NPs in terms of their capacity to deceive or be identified by the body's immune system is determined by a variety of circumstances. As previously stated, size, physical shape, and surface characteristics are all important factors that influence the immune response to NPs. Foreign bodies are recognized by the innate immune system based on their size, among many other factors. To prevent being dismissed as "foreign" entities, NPs must be created to be inside a specified size range. The surface-to-volume ratio of NPs decreases as their size grows, impacting their surface contact with different immunoreagents. Pinocytosis, macropinocytosis, phagocytosis, clathrin, or caveolar-mediated endocytosis, as well as the removal of lipids via the lipoprotein receptor, SCARB1, are the major mechanisms by which NPs are taken up by cells.

The first two are acted upon by nonspecific reactions. NPs larger than 200 nm circulate through the venous and lymphatic drainage system and promote antigen presentation, whereas NPs smaller than 200 nm interact with APCs prevalent on the tissues. NPs with diameters less than 50 nm were observed to boost the expression of cell markers like CD40 and CD80, as well as inflammatory cytokines like IL-6 and TNF-α, all of which are hallmarks of the immune system's main reaction. Another important stumbling block in the use of NPs is their persistence in the liver, most of which is determined by their size, with larger sizes accumulating more. Smaller NPs, on the other hand, are quickly removed by the lymphatic system and picked up by local dendritic cells.

Aside from size, the form of NPs plays a role in determining the optimal immune response. According to reports, rod-shaped NPs with a greater surface area are even more likely to be picked up by macrophages than spherical NPs. This was linked to the produced vesicles, which enable quicker micropinocytosis engulfment. The aspect ratio was shown to control cytokine release in rod-shaped structures; the higher the aspect ratio, the more inflammatory biomarkers like IL-6 and IFN-γ were produced.

The surface charge of nanocarriers, in addition to surface functionalization, has a considerable impact on their complex interactions with the body's immune system. Positively charged NPs increase the electrostatic interaction here between them and oppositely charged membranes, resulting in increased surface endocytosis.

Liposomes, a type of common drug-delivery vehicle, have been shown to cause an acute hypersensitivity condition called complement activation-related pseudoallergy by triggering an immunological response originating in the innate immune system (CARPA). DOXIL, a clinically authorized doxorubicin formulation, has also been linked to CARPA87. This is an acute hypersensitivity reaction that happens shortly after an injection and appears as edema, chills, and anaphylaxis, among other symptoms. As a result, the use of the doxorubicin preparations in individuals with cardiac problems is closely supervised, and it has also been documented to induce acute cardiotoxicity. The action of the complement system and the production of anaphylatoxins are thought to be the cause of this pseudoallergy. When anaphylatoxins link to macrophages, a chain of events occurs, including the production of histamine, prostaglandins, and platelet-activating factor (PAF). The size, overall shape, surface charge, packing density, morphology, and bioactivity of liposomes all play a role in

complement activation. A modest response has been documented for small, noncharged unilamellar structures. Liposomes as drug-delivery systems are being studied in a variety of ways to see if they can reduce the immunotoxic reaction they cause [92].

14. Nanotoxicology

Nanotoxicology is described as "the study of the impact of manmade nanodevices and nanostructures on live beings" [93]. Given the variety of nanostructure compositions and our developing awareness of the role of oxidative stress and aspect ratio in toxicity, the specific mechanisms of nanostructure-induced inflammation are complicated [94,95]. It is reasonable to assume that oxidative stress is a primary mechanism of toxicity, depending on the synthetic process used and the subsequent chemical content of a nanostructure [96].

Many factors continue to impact nanoparticle toxicity, including size, shape, charge, surface modification, aggregation state, and so on. While nanotechnology allows particles to have a variety of qualities, it also allows us to manage those tiny features, as well as their potential toxicity. Superparamagnetic iron oxide NPs have been altered to change their chemical characteristics, which have been demonstrated to have an impact on toxicity [8,97].

15. Recent developments in commercialization of nanoparticles

The majority of companies in this area are working on therapeutic formulations, mostly for the administration of drugs. Several businesses employ nanoscale effects in semiconductor nanocrystals to tag proteins, while others use bio-conjugated gold nanoparticles to mark diverse biological components. Nanoscale materials are being used in tissue regeneration and orthopedics by a range of enterprises. Many large and renowned drug manufacturers have corporate drug-delivery development programs that focus on compositions or colloidals with nanoscale components. Nowadays, biogenic nanoparticles are also used for drug delivery [98]. Antimicrobial treatments and dressings frequently contain colloid silver. Titanium dioxide nanoparticles have strong reactivity, either on their own or when exposed to UV radiation, and are also employed as filters for bactericidal applications. To destroy harmful toxins as well as other toxic organic

compounds, increased catalytic capabilities of nanoceramic coatings or noble metallic materials like platinum are utilized.

16. Future scope of nanoparticles

Currently, drug administration is the focus of the bulk of commercialized nanoparticle uses in medicine. Nanoparticles are replacing natural dyes in bioengineering applications demanding excellent photo-stability and multiplexing abilities. There have been some advancements in the direction and remote management of nanoprobe operations, such as driving magnetic nanoparticles to the tumor and then either releasing the drug load or just warming them to kill the damaged tissue. The main tendency in nanoparticle development is to create them with versatile and programmable properties by external signals or the local environment, thereby transforming them into nanodevices [98,99].

It is possible that NPs may be combined in the future to operate as "nanomachines," with their method of interaction being nonlinear in response to changes in parameters such as temperature or pH. This strategy appears to be working, and the future of nanotechnology appears to be approaching; nevertheless, possible hazards must be addressed, and the impacts of new procedures must be thoroughly investigated before they are used [100]. For example, before NPs are extensively employed in medicine, their toxicity is thoroughly examined to identify any possible issues. Synthesis facilitated by plant extracts, on the other hand, is believed to be ecologically friendly. One of the most noticeable emerging trends in the fabrication of metallic NPs is using plant extracts, which might be a beneficial technique for determining the mechanism of action of NPs. This is a controlled synthesis method that is simple to scale up and assures environmental safety while lowering the process's environmental impact.

Overall, the usage of organic NPs has demonstrated a variety of benefits and uses in medicine and the pharmacological sector. More specifically, studies show that NPs can act as antimicrobials alone or in conjunction with antibiotics, reducing the current problem of acquired resistance caused by antibiotic overuse and/or abuse [101].

In light of this possible use, future research should concentrate on two areas: determining the safety of plant-based NPs (both in terms of health and environmental security) and reducing the environmental impact of their synthesis. To transform plant-based NPs into a feasible approach capable of meeting society's desire for an effective remedy against antibiotic

resistance, more extensive research of synthesis techniques is required, as is the investigation of modes of action that influence the antibacterial impact of NPs.

17. Conclusion

Nanotechnology, a new emerging field of technology, is now being paired up with biotechnology for treating microbial infections as it can modulate the properties of materials easily. TiO_2 nanoparticles are increasingly being used in drug delivery, and Fe—Pt nanoparticles have been found to reduce T2 relaxation durations in MRI imaging and to function as effective drug carriers for targeted drug administration. Spherical and gold nanorods (AuNRs) have received a lot of interest because of their significant qualities. Thus nanoparticles stand out as more suitable agents in medical and life sciences as compared to conventional antimicrobial agents. These potent therapeutic agents hold significant functionality which will revolutionize medicine and play a significant role in reducing the global disease burden.

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SECTION 6

Functionalized nanoparticles-based antimicrobial coatings for devices

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CHAPTER 17

Nanomaterials-based antimicrobial coatings for medical devices

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1. Introduction

Nanomaterials have a size of about 1–100 nanometers (nm) or at least one dimension in the nanometer range. Nanotechnology is a multidisciplinary field in which the properties and structures of materials are manipulated at the nanometer scale through physical, chemical, and biological routes.

There are four kinds of nanomaterials which can be categorized as

(1) Inorganic-based nanomaterials
(2) Carbon-based nanomaterials
(3) Organic-based nanomaterials and
(4) Composite-based nanomaterials.

Generally, inorganic-based nanomaterials include different metal and metal oxide nanomaterials.

1. Metal-based inorganic nanomaterials are silver (Ag), gold (Au), aluminum (Al), cadmium (Cd), copper (Cu), iron (Fe), zinc (Zn), and lead (Pb) nanomaterials.
2. Metal oxide-based inorganic nanomaterials are zinc oxide (ZnO), copper oxide (CuO), magnesium aluminum oxide ($MgAl_2O_4$), titanium dioxide (TiO_2), cerium oxide (CeO_2), iron oxide (Fe_2O_3), silica (SiO_2), and iron oxide (Fe_3O_4), etc.
3. Carbon-based nanomaterials include graphene, fullerene, single-walled carbon nanotubes, multiwalled carbon nanotubes, carbon fiber, activated carbon, and carbon black.
4. Organic-based nanomaterials are formed from organic materials, excluding carbon materials, for instance, dendrimers, cyclodextrin, liposomes, and micelles.
5. Composite nanomaterials are any combination of metal-based, metal oxide-based, carbon-based, and/or organic-based nanomaterials, and

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these nanomaterials have complicated structures like a metal–organic framework.

Nanomaterials (NMs) are now creating smarter, stronger, and more durable coatings. Today, coatings not only provide physical protection but also serve as smart interfaces and multifunction barriers. Generally, nanofillers increase the diffusion pathway of deleterious species, enhancing the barrier performance of organic coatings. Thus the coatings containing NMs (nanofillers) are expected to improve barrier and mechanical properties. Advances in nanocomposite coatings have been made possible by the functionalization of nanomaterials, such as

1. Self-healing
2. Antifouling
3. Self-cleaning
4. Antibacterial and
5. Cooling coatings.

Researchers from different science disciplines have been exploring the field of nanotechnology. There are many applications, benefits, and advantages to this technology, making it a promising application. Coatings are one of the sectors where the use of nanoparticles is expected to make a significant contribution in the future. It has been demonstrated that the use of nanoparticles in coatings can enhance coating performance and add new functions to the system (Fig. 17.1 and Table 17.1). This will allow for multipurpose coatings to be developed. Examples of nano-modified coatings benefits include chemical resistance, abrasion and erosion resistance, UV light resistance, antifouling properties, etc.

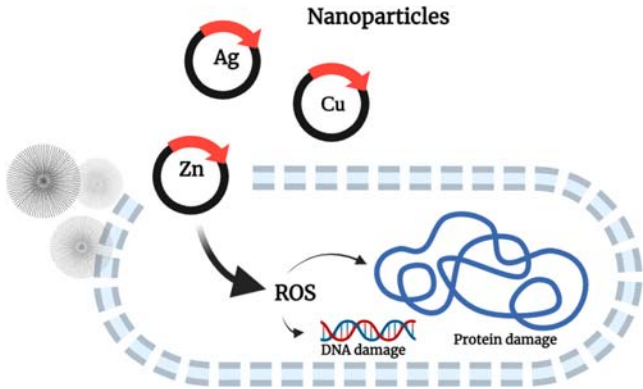

Figure 17.1 Mechanisms of nanoparticle action in bacteria cells.

Table 17.1 Antimicrobial polymers and nanocomposites used in biomedical applications.

Platforms/materials	Antimicrobial agent	Strategy	Application	Remarks	References
Hyaluronic acid hydrogel	Quaternary ammonium compounds	Contact killing	Wound healing	The hydrogel showed antibacterial activity against bacteria	[80]
Fe3O4	Quaternarized N-halamine polymers	Contact killing	Water purification systems and household sanitation	Effective antimicrobial impact against *staphylococcus aureus* and *escherichia coli* (Gram-negative)	[81]
Titanium dioxide core—shell nanoparticles	N-halamine	Drug release (cisplatin)	Anticancer	The nanoparticles showed effective antimicrobial activities against *S. aureus* and *E. coli*	[82]
Silica nanoparticles with nitric oxide (NO) release capabilities	Quaternary ammonium compounds	Drug release (nitric oxide)	Infection therapy	Very high bactericidal efficacy against *S. aureus* and *P. aeruginosa*	[83]
Polyethyleneimine (PEI), polyvinylpyrrolidone (PVP), and poly (2-vinyl pyridine)-b-poly(ethylene oxide) (PEO-b-P2VP)	Silver colloids	Contact killing	Antibacterial and antifungal	The materials exhibited high biocidal activities against fungi and bacteria	[84]

Continued

Table 17.1 Antimicrobial polymers and nanocomposites used in biomedical applications.—cont'd

Platforms/materials	Antimicrobial agent	Strategy	Application	Remarks	References
Chitosan	Silver nanoparticles	Contact killing	Infection therapy	Very high antimicrobial impact against *E. coli* and *S. aureus*	[85]
Polyethylenimine (PEI)	Silver nanoparticles	Contact killing	Infection therapy	PEI-Ag nanoparticles showed effective antibacterial activity	[86]
Porous amine-reactive (PAR) polymer films from poly(pentafluorophenyl acrylate) (PPFPA)	Porous amine-reactive films incorporating lubricant and silver nanoparticles	Contact killing	Infection therapy	This film showed a multimodal antibiofouling surface	[87]
Thin-film composite of polyamide reverse osmosis irreversible	Copper nanoparticles	Contact killing	RO desalination	The functionalized membrane exhibited significant antibacterial activity for three different model bacterial strains	[88]

Dopamine functionalized polyimide films	Silver nanoparticles	Contact killing	Antibacterial	Surface-silvered polymer film showed antibacterial activity using e*E. coli*	[89]
Poly(lactic-co-glycolic acid)/ZnO nanorods/ AgNPs hybrid coating on Ti	Silver nanoparticles and ZnO nanowire	Contact killing	Antibacterial	This platform exhibited high potential for biomedical application with excellent biocompatibility and self-antibacterial activity	[90]
Biodegradable Mg–Cu alloy film	Mg–Cu alloy	Contact killing	Orthopedic infections	The results indicated the potential utility of this biofilm in the treatment of orthopedic infections	[91]

Bacterial infections are one of the leading causes of chronic infections and mortality. For decades, infections caused by bacteria have been treated with antibiotics because of their effectiveness and cost-efficiency. Since antibiotics are widely used, multidrug-resistant bacteria have developed. It has been established that antibiotics have led to the development of multidrug-resistant bacterial strains. Scientists have discovered that these bacteria contain a gene known as NDM-1 [1] which confers super-resistance. Currently, three mechanisms of antibiotics target bacteria:

1. Cell wall synthesis
2. Translational machinery
3. DNA replication machinery.

The resistance mechanism includes the expression of enzymes that modify or degrade antibiotics, such as aminoglycosides and lactamases [2], modification of cell components, such as the walls of cells when vancomycin is resistant, and ribosomes when tetracycline is resistant [3]. Resistance to a variety of antibiotics can be provided simultaneously through efflux pumps. Nanoparticles (NPs) are unlikely to promote resistance in bacteria because their mechanism of action is in direct contact with the cell wall rather than penetrating the cell; this suggests that NPs are less likely to promote resistance than antibiotics. Therefore, nanoparticle-based antibacterial materials have drawn a lot of attention.

Bacteria often live as biofilms, which contain a variety of species interacting with one another and with their environment. Biofilms are microbial aggregates that rely on extracellular products, such as extracellular polymeric substances (EPSs) [4]. Bacteria can move on a solid surface, but the expression of EPSs makes the attachment irreversible. Once the bacteria have settled, the synthesis of their flagellum is inhibited, and they multiply rapidly, resulting in the formation of a biofilm. The bacteria at this point are clumped together, creating a barrier, which is resistant to antibiotics and can cause systemic chronic infections [5,6]. Furthermore, bacteria within biofilms can produce superantigens that allow them to escape the immune system. Therefore, despite the abundance of antimicrobial drugs and other antibacterial agents, bacterial infections remain a problem. Chronic infections caused by planktonic bacteria and biofilms are always challenging to treat due to their inherent resistance to antimicrobial agents and host defenses (Fig. 17.2). Specifically, biofilms are less susceptible to antibacterial agents than planktonic bacteria, when the latter are masked by them [7].

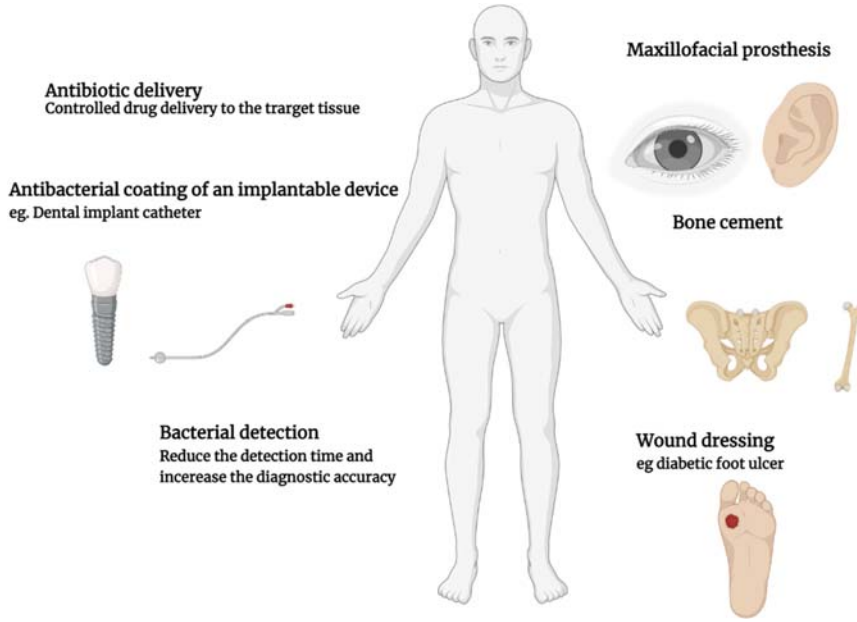

Figure 17.2 The antibacterial application of nanoparticles.

NPs, in particular, have demonstrated broad-spectrum antibacterial properties against both Gram-positive and Gram-negative bacteria. For example, ZnONPs inhibit *Staphylococcus aureus*, and AgNPs exhibit concentration-dependent antimicrobial activity against *Escherichia coli* and *Pseudomonas aeruginosa* [8] (Fig. 17.3). It has not been thoroughly explained how NPs exert their antibacterial effects, and the same types of NPs often exert opposing effects. As a general rule, the antimicrobial actions of NPs can be classified according to one of three models [9–11]:

1. Oxidative stress induction
2. Metal ion release
3. Nonoxidative mechanisms.

These three types of mechanisms can coincide. Some research has suggested that AgNPs can neutralize the surface electric charge on the membrane of bacteria, which alters the membrane's penetrability, resulting in the death of bacteria [12]. Additionally, the production of reactive oxygen species (ROS) inhibits the antioxidant defense system and damages the

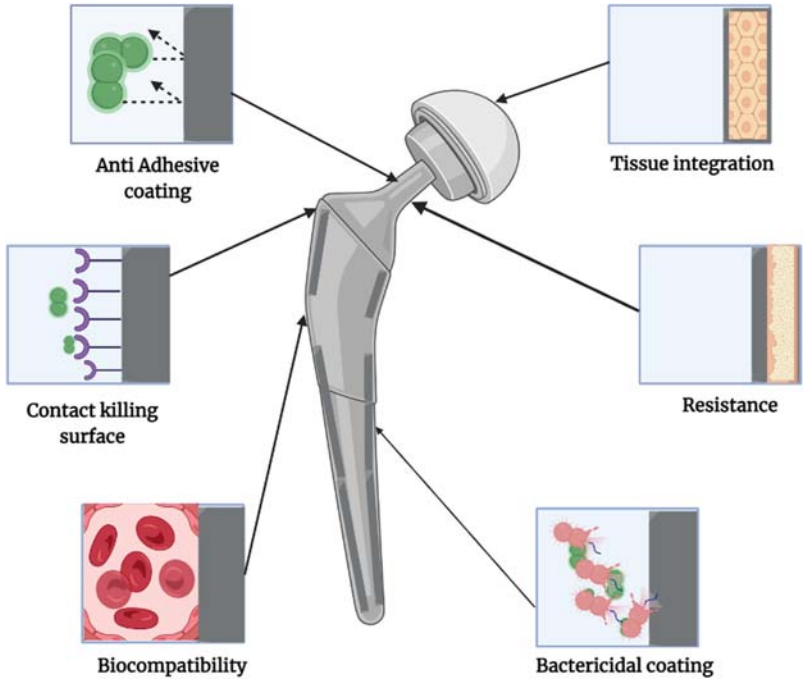

Figure 17.3 Multifunctional surfaces in total hip arthroplasty designed to simultaneously or successively respond to various biological and mechanical tasks.

cellular membrane mechanically. According to existing research, the primary processes underlying the antibacterial effects of NPs are as follows:

1. Disruption of the bacterial cell membrane
2. Generation of ROS
3. Penetration of the bacterial cell membrane
4. Interactions between DNA and proteins that cause intracellular antibacterial effects.

2. Bacterial resistance to nanoparticles

The main reason NPs are seen as an alternative to antibiotics is that NPs can be effective in preventing microbial drug resistance in some instances. The excessive use of antibiotics has created numerous public health risks, such as super-bacteria that are unresponsive to all existing drugs which could cause epidemics against which medicines provide no protection [13]. The development of new bactericidal materials is essential to combat drug resistance [14–16]. However, NPs could also potentially promote the development of bacterial resistance [17].

3. Antibacterial mechanisms of nanoparticles

The increasing use of NPs in medicine has led to an increasing number of studies examining the possible antibacterial mechanisms. For example, metallic NPs can change the metabolic activity of bacteria [18]. This ability is of great benefit in killing bacteria to cure disease. The ability of NPs to invade biofilms also provides a convenient method of inhibiting biofilm formation based on inhibited gene expression [19]. NPs have to be in contact with bacterial cells to fulfill their antibacterial function. Accepted forms of contact include electrostatic attraction [20], van der Waals forces [21], and receptor–ligand [22] and hydrophobic [23] interactions. The NPs then cross the bacterial membrane and accumulate along the metabolic pathway, influencing the shape. Subsequently, NPs interact with the basic building blocks of the bacterial cell such as DNA, lysosomes, ribosomes, and enzymes, which leads to oxidative stress, heterogeneous changes, changes in the permeability of the cell membrane, disturbances in the electrolyte balance, inhibition of enzymes, protein inactivation, and genetic changes [24–26].

4. The effects of nanoparticles on microbial resistance

The use of nanoparticles and nanoparticle-based materials is becoming a new line of defense against both microbial resistance and multiresistant mutants as an effective treatment method for resistance and MDR [27,28]. Different types of NPs have different mechanisms for combating microbial resistance. One of the accepted links between nanomaterials and antibacterial activity is: "Nanomaterials as antibacterial supplements to antibiotics are very promising and are gaining a lot of interest as they could fill the gaps in which antibiotics often fail." Nanomaterials enhance and supplement traditional antibiotics "as good carriers" [29].

Differentiating features and complementary advantages of the use of nanoparticles as antibacterial agents compared to conventional antibiotics can be summarized as follows:

1. They overcome the resistance mechanisms to existing antibiotics, which are listed in Section, including the modification of bacterial membranes and the obstruction of biofilm formation.
2. They combat microbes with several mechanisms at the same time.
3. Antibiotic carriers.

5. The interaction of nanoparticles with the cell barrier

Meanwhile, Gram-negative bacteria contain a thin layer of peptidoglycan and teichoic acid, as well as pores that allow foreign molecules to penetrate the membrane and damage it. In addition, compared to Gram-negative bacteria, Gram-negative bacteria have a high negative charge on the cell wall surface that NPs can attract [30].

The mechanism by which NPs cause bacterial death depends on the components and structure of the bacterial cell.

1. The antimicrobial effect of ZnO depends on the specific bacterial cell composition that could be improved for Gram-positive bacteria.
2. Gram-negative bacteria, such as LPS, can prevent the adhesion of ZnO nanoparticles to the bacterial cell membrane and regulate ion flow.
3. An NP's antibacterial function is affected by the thickness of the bacterial cell wall [31].

Phospholipid head-groups of LPS membranes in *E. coli* interact with ε-polylysine through electrostatic attraction and damage the cell membrane. However, the *Listeria innocua* film contains lysine-derived phospholipids, is amphoteric, and does not have a strong net negative charge to attract cationic peptides. Therefore, the cell membrane of *L. innocua* has a lower permeability than that of *E. coli* [32]. Coupling with intracellular components could further constrain critical enzymes and proteins, which could disrupt the bacterial metabolism and ultimately lead to cell death. Nanodiamonds can destroy a bacterial barrier to fulfill their antibacterial function.

As titanium dioxide NPs adhere to the surface of bacteria, they can produce ROS that damage the composition and structure of the cell membrane. This impairs cell membrane function and causes the cell contents to leak, [33,34] indicating that treatment with nanoparticles of TiO_2 causes honeycomb changes in the cell membrane and also causes cytoplasmic leaks. Iron can also cause bacterial cells to break down [35], and NPs can cause bacterial cells to be aggregated, resulting in inactivation by compression [36]. Bacterial membranes are the primary mechanism for graphene's antibacterial activity. Tu et al. [37] investigated the antibacterial molecular mechanisms of graphene nanosheets against *E. coli* based on molecular dynamics simulations that reveal the atomic details of the process by which graphene nanosheets cause cell membrane breakdown through graphene nanofilms leading to bacterial inactivation. Graphene of

membrane lipids was completely soaked with water, and the dispersive adhesion between graphene and lipids played a dominant role during the extraction [38].

One of the essential functions of the cell membrane is the respiratory activity of bacteria. NPs interrupt the respiratory activity of the bacterial cell membrane, which can be analyzed by detecting O_2 uptake or the reduction of 2,3,5-triphenyl tetrazolium chloride (TTC) [39]. Nanosilver ions have been shown to inhibit the growth of *E. coli* by causing pitting corrosion in the cell walls, increasing membrane permeability, and inactivating the respiratory chain, which is closely related to apoptosis. For example, the interfering effect of the TiO_2 NPs on the cell membrane potential of bacteria was measured by fluorescence microscopy [40], and changes in the fluorescence intensity of the cytoplasm were observed when the cell membrane potential was changed.

NPs can attack bacterial cells through several mechanisms: the formation of ROS, which damages the membrane, proteins, and DNA; there is a direct interaction with the cell membrane, as some metal-based NPs can dissolve to generate metal ions by inhibiting the electron transport chain; and the regulation of bacterial metabolic processes.

6. The penetrating mechanism of nanoparticles

Diffusion: NPs introduce ROS into bacteria by diffusion. Graphene oxide-iron oxide NPs are produced by chemical deposition of Fe^{2+}/Fe^{3+} ions on rGO nanosheets in aqueous ammonia. The combined materials showed maximum antibacterial activity due to the generation of large amounts of hydroxyl radicals and diffusion in bacterial cells that inactivated MRSA [41]. Zhang et al. [42] investigated the mechanism of ROS generation of nanoparticles made of silver (Ag), gold (Au), nickel (Ni), and silicon (Si) in an aqueous suspension under UV irradiation (365 nm). In contrast, AuNPs, NiNPs, and SiNPs only generated singlet oxygen, which penetrated the cells to exert an antibacterial effect. Mukha et al. [43] showed that 10 nm AgNPs can pass through the cell membrane's pores allowing the penetration of microbial cells.

Adsorption: Metal ions from NPs are released into the surrounding medium and bind to negatively charged functional groups on the bacterial cell membrane, such as carboxyl and phosphate groups, in a process known as bio-absorption. Different metal ions have different types of activity; for example, zinc ions can bind to −SH protein groups with high affinity.

Clean and closely spaced cell membranes become tangled and dispersed, destroying their inherent function and killing bacteria. Silver ion NPs (Ag^+ NPs) are firmly adsorbed on the cell membrane, which depends on Coulomb's gravity, causing proteins to coagulate. Similarly, a study showed that signs of surface charges on AuNPs significantly affect the adsorption of NPs on membranes and that the electrical properties of bilayers are also important [44].

NP-based antibiotic delivery systems: In most cases, osteomyelitis is caused by pyogenic bacteria found in healthy oral flora, but cases of fungus infection are also common. Bones are usually protected from external pathogens, so osteomyelitis is rare. Introducing antibiotics into an infection site directly correlates with the difficulty faced by invasive pathogens in colonizing bone.

Conventional antibiotic approaches have the following significant downsides:

1. Systemic toxicity of antibiotics and
2. The inability of antibiotics to reach adequate concentrations at local infection sites.

The use of NPs can be seen as a win−win solution in finding bactericidal and osteogenic properties simultaneously. Due to their large surface area and functionalization, NPs can be used like transporters to achieve targeted drug delivery. The efficiency of drug adsorption is directly proportional to the specific surface area of the adsorbent and inversely proportional to the particle size. The same delayed-release effect can be achieved, for example, by compacting antibiotic-laden calcium phosphate powder under pressure to reduce the side effects of antibiotics. Gentamicin undergoes a controlled release of NPs from Fucoidan, making NPs a multifunctional drug-delivery system with antibacterial and antioxidant activities that can be used to treat pneumonia [45]. In addition, coated alginate NPs increase daptomycin's ability to penetrate the limbal epithelium of the eye and increase its ocular accumulation and duration of action. The key features of a drug-delivery system are biodegradability, biocompatibility, controlled drug delivery, and delivery to the target tissue [46].

7. Metal-based nanomaterial coatings

Drug-resistant pathogens can be combated using biomedical devices modified with antimicrobial metal nanoparticles. Three categories of antimicrobial nanomaterial exist: intrinsically antimicrobial, antimicrobial

agent carriers, and those that occupy both functional features [47]. The ability of gold (AuNPs) [48], silver (AgNPs) [49,50], magnesium oxide (MgONPs) [51], copper oxide (CuO-NPs) [52], titanium oxide (TiO_2-NPs) and zinc oxide nanoparticles (ZnONPs) [53] to generate antimicrobial coatings has been demonstrated by several studies. Silver nanoparticles have strong bactericidal properties, and broad-spectrum antimicrobial activity, they are currently utilized for many purposes in medicine. Unfortunately, our understanding of their long-term effects on human health and the environment is limited. The possible organ accumulation and uncontrolled release of metal ions should be carefully investigated, and protective coatings might be helpful. Since they are used as trace elements in the human body, ZnO and MgO are among the metal-oxide nanoparticles reported to be biocompatible [53,54]. The possible antibacterial mechanisms of metal-oxide nanoparticles have not ultimately been revealed.

Among the possible mechanisms of action against bacteria, ions concentrations, oxidative stress, and membrane damage are mentioned [52,55]. A magnetron sputtering technique deposited monolithic ZnO and ZnO composites with carbon (ZnO—C) and copper (ZnO—Cu). All sputter surfaces were ethanol-sterilized and used for the antimicrobial test. *Pseudomonas aeruginosa* and *Staphylococcus aureus* were selected as resistant and sensitive strains to Zn^{2+} ions, respectively.

The coated surfaces were either submerged into bacterial solutions or placed in direct contact with bacteria in a solid medium, with the experiment being conducted under three light conditions: visible light, no light, and UV light (365 nm). Visible light exposure increased the antimicrobial effect of the nanocomposite surfaces, and under UV pretreatment, the antimicrobial activity of all surfaces increased because of the ROS generation. The ZnO—C nanocomposite coatings were reported as the most efficient surfaces against the resistant *P. aeruginosa* inhibition. Metal nanoparticles have been used for their antibacterial properties for over a decade. However, it is also important to emphasize their antiviral properties. Inactivation of viruses before their binding to the host cells is the most direct way to control the spread of viral infections. For example, heparan sulfate (HS) proteoglycans, which are expressed on the surface of almost all eukaryotic cell types, are the most conserved targets for viruses like herpes simplex virus (HSV), HIV-1, and human papillomavirus (HPV). Recently, AuNPs were modified with mercaptoethanesulfonate based on its mimicry of HS which was demonstrated to impede viral attachment, cellular entrance, and spreading [56]. Metal NPs, including Fe or Cu in the ionic

form, can be a catalyzer in generating free radicals (ROS) that oxidize the capsid proteins, thus preventing viral infection at an early stage. Polyethylenimine (PEI)-modified AgNPs can attach and deliver siRNA, which exhibited improved capabilities for cellular uptake and stopping enterovirus 71 (EV71) virus infection [57]. Some studies have reported that the addition of AgNPs to neutralizing antibodies has considerably improved the potential of neutralizing antibodies in preventing cell-associated HIV-1 transmission and infection [58].

8. Uses of nanocoatings

The implant should have properties to prevent the inflammatory response and osteolysis and stimulate osteointegration. A titanium implant has no antibacterial property and takes a long time for osteointegration; to overcome this, a graphene nanocoating (carbon) is used for dental and orthopedics implants to increase bone integration, prevent corrosion, and enhance antimicrobial properties. Graphene is not affected by inflammation in the body and it enhances bone integration to prevent implant loosening [59]. The hydrophobic property of graphene is useful to prevent bacterial and fungal biofilm formation. Titanium implant coating with titanium phosphate by a hydrothermal process compared with a titanium implant alone in a rat bone model showed better adhesion and osteogenic differentiation in titanium phosphate coating.

Ajdnik U. et al. in their study coated the implant model with chitosan and amoxicillin and found that it inhibits the growth of both Gram-positive as well as Gram-negative bacteria [60]. Chitosan ciprofloxacin coating on an orthopedic implant eluted the antibiotic at a slow rate and prevented postoperative infection. Magnesium acetate coating by micro-oxidation on a titanium implant increase osteointegration by enhancing proliferation and differentiation of stem cells [61]. A urinary catheter coated with chlorhexidine nanoparticles to prevent urinary tract infection is safe and not associated with skin and mucosa toxicity [62]. Biofilm formation on medical devices is a cause of persistent infection, and to prevent this polyphenols, catechin, and rare-earth ions were coated on the surface of the polyamide membrane [63]. Nanocoating with Cat—Re showed good antibacterial activities against *P. aeruginosa* and successfully prevented biofilm formation on the material's surface. A rare-earth—phenolic nanocoating has application in the prevention of medical device-related biofilm formation. Contact lenses can cause discomfort due to dryness, which leads

to infection and oxidative stress. Nanocoating of contact lenses with zinc oxide, chitosan, and gallic acid provides antioxidant property, increased smoothness, and antibacterial property, especially against *Staph. aureus*. Zinc copper oxide coating of contact lenses has shown antibacterial properties against *S. epidermis* and *Pseudomonas aeruginosa* without affecting the biological properties [64]. Coated contact lenses with different antimicrobials like zinc, gallic acid, and tobramycin are used to treat bacterial as well fungal ocular infections. Contact lens nanocoating with chitosan and timolol maleate could be used in the future for glaucoma treatment.

Urinary catheters coated with Zn−CuO have good biocompatibility in an animal model, indicated by low in vitro cytotoxicity and cytokine secretion, with the absence of tissue irritation.

A plant-based pectin nano-coating has been used for different implants because of the stimulation of osteogenic progenitor cells. Rhamnogalacturonan-I (RG-I) isolated from potato pulp stimulates the proliferation of osteoblast, osteogenesis, and bone mineralization. Rhamnogalacturonan-Is (RG-Is) contains antiinflammatory properties and is used in implant coatings for chronic inflammatory diseases like rheumatoid arthritis and periodontitis [65]. A titanium nanocoating on heart valves slows the complement pathway and immunogenicity and can be used to increase the life of heart valves [66]. A nanocoating with heparin scaffold improves vascular endothelization and prolonged anticoagulation. Vinogradov et al. described MIL101 (Fe) adsorbing up to 15% of heparin as a potential candidate for drug-delivery [67]. Hep MIL 101 addition to sol−gel combines both anticoagulant and thrombolytic activities and could be used as a nanocoating for PTFE vein implants.

Teichgräber et al. in their randomized controlled trial compared paclitaxel-coated angioplasty with uncoated balloon angioplasty and found paclitaxel angioplasty patients improve clinically and inhibit restenosis. Nanocoating of 316L stainless steel with trimethylsilane decreases metal ion release and corrosion in the coronary stent and this can be applied in orthopedics implants like total hip replacement to prevent metal ion disease [68]. Polyetheretherketone (PEEK) material has similar properties to bone and stimulates osteointegration, however, it is prone to infection. Nanocoating with graphene oxide, polydopamine, and oligopeptide on PEEK has shown enhanced bone osteointegration, remodeling, and antibacterial activity resulting from synergistic photothermal and photodynamic therapeutic effects [69]. Nanocoating of spinal PEEK cage with autologous bone graft compared with without coating showed greater spine stability and decrease motion at lumbar level fixation [70]. It is known that

hydroxyapatite coating on implants enhances osteointegration but there is a problem of particle aggregation and inadequate binding to the bone with different methods like plasma spray, micro-oxidation, sol–gel, etc. Wang et al. described a method to fabricate hydroxyapatite copper nanoparticles by pulse electrochemical polymerized pyrrole and improve the wear and friction properties of the material [71]. Silver nanocoating of sutures is promising in preventing infection without any additional toxicity and reduced health expenditure [72]. Silver is known for its antibacterial property and titanium implants were surface coated with silver by anodization and sintering technique. Silver hydroxyapatite nanocoating titanium implants inhibits bacterial growth (100%) and reduces bacterial biofilm (97.5%) without affecting the property of osseointegration and bone healing [73]. Nanocoating is also used in vascular stents and grafts to prolong the anticoagulation effect and vascular endothelialization.

Due to the COVID-19 pandemic, there has been increased use of surgical masks, resulting in increased economic cost. Kumar et al. described shellac copper nanoparticles (CuNPs) in a surgical mask to increase hydrophobicity and repel aqueous droplets. It showed photoactivity for antimicrobial action and the self-sterilizing ability of the masks. Under solar illumination, the temperature of this photoactive antiviral mask (PAM) rapidly increased to $>70^{\circ}C$, generating a high level of free radicals that disrupted the membrane of nanosized (~ 100 nm) virus-like particles and made the masks self-cleaning and reusable. A nanocoating design can be useful to prevent the transmission of viral aerosol and another infectious diseases. COVID-19 is mainly transmitted through aerosol and contaminated surfaces, and so surface coating with antiviral nanoparticles is a reasonable option to prevent its spread [74].

Biofilm formation on implants and medical devices is the cause of the persistence of chronic polymicrobial infection. Bacteria within the biofilm become resistant to the immune response and antibiotics due to which they become challenging to treat. Nanocoating stimulates osteoblast function, tissue regeneration, and bone growth, and so it can be utilized in orthopedic implants. A superhydrophobic nanocoating on medical devices is used to prevent the formation of biofilm through various mechanism, such as (1) to prevent the adhesion of microbial cells and (2) to rupture the cell membrane of microbes. Nanoparticles also contain antibacterial activity irrespective of the hydrophobic surface [75]. Vancomycin noisome coating

of orthopedic implants has been shown to prolong antibacterial activity without affecting normal cells, and so appears to be a good candidate to prevent biofilm formation.

The mesh used in hernia surgery is made of polypropylene because of its easy processability, inert nature, and flexibility. There are issues with polypropylene such as foreign body reaction, adhesion, decrease in mechanical strength with time, and infection. A nanodiamond coating on polypropylene results in increased strength without affecting the flexibility, thus preventing foreign body reactions and adhesion to the abdominal surface [76].

An organosilane nanoparticle coating used against food-borne pathogens like *Salmonella typhimurium*, *E. coli*, *Staph. aureus*, and *Yersinia enterocolitica* showed reduced bacterial adhesion of *Salmonella* and *E. coli* at 3 h after nanocoating glass surfaces in comparison with control ones.

Nanocoating of the implant with an organic molecule like proteins (collagen, fibronectin, laminin), polysaccharides (glycosaminoglycan), and peptide growth factors has been used to boost osteointegration. Polysaccharides stay longer on the surface and accordingly have a cell-attracting effect for a longer time. Polysaccharides showed improvement in the bone to implant contact and bone mineral density. A systemic review by Gurzawska et al. found that coating with polysaccharides and glycosaminoglycans improved the bone—implant interface and bone regeneration [77].

Chronic wound infection is associated with biofilm formation and antibiotic resistance. Nanoparticles are also used in the management of chronic wound infections by disrupting the biofilm, with immunomodulatory and regenerative effects, and by increasing growth factors [78]. Silver nanoparticles are used for the treatment of chronic wound infections, nonhealing ulcers, and burns. Zinc oxide, iron, gold, silica, magnesium oxide, nitric oxide, and copper are other inorganic nanoparticles used for wound healing.

Anterior cruciate ligament (ACL) reconstruction uses autograft and polyethylene terephthalate (PET) ligaments. There can be an issue with delayed healing between the reconstructed tendon and bone tunnel. To overcome this, PET is nanocoated with silicate-substituted strontium and bone marrow mesenchymal cells. Egawa et al. found that PET coated with silicate-substituted strontium results in new bone formation around the bone tunnel which can shorten the recovery time [79].

9. Future prospective

There has been increased use of technology in medicine starting from smartphone use for patient follow-up, to robotic knee and hip replacements, and different methods to tackle biofilm eradication. Nanocoatings are one of the promising technologies that are expanding rapidly. There is increasing use of nanotechnology in medicine, disease prevention, diagnosis, and treatment of disease, with nanocoating of implants like stents, heart valves, dental, orthopedic, and spine implants, and ligament reconstruction. Antibiotic nanocoating can be used in allogenic bone grafts to increase antibiotic elution and treat infections, and on implants to stimulate osteoblasts and healing of bone defects with nanocoated bone substitute. Stem cell nanocoating has a potential role in regenerative medicine starting from gene delivery systems, cell differentiation, tissue engineering, and cancer stem cell therapy. Stem cell nanocoating also has a role in neurodegenerative diseases like Alzheimer's disease, Huntington's disease, spinal muscular atrophy, and amyotrophic lateral sclerosis.

There is a great deal of scope for nanoparticles in cancer treatment starting from drug delivery, immunotherapy, photothermal ablation, and tumor imaging. Nanoparticles are currently used to increase the bioavailability and pharmacokinetics of chemotherapy drugs, especially in fibrous tissues. Genetically modified viruses to kill cancer cells (oncolytic virus) combined with chemotherapy and radiotherapy are a new advance in cancer treatment.

Nanocoatings are now frequently used in medicine but there is an opportunity for future research and improvement.

10. Conclusions

Nanotechnology is a promising field of science with potential applications across many fields of medicine. We have discussed how nanoparticles can either be friends or foes throughout this chapter. Although reports suggest that nanoparticles may be toxic, there is the possibility of developing new nanoparticles or nanocomposites that are safe and effective. As a potential tool for nanoparticle coating and targeted tumor therapy, nanoparticles play a crucial role, and enhancing drug efficacy is another potential application for nanomaterials. Nanoparticles affect inanimate objects effectively, even if their use in vivo remains debatable.

As nanoparticles become more widely used, the future will undoubtedly see their use increasing in many fields, hopefully for the benefit of humanity.

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CHAPTER 18

Antiviral and antimicrobial polymer-based biomedical device coatings

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1. Introduction

Medical devices such as catheters, prosthetics, surgical sutures, and various other devices have become increasingly popular in terms of use of surgeons and surgical implementation performance and enhancing patient quality of life. Although they have important roles in treatment strategies, they cause considerable amounts of serious nosocomial infections and even septic shock [1,2]. It is known that implant-associated infections are the most common and severe complications caused by biomaterials usage in medicine [3]. These biomedical device-associated infections are estimated as approximately 26% of healthcare-associated infections and one of the top 10 leading causes of death in the United States [4,5]. It is the main rule in the infection world, prevention is always better than the cure. Therefore, there is great demand for the development of prevention strategies for pathogen-related infections in order to protect patients [6].

Medical devices can be used to improve an organ's functionality or replace missing/surgically removed organs. Many medical devices are commonly used in the human body in several forms, such as catheters, tubes, fillers, implants, shunts, and stents, that can be implantable or non-implantable. The most commonly used biomedical devices are presented in Fig. 18.1 [7].

The design of a biomedical device requires control and consideration of many physical (including size, shape, mechanical properties, surface texture, and compartmentalization), chemical (adhesion, surface functionalization),

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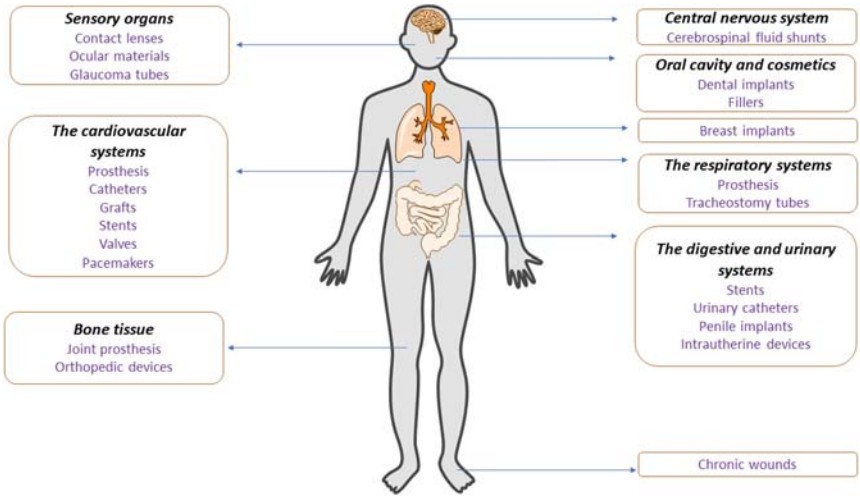

Figure 18.1 Commonly used biomedical devices (implants, shunts, catheters, etc).

and biological parameters (biocompatibility, toxicity) for the intended usage and location. To provide optimum conditions for the interaction of biological surrounds, various coating strategies may be used [8–10]. Medical devices can be categorized according to the device type, site of application, and timescale of use (Fig. 18.2). Coating materials and regulatory implications should be considered regarding these categories [11,12]. Coatings on biomedical devices can be performed with several techniques such as drop casting, dip-coating, cast-coating, doctor blading, spray-coating, spin coating, electrodeposition, plasma spray, sol–gel, micro-arc oxidation,

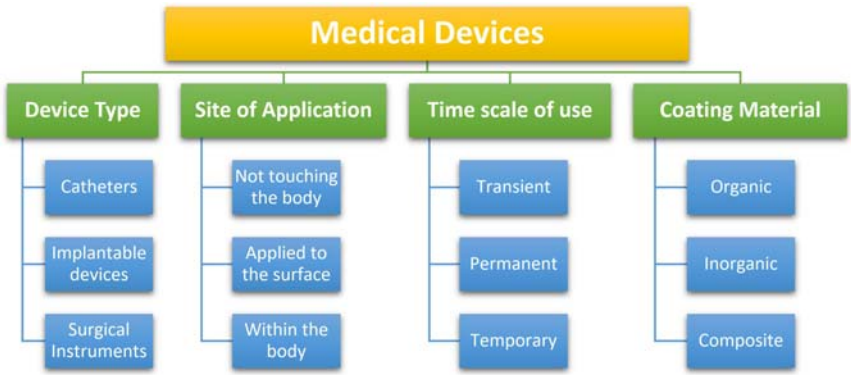

Figure 18.2 Medical devices categorization.

anodization, plasma electrolytic oxidation, magnetron sputtering, and pulsed laser deposition, etc. [13–15].

Polymers and inorganic materials are the most commonly used materials in medical coatings. They can be used as separate or composite ways to compensate for their limitations. Polymers are usually flexible materials for coating strategies but they may not have sufficient mechanical strength and chemical stability. They are chosen for their good functionalization but due to the nonhomogeneous molecular weight distribution they may not be the best option for some applications. These type of drawbacks are also valid for inorganic materials, which can have some advantageous properties such as antibacterial or antiviral effects, photothermal property, and increased biological activity or biocompatibility, but they generally exhibit weak adhesive strength on surfaces, film-forming ability, the tendency to aggregate, and sometimes cytotoxicity. It is very important to consider the application area of the designed coating to optimize the ratio and provide the best compatibility between the components in terms of comprehensive interactions between polymers and inorganic matter [16].

In this chapter, we focus mainly on the importance of antiviral and antimicrobial coatings, the most commonly used polymers for the surface coatings, and the most important examples provided in the literature. It is clear that antiviral and antimicrobial coatings are gaining importance for biomedical devices, masks, and other equipment, especially in the current pandemic circumstances. Therefore, this chapter emphasizes the current status of the coating strategies with regard to the COVID-19 pandemic and concludes with future remarks on this area.

2. Importance of antimicrobial and antiviral coatings

The medical device's surface is crucial to its use in the human body. Choosing the proper coating is the main step in the design process, because the best coating makes it possible to enhance the acceptance and function of the medical device. The coating layer has a role in decreasing the friction, irritation, and inflammation caused by the medical device that is integrated into the body [17].

Medical device coatings have functions in protecting medical devices from pathogens and microbial interactions as well as improving device maneuverability and performance. It is also crucial to mention the global market for medical devices coatings. According to an economical report on this issue, medical devices are predicted to reach an estimated value of

US$14 billion by 2026, with a CAGR of 5.8%. On a country basis, the market in the United States was estimated at US$4.2 billion in 2021 with an annual 39.94% share in the global market. China is predicted to reach a market size of US$1.4 billion in 2026 with a CAGR of 7.4%. Japan, Canada, and Germany follow the United States and China in the medical device coating market [18].

However, of course, they can be diversified and specified regarding specific applications. We briefly describe the main advantages and disadvantages of the coating strategies here in order to highlight their usage in biomedical devices [19,20].

Antimicrobial and antiviral coatings have important roles in the inhibition of biofilm production and preventing bacterial adhesion, killing bacteria by creating hydrophilic, bacteria-repelling, and charged surfaces, and releasing biocidal agents [21,22]. There are four essential properties that can change the persistence of pathogens on surfaces: (1) material form; (2) physical, abiotic factors (relative humidity, temperature, exposure to light, and type of surface); (3) biological, including the structure of the pathogen or the presence of other microorganisms; and (4) chemical (pH, presence of reactive ions, adsorption state, organic matter, or the presence of specific substances) [23,24]. Prevention and control of infectious diseases and their transmission are vital, especially in a pandemic situation. Surfaces have a significant role for human/animal pathogenic infections in terms of transmission by respiratory, fecal—oral, and sexual routes. The survival of these described pathogens on surfaces can be directly related to the surface properties and has implications for the clinical measurements, ER applications, preparing hygiene guidelines, and disinfection strategies [25,26].

Designers or engineers of these materials should bear in mind that the targeted application and desired environmental conditions directly affect the choice of materials. In order to create the best and highly effective coating materials, design and testing should be conducted in the following way [27]. Multidisciplinary and team working are crucial in the healthcare field.

3. Coating strategies of polymer-based devices

Various coating methods for polymer-based devices have been developed in recent years. The optimal technique is chosen according to the following parameters:

1. Substrate materials
2. Coating materials

3. Film accuracy requirement
4. Cost considerations.

Most of these coating methods require pretreatment of the substrate and deposition material, dissolving the deposition material in an appropriate solvent, achieving deposition through different coating methods, and then drying to form a film of specific thickness.

Drop coating is the simplest and fastest process, with low material consumption and no special environmental requirements. However, excessive polymer needs to be removed, and a thin film can form only a simple coating shape. Generally, only a specific volume of pretreated material needs to be dropped on the substrate and dried under natural conditions. Wu et al. dropped 5 μL multiwalled carbon nanotube (MIP-MWCNT) suspension onto the pretreated glass carbon electrode (GCE) surface, followed by infrared drying (Fig. 18.3A) [28]. Subsequently, a 5 μL tryptophan–chitosan (Trp-chitosan) mixture was applied on the surface, followed by solvent evaporation and repeatedly immersed in ethanol to remove the Trp template molecules. Finally, MIP-MWCNTs/GCE for Trp detection was formed. Laube et al. made a copolymer composed of vinyl benzyl dimethyl octyl ammonium chloride (VBCOQ) with metal adhesion mediating phosphonate (VBPOH), vinyl benzyl dimethyl

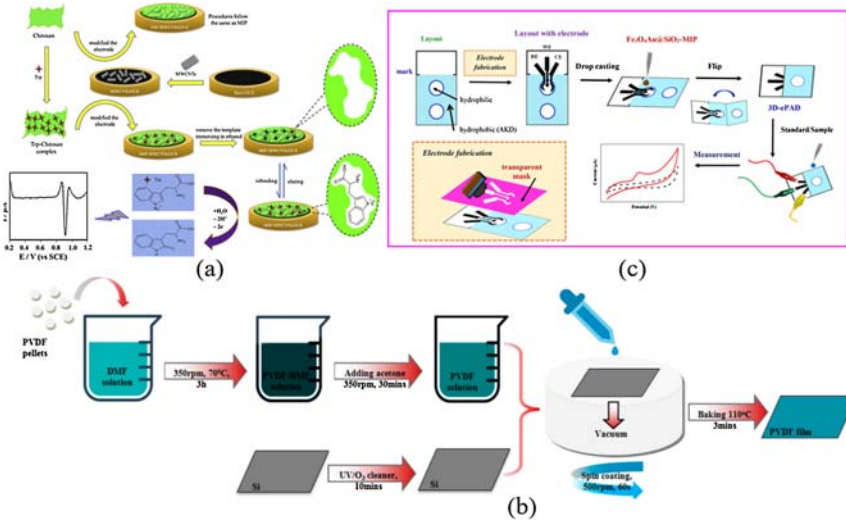

Figure 18.3 (A) The procedure for fabrication of the MIP-MWCNTs/GCE. (B) Scheme of the PVDF thin-film elaboration steps through spin coating. (C) Procedure for preparation of the Ser sensor and Ser detection using the 3D-ePAD by screen printing.

octadecyl ammonium chloride (VBCODQ) with VBPOH, and atom transfer radical polymerization (ATRP) with VBCOQ, then dissolved the copolymer in methanol/dichloromethane, pipetted 75 μL onto the Ti discs, and realized a film with thickness less than 10 nm after a drying and ultrasonic process [29]. Wang et al. dropped a solution of pendant poly(-ethylene oxide)-ureido-pyrimidinone (PEO-UPy) dissolved in anhydrous tetrahydrofuran (THF) with a concentration of 0.5 wt. % on lithium (Li) foil to form a LiPEO−UPy layer, with a thickness of 70 nm, serving as a sealed and dense protection layer on the surface of Li metal [30].

The spin coating method is fast and easy to operate, and the operating system is inexpensive. It is widely used to produce smooth and uniform polymer coatings of controlled thickness on flat substrates. The main operation is to prepare a polymer solution in advance, apply it on a stationary or low-speed rotating substrate, and control the spin coater speed and time. Shojaeiarani et al. injected a mixture of poly(lactic acid) (PLA) and dispersed cellulose nanocrystals (p-CNCs) solutions through a needle onto the center of rotating glass substrate loaded on the spin-coater machine [31] (Fig. 18.3B). The spinning speed was kept constant at 400 rpm for 180 s, and the films were dried simultaneously with a thickness of 1.12 mm. Nguyen et al. spread the poly(vinylidene fluoride) (PVDF) solution over the substrate at a low speed (500 rpm) and made a uniform film with the required thickness [32].

Screen printing uses the screen as the base and requires permeable meshes of specific shapes to transfer the ink to the substrate, controlling other penetration areas of the ink by blocking the template simultaneously to prepare the film. Brisset et al. mixed the synthesized polymer electroactive molecularly imprinted polymer (e-MIP) and corresponding non-imprinted polymer (e-NIP) microbeads with graphite in hydroxyethyl cellulose solution to produce e-MIP/e-NIP modified pastes [33]. Then it is printed on PVC substrate through a screen-printing system. Amatatongchai et al. fabricated graphite electrodes through screen printing using a graphite paste comprising graphite powder, carbon nanotubes (CNTs), and mineral oil mixed in specific ratios [34] (Fig. 18.3C).

Inkjet printing is also a standard printing method; the system is composed of a system controller, inkjet controller, nozzle, and substrate drive mechanism. Under the control of the inkjet controller, the ink is ejected from the nozzle and printed on the substrate. Deng et al. prepared a uniform emulsion consisting of polystyrene, hexadecane, and poly(vinyl alcohol) via microfluidic channels, transferred to the inkjet printhead [35]

(Fig. 18.4A). After shaking, picoliter drops of the emulsion from the printhead were ejected onto the modified glass substrate, followed by natural dry. Nasir et al. used FC-V-50 polymer in a mixture of ethanol and cyclohexanone doped with pyrromethene as ink for the fabrication of microdisk lasers on the modified fluorinated ethylene propylene (FEP) substrate [36].

Spray coating can provide thick films at high deposition rates over large areas (approximate thicknesses ranging from 20 microns to a few millimeters, depending on the process and feedstock). Coating materials are fed in powder or wire form, heated to a molten or semimolten state and produced in the form of micron-sized particles that are accelerated toward the substrate, and the accumulation makes the final coating of a large number of spray particles. Rezzoug et al. used wire zinc (Zn) metal as feedstock material and arc sprayed it onto the pretreated carbon fiber reinforced polymer (CFRP) composite plates to form continued zinc film, with a thickness of between 100 and 200 μm [37].

Electroplating on polymers is a vital coating technology. Based on electrolysis, the pretreated substrates to be plated are put into the coating metal compound's electroplating solution. Under the action of an external electric field, the electrode reacts to form a deposited metal layer on the substrate. Eßbach et al. prepared the solution for electroplating nickel (Ni) containing nickel sulfate, nickel chloride, and boric acid, then electroplated it on the acrylonitrile butadiene styrene (ABS) plastics with an applied voltage of 2 V for 10 min to form an Ni layer [38] (Fig. 18.4B).

In Table 18.1, the above-mentioned studies related with coating techniques for polymer-based devices are summarized according to techniques, substrates, coatings materials, thickness, and volumes.

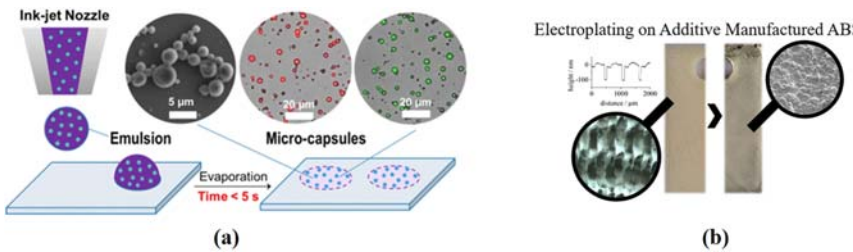

Figure 18.4 (A) Schematic diagram of the fabrication of polymer microcapsules by ink-jet printing. (B) Schematic diagram of electroplating on additive-manufactured ABS.

Table 18.1 Other coating techniques used in polymer-based device coating.

References	Technique	Substrate	Coating materials	Thickness	Volume
[28]	Drop coating	Glass carbon electrode	MWCNT suspension, Trp-chitosan	—	5 μL
[29]	Drop coating	Ti discs	Copolymer	<10 nm	75 μL
[30]	Drop coating	Li foil	PEO-UPy dissolved in THF	70 nm	
[31]	Spin coating	Glass	PLA mixed with dispersed p-CNCs	1.12 mm	
[32]	Spin coating	Glass, silicon, silicon coated with aluminum	PVDF solution	90 nm	
[33]	Screen printing	PVC	e-MIP/e-NIP		
[34]	Screen printing	Filter paper coated with alkyl ketene dimer (AKD)	Graphite powder, CNTs		
[35]	Ink-jet printing	Glass coated with HMDS	Polystyrene, hexadecane, poly(vinyl alcohol)		
[36]	Ink-jet printing	Fluorinated ethylene propylene substrate	FC-V-50 in a mixture of ethanol and cyclohexanone doped with pyrromethene polymer		
[37]	Spray coating	PTFE membranes	PVA/SPTA		42 μL
[38]	Spray coating	CFRP composite	Wire Zn	100–200 μm	
[39]	Electroplating	ABS plastics	Nickel sulfate, nickel chloride, and boric acid		

4. Polymer-based coated surfaces

In today's world, control of microbial infections is a critical issue. Increasing hygiene standards and the threat of infectious disease necessitate materials with surfaces that prevent germs from surviving and multiplying. Because the number of resistant microbial strains and antibiotic immune individuals grows more quickly than the number of useable antibiotics, treating microbial diseases is becoming increasingly challenging. Antimicrobial polymers have the potential to improve the efficacy of some existing antimicrobial agents while also reducing the environmental problems associated with conventional antimicrobial agents by lowering residual toxicity, increasing selectivity, and extending the antimicrobial agents' lifetime. Because bacteria or other microbes capable of producing serious transmitted diseases can easily colonize polymeric materials used in food packaging, textiles, and medical devices, the usage of synthetic polymers containing biocidal compounds has progressively expanded. Antimicrobials are gaining popularity in academia and industry due to their ability to improve the quality and safety of a variety of materials. Antimicrobial polymers are made by using an alkyl or acetyl linker to attach or introduce an active antimicrobial ingredient onto the polymer backbone [40].

The optimal antimicrobial polymer should be able to meet the following criteria:

(a) Biocidal against a wide range of harmful microorganisms
(b) Active for a long time (ideally permanently)
(c) Stable (doesn't break down into a harmful substance)
(d) Safe for the environment
(e) Simply and cheaply synthesized
(f) Can be regenerated after a period of inactivity
(g) For a variety of applications, it is not soluble in water [41].

5. Most commonly used polymers

Polymer coatings are becoming more popular in a variety of applications and markets. These polymer coatings provide substantial functions to their host materials, ranging from simple coatings to nanoparticle-included functionalized composite coatings. They can be used with a variety of materials, including metals, ceramics, polymers, and nanoparticles. Polymeric coatings could be crucial in the creation of next-generation biomaterials and devices in the biomedical industry. They can be employed for

corrosion resistance, surface functionalization, wear resistance, bioactivity improvement, and even as switchable smart materials. Smart polymer coatings are a relatively new development in the field of polymer coatings. The importance of polymer matrices in hybrid biomaterials has been established over the last several decades, owing to the wide range of options available, which include synthetic and natural biopolymers with a good combination of flexibility, biodegradability, adjustable mechanical properties, bioactivity, and low toxicity. Furthermore, "smart" polymeric hybrid materials can be created, with functionality gained through physical, chemical, or biological stimuli [10].

PVDF (polyvinylidene fluoride) is a polymer that has been extensively investigated and is frequently used in medical applications. It is a highly nonreactive thermoplastic fluoropolymer with improved biological, textile, and piezoelectric properties. Nonreactivity is required for surgical meshes and sutures, whereas piezoelectricity is required for wound-healing applications. As a result, this material is appropriate for a variety of biomedical applications, including tissue engineering, physiological signal detection, and the production of antibacterial and antifouling materials [42].

PMMA (polymethyl methacrylate) is a synthetic polymer that is lightweight, inexpensive, easy to handle, and includes nontoxic subunits, making it ideal for biomedical applications. PMMA is also the material of choice in dentistry for denture bases, orthodontic retainers, and repairs. It has good mechanical qualities, is slow to degrade, nontoxic, and inert. Its nonbiodegradable characteristic makes it ideal for creating long-lasting, mechanically stable structures, such as those utilized in bone tissue engineering. Poor adherence between these two components is one of the problems in coating organic compounds on metal surfaces. Polymers can be covalently attached to the substrate surface to provide an adhesive interlayer to remedy this [43].

Polyurethane (PU), despite its wide range of applications, is only used in a small percentage of synthetic polymers used in medical applications. PU coatings have numerous applications, including biomedical applications. They are generally utilized to make pacemaker lead coatings, breast implant coatings, and vascular devices in the medical profession. Because of its bioactivity, biodegradability, and adaptable physical and chemical forms, PU has recently received a great deal of attention. Its physical and mechanical properties are also comparable to those of natural tissues [44].

Due to its excellent properties, such as bioactivity, greater flexibility, ease of fabrication, oxygen permeability, optical transparency, and low

toxicity, polydimethylsiloxane (PDMS) is widely used in various biomedical tools such as surgical implants, catheters, contact lenses, pacemaker encapsulants, and biosensors, as well as drug delivery and DNA sequencing. It can also be utilized as an organ-on-a-chip substrate for studying stem cell activity. This material's properties make it a good option for examining cell activities like topography, stretching, and mechanical and electrical stimulations in order to develop materials for tissue engineering applications [45].

Aside from these polymers, biopolymers including poly(lactic acid) (PLA), poly(lactide-co-glycolic) acid (PLGA), polycaprolactone (PCL), polyethylene (PE), and natural polymers like collagen and chitosan are employed in biomedical applications. PLA is a biodegradable, hydrophobic aliphatic polyester utilized in medical devices, tissue engineering, medication delivery, and 3D-printed scaffolds, among other biomedical applications [10].

Polycaprolactone (PCL) is another biodegradable polyester that has impressive bioactivity, biodegradability, and flexible mechanical qualities. PCL can be utilized in the biomedical area for tissue engineering, medication delivery, and bone transplant material [46].

Natural polymers like chitosan and collagen have been employed as coatings to increase the biomaterials' functionality. Chitosan is a nontoxic material with excellent biocompatibility and biodegradability, making it a renewable, sustainable, and cost-effective product [47]. Collagen is a natural polymer that is the most abundant component of extracellular matrix [48]. Collagen coating improves bioactivity and the capacity of a biomaterial to build an interface between the host tissue and the implants, as expected. Collagen coatings have increased cell proliferation, differentiation, and adhesion, as well as new tissue creation, according to various studies [10].

6. Functionalization

Polymers are the most widely used compounds, with numerous advantages including lightweight materials, low cost, ease of production of various goods, and long durability. Modifications to the particles are required to improve the application and specificity of polymers [49].

Over the last several years, the utilization of polymers and nanomaterials in the industrial and biological sectors has skyrocketed. It is critical to recognize the targeted applications that require these platforms to be adjusted before any designation or selection of polymers and their nanocomposites. Surface functionalization is a critical step in improving the

physicochemical and biological properties of these materials by introducing the necessary type and quantity of reactive functional groups to target a cell or tissue in the human body [50]. Modifications can be applied in the carrier's bulk, such as adding metals to nanospheres to improve imaging and photocatalytic characteristics. The surfaces of the polymers are another important target for modification. For increasing polymer/polymer or polymer/ceramic adhesions, dry surface treatment techniques such as oxygen plasma, ultraviolet light-ozone, and cold atmospheric jet have been used. The wettability properties of polymers can be changed to control the adhesion of various coatings on polymer surfaces to make repairs [49].

For the functionalization of the antimicrobial polymers, before polymerization, antimicrobial compounds containing functional groups with high antibacterial activity, such as hydroxyl, carboxyl, or amino groups, are covalently linked to a range of polymerizable derivatives or monomers. Acrylic kinds of pharmaceutically active chemicals make up the majority of drug monomers and polymers produced. Acrylic-type drug conjugate monomers can be copolymerized to change the drug concentration and to create varied hydrophilic/hydrophobic functionalities in the polymer drug. Polymerization can either decrease or increase the active agent's antibacterial effectiveness. This is dependent on the monomer type and how the agent kills bacteria, either by decreasing the bacterial food supply or by disrupting the bacterial membrane [40].

There are three approaches to give a platform antibacterial action. The first is antimicrobial functionalization of polymers or nanomaterials, such as quaternary ammonium compounds [51,52]. Through a contact-killing action, these chemicals have been widely used to improve the antibacterial efficiency of diverse surfaces. Antimicrobial and disinfecting materials are typically made of quaternary ammonium compounds, especially those with long alkyl chains [53,54]. These chemicals have powerful antifungal and antiamoebic properties, as well as the capacity to encapsulate viruses. Surface modification of polysaccharides using quaternary ammonium compounds is another example that might be addressed in this connection. Polysaccharides are known as abundant renewable biosubstrates because of the accessible functional groups [55]. Encapsulation of antimicrobial medicines or biomolecules like antibiotics is the other method. The antibiotic is a powerful broad-spectrum antibiotic with excellent toxicity effectiveness against a wide range of Gram-positive and Gram-negative bacteria. Antibiotics such as gentamicin, cephalexin, amoxicillin, meticillin, and

vancomycin were also applied to various surfaces in order to offer active surfaces [50].

In the concept of polymer-based coating, the other method involves adding fillers to composites, such as metal-based nanomaterials or metal nanoparticles. Soon after its discovery as an excellent antibacterial agent, silver was utilized for wound healing. It can be utilized as a powder or even salt in its solid condition [56]. AgNPs' antimicrobial activities are divided into four steps: approaching the bacterial surface, disrupting the bacteria's cell wall and membrane by changing its permeability, inducing toxicity and oxidative stress by producing reactive oxygen species and free radicals, and modulating signal transduction pathways [57].

7. Applications of antimicrobial and antiviral surfaces

Antimicrobial and antiviral surfaces can be used in many areas in which these properties are important. When thinking about the term antimicrobial and antiviral effect, the first thing that comes to mind is generally the health sector. Of course, it is true especially in the on-going pandemic situation. However, these surfaces have also very significant practical applications for use in daily life. Examples of the implementation of antimicrobial and antiviral surfaces could be in crops, food, and agricultural industries, textiles, furniture, marine areas, public transport, and supplementations. These examples are illustrated in Fig. 18.5. These applications dictate the different properties of materials.

The importance and application of antibacterial and antiviral surfaces in order to prevent infection, especially in the COVID-19 situation, are discussed in the following section.

8. Current status with regard to COVID-19

Curtailing the ongoing infection and reinfection is an important aspect of bringing the COVID-19 pandemic to an end. To achieve this, prevention of viral shedding is important. Additionally, the duration of COVID-19 infection differs between a typical individual and one with associated comorbidities. Many portable and rapid sensor systems have been developed to overcome the gap in detection and viral transmission. Polymer-based sensors have been used previously and also developed for COVID-19-specific viral detection. Conductive polymers (CPs) are a class of polymers which have potential as nanowires, nanotubes, and

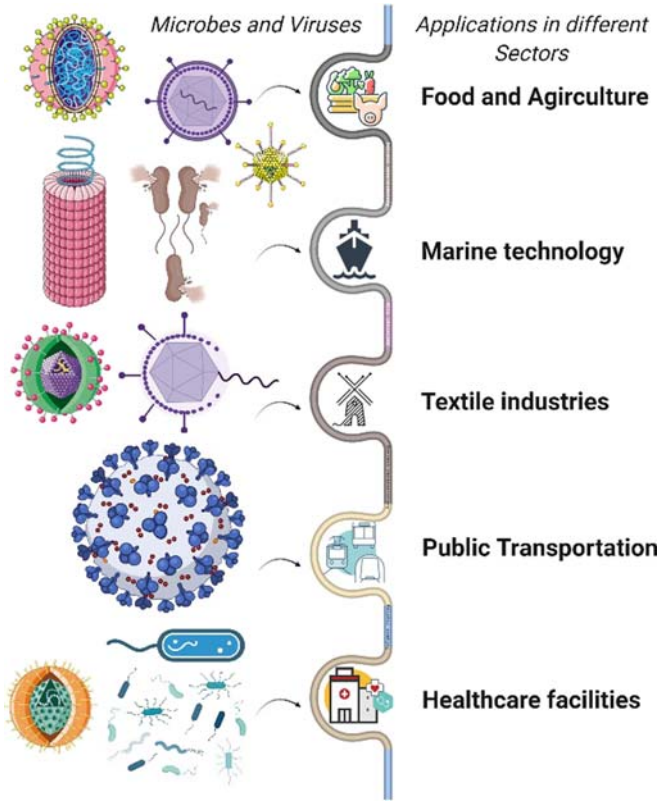

Figure 18.5 Applications of antiviral and antimicrobial coatings techniques applied in different sectors.

microspheres, with potency improved when employed as composites [58]. CPs have been extensively used as electrochemical biosensors for the detection of various biomarkers including nucleic acids, proteins, antigens, and whole viruses. Single polymeric nanowires using polypyrrole (Ppy) have been developed for label-free detection of viruses [59]. Electrochemically, Ppy is polymerized onto alumina template, followed by antigen-specific viral antibody immobilization on the nanowires by EDC-NHS coupling. Different viral pathogens were detected with target specificity, and exhibited comparable LOD to existing techniques [59]. A recent study developed conductive polymer-based vesicles functionalized with hemagglutinin-specific peptides for H1N1 virus. The study exploited polyaniline (PANI) as a response agent owing its resonance-based electro-optical properties. Low solubility of PANI was resolved by using

amphiphilic block copolymers, mPEG-b-pPhe, and CM-PEG-b-pPhe. The increased solubility along with peptide conjugation facilitates viral interaction and identification in a given sample. The peptide conjugated conducting polymeric vesicle (PCPV) agglomerates in recognition of target virus, stimulating a mechanical force. An optical response is generated due to $\pi-\pi$ interaction changes, enhancing rapid detection with high specificity [60]. Another methodology for polymer-based detection is by molecular imprinted polymers (MIPs). This is based on the design of synthetic receptors from monomers polymerized around a target molecule acting as template [61]. The polymer can be integrated with various sensor types. The earliest reported design of MIP sensor for SARS-CoV-2 used a gold conjugated thin-film electrode (Au-TFE) integrated as a disposable chip. The interaction of viral particles with MIP leads to a signal transduction through a potentiostat which is interpreted via software. The MIP film was generated using poly-m-phenylenediamine (PmPD) and nucleocapsid proteins of the SARS-CoV-2 envelope (ncovNP) as the template. The sensor exhibits specificity for ncovNP without reactivity for S1 protein [61]. Besides CPs and MIPs, polymers are also used as stabilizing platforms. Lateral flow assay (LFA) strips offer popular POC diagnostic devices. Such a system utilizes a stationary phase (cellulose/nitrocellulose) and a mobile phase (usually nanoparticles). A study has reported SARS-CoV-2-specific LFA, wherein glyco-AuNPs are stabilized using polymers. The AuNPs are conjugated via the polymer poly(N-hydroxyethyl acrylamide) (PHEA) to sialic acid residues which binds the SARS-CoV-2 spike glycoprotein. Specific amino acid residues bind the sialic acid, conferring a rapid detection method [62].

9. Conclusions

Remarkable progresses have been made in the formation of polymer-based coating devices for the improvement of unique mechanical and physical properties. On keen observation of the present chapter, it appears that although much work has been performed to fabricate efficient construction of polymer-based nanomaterial composites with good detection limits, high selectivity and sensitivity are still required especially for various pharmaceutical drugs, pesticides, and herbicides. It is important to understand the mechanism responsible for the interfacial interaction at the molecular level to further optimize the design of the interface. Therefore, active investments in this area are still required and would emerge help in fruitfully

developing sensitive and selective biosensing devices for multifunctional applications. The possibilities of different coating methods alone in combatting COVID-19 virus through its current uses of antimicrobial coating, nano-spray product, as personal protective equipment (PPE), air filters, and in textile products and drug delivery could become the future emerging solution alternative for better safety and precautions, as stated in the title of this chapter as a highly probable potential option.

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CHAPTER 19

Orthopedic applications of implant coatings

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1. Introduction

The biocontamination of medical devices and implants is a growing issue that causes medical complications and increased costs. In the fight against biocontamination, developing synthetic surfaces, which reduce the adhesion of microbes and provide biocidal activity or combinatory effects, has emerged as a major global strategy. Advances in nanotechnology and biological sciences have made it possible to design smart surfaces for decreasing infections. Nevertheless, the clinical performance of these surfaces is highly dependent on the choice of material.

The application of nanotechnology in medicine (i.e., nanomedicine) has been realized through the development of several sophisticated techniques for the prevention, diagnosis, and treatment of many diseases including cancer therapy, scaffolds for tissue engineering, medical imaging, drug delivery, and immunotherapy. Because of the capability to mimic or replicate the constituent organs of natural bone, nanomaterials are highly promising candidates for the construction of future orthopedic implants [1,2]. In orthopedic applications, the demand for bone substitutes is indispensable to cure irreversible damage of natural and healthy bone. Over the past few years, the impact of nanotechnology on the implant field has begun to increase significantly. Especially, nanomaterials with biological-inspired features are motivating researchers to explore their role in performance improvement of conventional implants. This chapters establishes a sound platform for the integration of nanotechnology-driven orthopedic implants into the human body.

In orthopedic applications, the aim of biomaterials is either to reestablish the structural integrity of injured bone or to replace it. There are major necessities to be considered in the design of each biomaterial, such as appropriate mechanical properties (e.g., specific weight and elastic modulus),

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biocompatibility, good bio-stability (resistance to corrosion, oxidation, and hydrolysis), osseo-integration (in the case of bone prosthetics), high wear resistance, high bio-inertness (nonirritant and nontoxic), and ease of surgical application [3,4]. Biomaterials have shown success in cell proliferation and tissue remodeling. Over time, significant research efforts have been made to devise and regulate biomaterial properties to obtain specific application-oriented biological responses [5]. For instance, it is possible to optimize the growth of muscle cells by modulating the stiffness of the cell substrate [6]. In a modern context, orthopedic biomaterials can be classified into two major categories: classical biomaterials and nanophase biomaterials.

2. Nanotechnology for orthopedic implants

Nanomaterials have been examined for bioimplant applications due to their tunable surface properties and bioactive nature. Nanomaterials offer increased surface area, effective stiffness, roughness, and altered physiochemical properties to enhance (1) adhesion, (2) proliferation, (3) synthesis of bone-related proteins, and (4) deposition of calcium-contained minerals [7]. Because nanomaterials can mimic the proportions of constituent components of biological bone, these materials are promising candidates in orthopedic implants. For example, nanostructured polymers and composites have been widely investigated in bone tissue engineering to enhance osteoblast functions, to promote osteointegration, and to support the healing of bone-related diseases [8]. The choice of nanostructures, such as quantum dots, nanotubes, nanocubes, nanoflowers, nanopillars, nanorods, metal-organic frameworks [9], etc. is significantly important to consider in order to ensure the functionality and reliability of implants. A number of studies have been carried out to explore the favorable surface properties of nanostructured materials that may promote or facilitate: (1) a large amount of specific protein interactions, (2) better osteoblast attachment, and (3) good osteoblast differentiation and migration for more efficient growth of new bone than conventional materials.

The nanostructured Ti6Al4V alloy exhibited better mechanical properties over conventional titanium including: (1) ultimate tensile strength of 1240 MPa over 700 MPa, (2) a yield stress of 1200 MPa over 530 MPa, and (3) elongation of 12% over 25% of pure titanium. Regardless of the material chemistry, the nanometer surface roughness exerted a great impact on osteoblast function; the surface roughness values of conventional titanium

and three nanostructured materials (i.e., Ti, Ti6Al4V, and CoCrMo alloy) were measured as 4.9, 11.9, 15.2, and 356.7 nm, respectively. The increased osteoblast functions have been confirmed by a wide range of nanostructured materials (e.g., Ti, Ti6Al4V, and CoCrMo) along with reduced functions of competitive cells [10]. Enhancement in osteoblast proliferation (determined after 5 days in terms of cells/square cm) was observed from all forms of the nanophase materials including alumina (~6000), titania (~8000), and HA (~9000) relative to conventional borosilicate glass (~5000) [11]. The carbonaceous materials have not been fully explored for orthopedic applications due to their safety doubts. Hence, only a few studies have explored the appropriate synthesis procedures for carbon nanotubes/nanofibers (CNTs/CNFs) for orthopedic prosthetic devices [12]. However, the structural and mechanical properties of CNTs make them promising for implants. Further, CNT-based composites are found to possess fewer toxic effects than asbestos. The incorporation of CNTs into polycaprolactone (PCL), polycarbonate-urethane (PCU), or polystyrene (PS) matrices has been proposed to enhance the mechanical properties (in terms of tensile and compressive moduli) of the composite scaffolds.

Due to the flexible nature of nanocomposites, it is possible to optimize their properties for specific applications. For instance, the tensile strength is different among different forms of PLA-HA nanocomposites, for example 770 ± 350 N/mm^2 for PLA, 840 ± 330 N/mm^2 for PLAHA (20 wt.%), and 1030 ± 390 N/mm^2 for PLA-HA (50 wt.%). Similarly, the porosity of these three forms was also clearly distinguished as $80 \pm 3\%$, $91 \pm 2\%$, and $70 \pm 4\%$, respectively.

3. Nanotechnology-derived surface modifications

Surface modification of structural materials is a potential way to improve the performance and durability as well as modulate the unsafe side effects that may occur in the degradation of bioimplants. Surface properties of the implants play a determinant part in biological interactions. In particular, the nanoengineered surfaces have the capacity to exert a direct impact on the molecular and cellular events; this property helps in determining the inclusive biological response for an implant (e.g., cell adhesion, protein adsorption, and proliferation). To this end, different strategies have been developed to engineer nanosurfaces for orthopedic implants, such as the electrochemical method (like anodic oxidation), electrochemical plating, plasma electrolytic oxidation, physical vapor deposition (PVD), chemical

conversion coating, laser surface alloying, thermal spraying, organic coating, and microwave-derived coatings. These techniques offer novel implant surfaces with controlled features at the nanometer scale. The specific technique can be selected depending on a number of parameters, such as (1) to achieve complex geometries and (2) to integrate in the industrial process line [13].

4. Surface nanostructuring

Nanocrystalline metallic surfaces have demonstrated success for improving the cell–substrate interface and healing bone. In recent years, growing attention has been paid to severe plastic deformation (SPD) [14,15] of bulk billets in comparison to other synthesis techniques such as high-energy ball milling, the gas-phase evaporation method, and physical/chemical deposition approaches. This is because the majority of these techniques result in low ductility, residual porosities, and other dimensional issues. On the other hand, the SPD technique is based on heavy straining under very highly imposed pressure. The main feature of the obtained nanostructures is their ultrafine grain characteristics along with enhanced mechanical strength and biological characteristics [16]. Plastic deformation can be easily achieved in metallic materials by twinning, phase transformation, or grain boundary sliding at low temperatures and relatively high strain rates.

A number of parameters (including the grain structure, surface roughness, wettability, and surface functional groups) play significant roles in mediating the cell activities at the cell–substrate interface [17]. Osteoblasts adhere specifically to grain boundaries of the nanophase materials; thus, by increasing the proportion of grain boundaries, cell adhesion to nanophase material can be improved significantly. The ultrafine grain nanostructures are efficient at promoting osteoblast differentiation and increasing bone integration by forming nano-defects, affecting surface energy, and other effects. The degree of wettability is directly correlated to the solid surface's ability to decrease the surface tension in the liquid phase (in contact with the implant material). (Note that the small contact angles [$\ll$90 degrees] of liquid to the interface correspond to a high degree of wettability [18].) Nanotopography is beneficial in provoking downregulatory effects on early conscription and activity of inflammatory cells, while enhancing the osteogenic activity and early woven bone formation [19].

5. Functional nanocoating

Surface coating can efficiently modify the surface-dominant properties (e.g., ion release or wear), resistance to corrosion, and biological properties, without compromising the properties of the bulk material [20]. The coatings applied to orthopedic implants help encourage the bioactivity so that the implants fuse with the bone and other tissues to ensure proper implant fixation and longevity. The dissolution of metal ions can be reduced with the help of suitable biocompatible inorganic coatings [21]. The coating can also increase the hardness of the implants and provide excellent surface finishing, while helping reduce the friction and wear rate of the implant.

As such, the selection of a particular coating technique may alter the surface roughness of the implant as well as the bone–implant interaction. Electrospray deposition of nanoparticles is particularly attractive for maintaining surface topography [22], whereas the dip-coated layer may moderate surface roughness to prohibit bone–implant interaction, ultimately delaying bone growth [23]. Many studies have assessed the potential use of carbon nanostructures as coatings for orthopedic implants [24]. For graphene-coated substrates (e.g., stainless steel, soda lime glass, and silicon wafers), cell adhesion was enhanced and osteoblasts were more uniform than the pristine substrate alone [25].

6. Microwave-derived surface modifications

Conventional thermal spray coatings contain defects like higher porosity, oxidation, inadequate adhesive strength, and degradation of the substrate materials, and microwave is an emerging surface modification technique that can meaningfully address these potential drawbacks [26]. In contrast to conventional thermal spray and CVD/PVD coatings, microwave-derived coatings are homogeneous in crystalline structure due to the absence of the lamella/columnar structure and the associated splat/grain boundaries [27].

Unlike thermal spray, the microwave technique (MWT) process is capable of producing dense and thick coatings with negligible porosity (<0.5%), while avoiding oxidation, phase transformations, and adverse residual stresses for a wide selection of metals, cements, and other material

mixtures [28]. The prime benefit of using MWT lies in the flexibility of depositing the coatings with a desired composition. The deposition of high-quality nanocomposite coatings by thermal spraying is extremely difficult due to the high porosity content and high proportion of unmelted particles present in the suspension for thermal spraying. Both the unmelted properties and porous nature of the particles cause an inhomogeneous coating (in terms of voids and cracks) over the implant surface [29]. In contrast, MWT can easily accommodate high-quality nanocomposite coatings [30]. This is due to the combination of the volumetric and conductive heating approaches used in MWT in contrast to conduction heating in thermal spraying.

7. Antibacterial surface treatment strategies

Although the success rate of orthopedic implants is generally high, there are several device-related issues that can compromise patient outcomes. The major causes of implant failure are: local tissue inflammation (5.3%), aseptic loosening (18%), and infection (20%) [31]. These issues are intimately related and originate from different sources. They can cause wear, impair the function of the bone—implant interface, and promote bacterial adhesion to the implant surface. Therefore, strong osseointegration and inhibition of infection are essential for a successful implant. The osseointegration of an implant can be improved with appropriate selection of nanophase biomaterials, as discussed in an earlier section. Beyond this, infection of an orthopedic prosthesis can cause a certain decrement in the success rate of an implant. Further, the use of bioimplants is projected to increase the number of related infections. For instance, the most common implant materials (i.e., titanium and its alloys) offer enhanced biocompatibility; however, imperfections can arise at the implant surface due to inhomogeneity of microstructures including impurities, grain boundaries, and second-phase particles. Under external loading, these imperfections led to the creation of weak sites for the expression of the immune system. Even bacteria with a low level of virulence could lead to catastrophic consequences [32]. Once bacteria adhere to the implant surface, they start to proliferate, leading to the formation of a biofilm. The biofilm plays a role in protecting the bacterial colony by offering resistance to antibiotics and other infection-defense mechanisms [33]. Thus, it is crucial to address pathogenic bacteria in their early stages to minimize biofilm formation. Infections lead to osteolysis, and there are several treatments to avoid osteolysis such as

immunomodulatory treatments [34] and antiinflammation treatments [35]. There are several strategies to prevent bacterial attachment on the implant surface or kill bacteria upon contact, as shown in Refs. [36,37]. Ultraviolet (UV) functionalization of Ti and Ti6Al4V implants enabled the recovery of osteoconductivity and bioactivity along with antimicrobial properties; however, the effect of UV treatment on the antimicrobial properties of Ti persists only for a short time; for instance, bacterial growth can be seen after 7 days of UV treatment [38]. A fast re-absorbable antibacterial-loaded hydrogel coating was effective at preventing the bacterial colonization and formation of a biofilm along with a retrievable efficiency of 80% on the implant surface after press-fit insertion [39]. Inzana et al. [40] demonstrated the local delivery of rifampin- and vancomycin-laden three-dimensional (3D) printed CaP scaffolds (implanted in a mouse model) to overcome bone infection. The 3D-printed CaP scaffolds offer regeneration of a bone defect, avoiding the revision of further surgery. However, the existing antibiotic treatments were suspected to be ineffective at eliminating infections entirely, creating another issue of an increased number of drug-resistant bacteria [41]. Some of these treatments are too fleeting and costly, and are highly susceptible to mechanical abrasion and delamination that ultimately lead to implant removal and debridement [42]. Advanced antiadhesive and antimicrobial coatings are also promising to prevent early-phase bacterial colonization and biofilm formation [43–45]. The nanomaterials can exhibit significant antimicrobial activities [46], e.g., Ag nanoparticles (cell membrane disruption, and electron transport), TiO_2 nanoparticles (cell membrane damage), chitosan (rupture of membrane, and increased permeability), CNTs (destruction of cell membrane, and oxidation of cell membrane lipids and proteins), and nanoemulsions (membrane disruption). The antimicrobial properties of nanomaterials are effective for their use as antibacterial and antifungal agents in surface coatings of implants [47,48]. Silver and its compounds are good alternatives to antibiotics due to their broad spectrum of antimicrobial activities against various microbes, e.g., antibiotic-resistant bacteria, yeasts, viruses, and fungal species [49]. Improvements in antibacterial coatings can be achieved by coating thin nanostructured films (e.g., chitosan-deposited Ag nanoparticles carried by Ti nanowires). The chitosan nanofilms help reduce the toxic effect of Ag-doped Ti nanowires to improve the antibacterial activity. The local delivery coating technique may provide protection to implants from infectious pathogens and promote faster bone healing. Yazici et al. [50] engineered in vitro chimeric peptides with biofunctionality

(e.g., antimicrobial properties) through a robust solid surface coating. Zhu et al. [51] described an atomic layer deposition of one-dimensional (1D) ZnO nanostructures on chitosan-modified CNTs; after that, modified CNTs were coated onto the implant substrate. This hybrid coating endowed the implants with high self-antibacterial efficacy against *Staphylococcus aureus* (*S. aureus*) by 98% and *Escherichia coli* (*E. coli*) by 73%. Li et al. [52] developed an N-halamine-immobilized silica-coated polystyrene-acrylic acid (PSA)-ZnO nanoparticle coating on Ti implants with promising self-antibacterial activity (without antibiotics: e.g., against *Pseudomonas aeruginosa* (*P. aeruginosa*), *E. coli*, and *S. aureus*). Silver-based coatings on titanium and Ti6Al4V have in vitro antimicrobial efficacy against *E. coli*, *P. aeruginosa*, *S. aureus*, and *Staphylococcus epidermidis* (*S. epidermidis*) with well-maintained biocompatibility [53]. Silver cations bind to the negatively charged membrane, leading to its perforation and leakage of cellular compounds, ultimately resulting in cell death. Silver ions also bind with phosphoryl and sulfhydryl groups of proteins; these bindings cause aggregations of different groups of protein while reducing their activity to almost inactive. Further, DNA molecules also get condensed and lose their replication abilities due to the denaturation effects of silver ions. The complicated production and diffusion of silver ions make the device less efficacious. However, it is possible to passively diffuse the silver ions from the implant surface to the surrounding biological environment. The antibacterial mechanism of silver nanoparticle-coated Ti can be improved by plasma immersion ion implantation through the generation of reactive oxygen species that can burst both bacteria cells and the culture medium [54]. Thereby, reactive oxygen species lead to bacteria death through intracellular oxidation, variation in membrane potential, and release of cellular contents. Others have focused on developing nanotechnology that can be built directly on the implant surface using battery-activated devices [55]. The idea behind the use of battery-activated devices is to improve the antimicrobial efficacy of silver coatings by electrically activating the microscopic germ killers. Antibiotic-resistant bacteria such as meticillin-resistant *Staphylococcus epidermidis* (MRSE) and meticillin-resistant *Staphylococcus aureus* (MRSA) are of particular concern. Spadaro et al. [56] demonstrated in vitro antimicrobial efficacy of silver ions that are generated with the application of low-intensity direct current (LIDC) in the range of 0.02−20 μ A. The LIDC-generated silver ions have 10−100 times lower inhibitory and antimicrobial concentrations than those of silver sulfadiazine. The antimicrobial efficacy of silver has been evaluated in vitro and in vivo

for use in orthopedic implants [57]. Tan et al. [58] demonstrated the in vitro antibacterial efficacy and cytotoxicity of LIDC-activated silver/titanium implant. The implants without LIDC activation were not able to suppress the bacterial growth. In contrast, in the case of LIDC activation (6 μA), the bacterial concentration was lower than that without activation; the bacterial concentration was lower by two orders of magnitude after 24 h and by one order of magnitude after 48 h. The current intensity and the anode surface area are the most dominant system parameters that impact the antimicrobial efficacy as well as the formation of anodic oxide films. The chitosan−Ag/HA composite coating was fabricated over the titanium substrate through electrochemical deposition [59]. The coating exhibited excellent antibacterial activity due to the synergistic effect of chitosan and silver with a nontoxic nature to MC3T3-E1 cells. Sathishkumar et al. [60] fabricated a samarium/gadolinium-substituted HA coating on borate-passivated AISI 316 L stainless steel through electrodeposition techniques to yield a uniformly covered granular texture with good anticorrosion ability. The samarium/gadolinium-substituted HA coating also exhibited antibacterial activity while promoting cell viability and proliferation of MC3T3-E1 cells.

8. New trends in orthopedic biomaterials

The development of stimulus-responsive biomaterials along with easy-to-tailor properties is the most vital aim of the research into tissue engineering and orthopedic implant applications. In recent years, significant progress has been reported with new trends such as engineered biomaterials from natural sources [61], porous structures, smart biomaterials, and 3D implants. The ideas for new biomaterials have been driven by blending synthetic polymers with natural polymers as well as combining the properties of the different forms of polymers such as natural polymers with high biocompatibility (e.g., silk, elastin, chitosan, collagen, and keratin) and synthetic polymers with good mechanical properties (e.g., polyethylene, polyester, epoxy, and teflon). These biomaterials can be designed to efficiently mimic living tissues for tissue engineering, cell-based transplantation, and gene therapy. Along with the introduction of new natural biomaterials, remarkable progress in fabrication technologies has empowered a new generation of intelligent nanomaterials such as nanoporous anodized alumina (NAA) [62]. Nanopores are highly attractive due to (1) a large surface area to promote high surface loading and (2) nano-confined volumes to modulate protein dissolution rates. The large surface area of nanopores should efficiently

facilitate the linking of bio-active molecules to implants, avoiding the role of intermediate linkers such as oxylanes and phosphonates. The nanopores have a great impact on protein adsorption and cell adhesion and also promote their usage as bioactive coatings on diverse biomaterial substrates. Porous metals with structures feasible for orthopedic applications have been reported to replace damaged bones with ones having similar properties to bone.

9. Smart orthopedic biomaterials

The development of smart biomaterials has been the focus of intensive research interest. Here the term "smart" corresponds to the nature of the interactions between a biomaterial and its surrounding biological environment (including cells and tissues). The smart biomaterials differ from traditional biomaterials in terms of their instructive/inductive (or triggering/stimulating) effects on the surrounding cells and tissues.

Besides making direct contact with the host, the incorporation of nanomaterials (including ceramic nanoparticles, clay-based platelets, CNTs, and graphene) within hydrogels can generate multifunctional scaffolds that exhibit compatibility with electroactive and load-bearing tissues [63]. However, there is a need for further improvements in matrix-directed regulation of the cell function to resolve the cellular interaction with the biomaterials and their own matrices.

10. 3D orthopedic implants

3D implants are one of the most promising future trends over monolithic structures to acquire target material properties in desired structures. Recent advances in 3D bioprinting techniques make it possible to generate complex organs (involving bone, skin, cartilage, and vascular tissues) and scaffolds for stem cell differentiation with successful in situ transplantation of cartilage tissues in humans. Presently, 3D printable nanocomposite-based orthopedic implants include 3D-printed porous titanium implant, 3D-interconnected macroporous TCP with good compressive qualities, 3D-printed bioactive glass–ceramic (strontium-doped hardystonite-gahnite) with high fatigue resistance and 150 times greater compressive strength than those reported for polymeric and composite scaffolds, which is a good choice for load-bearing bone applications, and 3D alginate-PVA-HA hydrogel and 3D-printed porous scaffolds based on a

hydroxyl-functionalized polyester (PHMGCL) with enhanced hydrophilicity, improved cell—material interaction, and increased biodegradation rate as compared to poly(caprolactone).

11. Challenges

Before commercialization of any new innovation in the biomedical field, there is a need to keep in mind their effects from a value-aware point of view. These effects can be classified into: (1) the impact on treatment quality in comparison to the preexisting treatment options, e.g., reduction of morbidity, increase in implant life, and pain relief; (2) the effect on value of treatment (relating to quality of treatment); and (3) the effect on treatment costs in relation to already existing treatment options [64]. In the market, there are several companies that are particularly involved in the development and commercialization of nanomaterials for bioimplant applications such as tissue engineering and orthopedics [65]. There are several issues that hinder the market growth of bioimplants, e.g., high cost and lack of favorable reimbursements. Nanostructures have unique physical, chemical, and biological properties that modify the functionality and reliability of implants. However, the challenge is how to properly mimic living bone tissue. There are three key parameters that significantly contribute to the development of improved orthopedic implants: surface topography (i.e., nanoscale surface structuring for better optimization of osteoblast functions), surface chemistry (to control chemical surface properties of bioimplants), and wettability (i.e., better cell adhesion on hydrophilic surfaces) [66]. The major challenge for coating techniques is to produce coatings with dissolving capabilities at a similar rate in comparison to bone apposition, which would help in obtaining direct bone contact on the implant nanosurface. Beyond these limitations, detailed case studies are required for nanomaterial-based orthopedic implants. Overall, significant research has elucidated the importance of nanophase materials for implant applications to improve the bonding of the implant with its surrounding bones [67]. The effects of exposure of engineered nanomaterials to air and water remains unclear. Upon exposure to a nanomaterial-contaminated environment, their impact on humans and animals needs to be accurately assessed for any negative consequences. In order to determine the potential health risks of nanomaterial-based bioimplants, considerable attention must be paid during the production, implantation, and wear patterns of these implants before approval for clinical use.

12. Conclusions and future perspectives

Nanotechnology is advantageous in controlling the topography and chemistry of bioimplant surfaces that would help (1) understand the biological interactions and (2) develop novel implant nanosurfaces with predictable tissue- or organ-interactive properties. The nanophase biomaterials can offer favorable properties to osteoblast functions, regeneration of tissues, and bone ingrowth, which promotes their role in orthopedic implants. The nanomaterials in implants can be utilized in different ways either through nanostructured surfaces or functional nanocoatings over the implant surface. The future of nanophase biomaterials relies on the development of enhanced design methodologies that are capable of combining the benefits of nanomaterials and advanced fabrication technologies. Undoubtedly, nanomaterials are driving the future of orthopedics through resolving several unanswered questions in terms of enhanced osteointegration and effective healing of bone defects with bioactive scaffolds, however, before clinical/commercial use of nanotechnology-driven orthopedic implants, it is significantly important to examine the potential health risks of cell nanophase biomaterial interactions. Overall, in the realm of medicine, nanotechnology holds great promise for providing exciting orthopedic implants to society in the near future.

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SECTION 7

Functionalized nanoparticles-based antimicrobial coatings: Safety, risk and sustainability

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CHAPTER 20

Nanoparticle cytotoxicity: From beneficial uses to carcinogenic effects

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1. Introduction

1.1 Nanocomponents: from potential applications to toxigenic behavior

The rise in microbial drug resistance poses a serious threat to the worldwide population health and well-being, with a significant increase in mortality rates leading to prolonged treatment, as well as an increase in medical expenses, mortality risk, and a reduction in life expectancy. To combat the spread of bacteria, better science-based antimicrobial agents must be developed. These formulations must be able to traverse biological barriers, elude the immune system, and effectively target injured or diseased cells to be successful. The acknowledgment that nanoparticles are indispensable in a wide range of industrial and biomedical processes, including flexible and transparent electronics, biomolecular electronics, optics, consumer products, alternative energy, and soil and water remediation, or for medicinal uses as therapeutic and diagnostic devices, has fueled rapid growth in nanoscience research over the last decade. A broad range of nano-applications have been recorded in industries, the agricultural sector, environmental areas, pharmaceutics, chemistry, medicine, etc. [1]. Despite having lots of advantages related to this field, studies/evidence in the literature focus on the special physicochemical properties. Increasing evidence suggests that the special nano physicochemical properties pose great risks to human. Therefore, studies should be targeted to identify potential toxicity factors related to cells, tissues, and organisms that these

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nanomaterials potentially pose to human health [2]. Therefore, considerable effort has been placed to identifying the potential toxicity and toxigenic behavior of nanoparticles to cells and organisms. In addition, many examples such as the utilization of coal and silicates (mineral dust particles), experimentation related to asbestos and carbon black nanoparticles inducing oxidative failure/injury, increased risk of cytotoxicity and inflammation, fibrosis, active release of some proactive inflammatory initiators/mediators have been identified [1,3–5]. Oxidative stress develops in cells and live tissues as a result of an imbalance between the production and accumulation of oxygen reactive species (ROS).

ROS are metabolic by-products of biological systems that are produced by mitochondria under both pathological and normal settings.

They are also known as free radicals, because they combat pathogens, are essential for cell communication, and help create different cellular structures and proteins at low or moderate quantities. However, at high amounts, oxidative stress (OS) occurs in which ROS inhibit the capacity of living cells and organs to detoxify; regrettably, this can cause serious damage to proteins, lipids, and nucleic acids and result in cell death and the onset of diseases like cancer. Physical and chemical features of related NPs have an impact on the ability of NPs to enter particular organs through particular pathways and their propensity to accumulate in cell organelles or be transferred to other organelles. Additionally, as they can alter the mechanism of the toxicological response as well as the accumulation, absorption, and translocation of NPs, their physicochemical characteristics have a significant impact on their toxicity. For instance, the same substance can significantly alter the reaction of live tissue and reveal whether NPs will have a safe or hazardous fate. Morphological characteristics including size, shape, roughness, and surface area, homogeneity of agglomerates, and the chemical composition of nanomaterials are significant physicochemical factors connected to the cytotoxicity of nanomaterials. Similarly, many animal studies have proved that by the exposure of these nanomaterials/nanoparticles a continuous disturbance pattern has been observed in breathing (oxidative stress) and inflammation in the lungs (pulmonary disturbances), etc. [6–8]. Various literature reports have also highlighted the gradual increase in ROS (Fig. 20.1) in cells that were exposed to nanotreatments [10–13]. Furthermore, some reports have raised concerns about using TiO_2, like lipid peroxidation, activation of caspase leading to cell death, damage to DNA, damage to plasma membrane, and deterioration in the functioning of mitochondria [14–23]. Similarly, nanoparticles

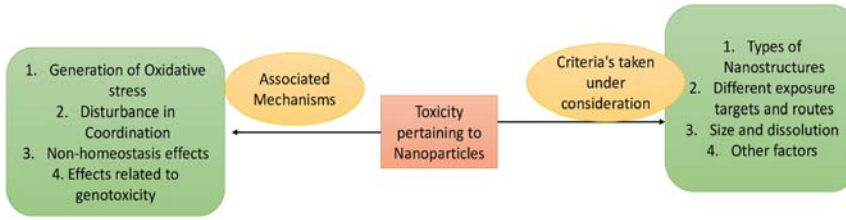

Figure 20.1 Mechanism linked with factors; an illustration highlighting a sneak peek through various toxic parameters linked to the shape, size, and chemical structure of nanoparticles [9]. Because the toxicity phenomenon is a very complex issue that depends on a wide range of physicochemical factors, distinct metallic NPs with their unique properties exhibit different toxicity processes and suggest changes in the toxicity level.

coated with silicon oxide (SiO_2) activate micronuclei formation and cell deuteriation process by activating caspase and finally leading to early cell death or apoptosis [24–26]. Though different studies showcased different reasons related to nanoparticle toxicity, one study observed that the initiating factor was lysosomal dislocation [25], whereas other studies concluded that deuteriation of membrane integrity of mitochondria was the initiating/predominant factor leading to cell death [24,26–28], while some pointed to the nontoxic behavior of nanotubes [29]. The variation reported by different studies indicates that different variables are employed to study the toxigenic effects of nanocomponents as different cell types will be responding differently to nanocomponents varying with protein adsorption process, agglomeration/dispersion recorded in the particles, experimental procedure, different in vivo models, and varying cell types, respectively [27,30–32]. Keeping in view the hazardous nature of nanoparticles and their wide application in environment and medical fields we need to access proper mechanisms and responses so that the obtained information can be used to enable the synthesis of stable, safe, and efficient nanoparticles [33–36].

It is well known that cytotoxicity typically rises with elemental atomic number, probably as a result of band-gap energy. Additionally, it has been demonstrated that certain substances trigger particular toxicity processes. Therefore, it is important to study the mechanisms of nanotoxicology involved in the effects of common metallic and metal oxide nanoparticles, such as Ti, Ag, Au, Zn, and Cu, on biological environments.

The need of the hour is to address the adverse and detrimental results and effects of nanomaterials on human health. They differ in size and shape

and have greater stability in hostile human environments as compared to their larger counterparts. Further, they can be ingested, inhaled, or can penetrate through open pores/cuts in the skin. Therefore, interest has been shifted from basic nanotechnology to a different science "Nanotoxicology" deals with nanotoxicity and its detrimental impacts on human health and the environment. The purpose of this chapter is to focus on the toxicity information present in the literature on nanomaterials while considering the variability and diversity of toxigenic and hazardous areas that may pose greater risks to human health [37]. Fortunately, high-quality toxicological results have been accumulating as a result of improvements in analytical techniques and study methodologies. The risk evaluation and management of produced nanomaterials require integrated efforts from the industrial communities and regulatory bodies in addition to the fundamental nanotoxicological research contributed by scientific communities. It is necessary to gain a thorough understanding of the underlying toxicological knowledge of nanomaterials in order to accomplish these goals. Nanotoxicological studies primarily concentrate on the toxicokinetics [absorption, distribution, metabolism, excretion; ADME)], cellular uptake and trafficking, toxicity, and underlying mechanisms of nanomaterials in order to better understand how nanomaterials interact with organisms at the organ/tissue, cellular, and molecular levels. To ensure the accurate safety assessment and appropriate regulation of nanomaterial production, usage, and deposition, nanotoxicology examines the harmful effects of nanomaterials or nanoproducts on living things throughout their lifecycle [3]. It is necessary to gain a thorough understanding of the underlying toxicological knowledge of nanomaterials in order to accomplish these goals.

1.2 Associated mechanism and interaction patterns of nanocomponents

The mechanism defining the interaction patterns of nanomaterials with cellular organelles remains unexplained clearly. However, oxidative stress is regarded as the most important initiator and factor/mechanism contributing to cytotoxicity via a broad range of nanomaterials/chemicals. Oxidative stress introduces a pathway of cellular stress by damaging the mitochondrial membrane, leading to a cascade of mitochondrial deuteriation/degradation and dysfunction. This leads to injury of the affected cell and finally cell death. Nanoparticles accessing the advantage of their small size and specific chemical composition can easily localize into mitochondrial spaces, leading to enhanced oxidative stress and cell damage [38–41]. Literature reports on

various aspects of this have been documented, for example a study traced a dose-dependent decrease in viability of cells, leading to an increase in reactive oxygen species and GSH reduction. This was also correlated with an increase in oxidative stress. However, some reports indicate the absence of oxidative stress and showed inflammatory actions and the role of inflammatory mediators (cytokines) which were linked to the mechanism of toxicity. Therefore, limited reports have concluded that inflammation and oxidative stress play important roles in provoking the toxicity of nanoparticles. However, the exact molecular mechanism is lacking to provide deeper insights into the process (Fig. 20.2).

1.3 Characterization and channelization of nanomaterials

The characterization process should be properly channelized for the critical toxic evaluation as it is the most important component relating to toxicity [10,24–26], as the quality of nanomaterials depends on the dispersion medium, method of preparation, and solubilization [42]. Therefore, toxicity testing of nanomaterials requires stable dispersion media with accuracy in particle size and distribution, as this will ultimately affect the biological activity. Further, the dispersion state examines the extent of the agglomeration process which is a measure directly linked to particle size, shape, proximity percentage, surface area, and chemistry [43]. In addition, the biological and physiological media utilized in studies related to toxicity

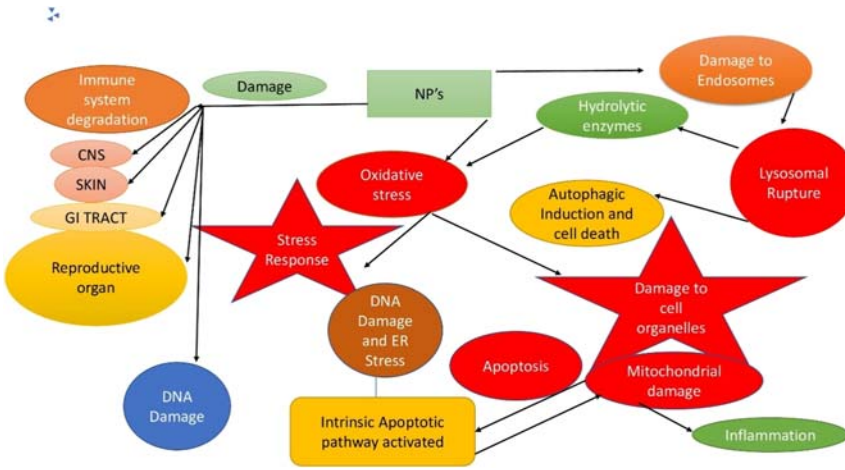

Figure 20.2 Nanomaterial-induced toxicity: mechanism highlighting various toxic processes [41].

may affect the state of dispersion, which makes it essential to measure the particle size as both "as dosed" and "as received" beforehand [27,44]. Protein corona can also significantly impact the toxicological profile of nanomaterials as it is directly related to cellular uptake mechanisms. There is currently a lack of optimized protocols related to the characterization process, invalid toxic data profiling, no well-defined battery of tests, and inaccurate parameter analysis [10,24,26], therefore valid time-dependent and dose-dependent evaluation criteria are needed. More research is needed to define the effects of shape and size and finally on the agglomeration process to provide an accurate picture of the toxic activities through electron microscopy. The techniques presently used (ultra-high illumination light microscopy and disc sedimentation) are limited by the drawbacks associated with the measurement sizes. A differentiation biotransformation pattern can be drawn between in vitro and in vivo analyses, where the biotransformation related to chemicals is reported in lower quantity in in-vitro analysis as compared to in vivo studies due to the limited metabolic activity. All the listed reasons point toward designing validated, predictive, and mechanism-based protocols/assays to evaluate accurately the toxicity of nanomaterials/nanocomponents that causes detrimental effects on human health.

2. A toxic assessment complex: rapid need for assessing the toxicity patterns of nanomaterials

The design criteria in terms of synthesizing a nanocomponent/nanomaterial related to size, shape, composition, surface area, dispersion, surface variability and chemistry, reactivity, and specificity contribute to the toxicity aspects by creating a "toxic assessment complex" [18,19]. However, the currently utilized parameters and validated test series may not provide suitable safety evaluation criteria, and also there is a lack of validated methodologies/protocols or internationally accepted tests related to toxicity or safety concerns (Table 20.1). In this regard the National Center for Toxicological Research is searching for positive solutions to toxicity testing, but the evaluation criteria require the proper establishment of standard protocols, both for the reference material and dispersion phase, respectively. Further, a stringent toxicological testing strategy should be devised by taking into account the novel biomarkers and more validated tests which can easily provide a deeper insight into the toxic impacts on biological

Table 20.1 The characterization, exposure journey, in vivo observation, and accumulation and toxic effects of nanoparticles.

Nanoparticles	Characterization of nanoparticles	The exposure journey	Utilization of animal models	In vivo observations	Accumulation and toxic effects
Nanoparticles pertaining to different sizes, configurations, and finally toxic/lethal effects on major organs					
1. Carbon black	Around 14 nm with 300–350 m^3/g	Inoculating single dose of 0.16 mg, analysis to be done at 28–29th day	Mice	Inflammation and infection of pulmonary tract initiated by granulomatous formation	Heavy accumulation in lungs, kidneys, brain, and spleen
2. Graphene nanoplatelets	Around 5 micrometers analyzed by SEM, 150 m^3/g	50 μg/mouse for 1 and 7 days	Mice	Lung inflammation	
3. Silver	250 nm	100–150 μg/kg for 1–28 days	Mice	Pulmonary inflammation and granuloma formation	
4. FeO	30–35 nm, 45 m^3/g	0.5 mg/mouse	Mice	Pulmonary inflammation and granuloma formation	
5. TiO_2	10–60 nm	Dorsal skin exposure, about 60–65 days	Hairless mice	Inflammation in essential organs	Accumulation in brain, kidney, stomach, and Muscles

systems, as antibacterial agents, including silver nanoparticles (AgNPs), are being used increasingly in consumer goods [105].

Because of inadequate data on the toxicology of AgNPs and their rate of release into the environment, regulatory control over the use or disposal of such products is missing. The increased use of products enhanced with AgNPs may result in an increase in the toxic levels of silver in the environment. Ag-enhanced products with antibacterial properties are being commercialized at an accelerated rate. AgNPs are the subject of an increasing number of toxicological investigations, however the majority of these are carried out in vitro on cell cultures, with lower-order life forms, or with embryos.

AgNP toxicological evaluations on higher-order species remain far behind schedule and may be constrained by the lack of suitable methods for in vivo characterization and evaluation. Additionally, there is still a lack of knowledge regarding how AgNPs are transported from consumer-related activities via the environment, necessitating further research. While AgNPs pose certain difficulties for conventional toxicological assays, they also possess special properties that allow for completely new methods to investigate their toxicological effects on cells and organisms.

These include the use of self-referencing microsensors for real-time physiological monitoring as well as cutting-edge imaging techniques that make use of AgNPs' potent plasmon resonances to track objects without the usage of labels. These recently created techniques are simple to include in experimental plans that will improve accuracy for AgNP risk assessment.

2.1 A rapid screening methodology for checking the toxicity of nanomaterials: in vitro and in vivo complexes

The assays corresponding to the in vitro analysis provide a rapid, cheaper, and cost-effective mode of screening methods for toxicological studies and also for the characterization process of nanomaterials in comparison to the more time-consuming and costly in vivo methods. The utilization of human cell culture lines or systems illustrates the potential to eliminate interspecies extrapolation and a need to increase specificity and effectiveness in testing while eliminating the need for animal models [29,30]. However, the uniqueness in terms of chemical and physical properties of nanomaterials drive the purpose for high-throughput standardized and validated in vitro testing process to accurately report the potential toxicity. Also, the effect—exposure relationship can be recorded in in vitro analysis for their toxicological and pharmacological properties if the tests are properly and

accurately validated [43]. Nanomaterials procured from various sources can produce variable results in different animal models, for example zebra fish and mouse lung have been used for toxicity testing [45]. In vivo studies have demonstrated oxidative damage, detoxicating DNA, and suppression when exposed to silver nanoparticles. It was observed that in vivo models such as mice experienced gastrointestinal distortions and disturbances when they were exposed orally to gold nanocomponents and also a rapid translocation of these nanocomponents was visualized by blood affecting other essential organs such as the lungs, liver, spleen, kidney, and brain, etc. [39]. Further, these nanocomponents can excessively accumulate in the liver following inhalation or intravenous exposures [38,39].

2.2 The accumulation and metabolism process to observe the molecular mechanism and interaction of nanocomponents with cells: from cytotoxicity to genotoxicity

The accumulation of nanocomponents can lead to various disorders affecting the organ systems in the body, and so a deep insight is needed to understand the mechanisms of its accumulation [41]. The reports of in vivo testing in mice indicate an excessive accumulation in the liver and spleen when doses are administered orally due to which nanoparticles are retained and trapped, leading to serious tissue injuries. Similar reports have been recorded on the metabolic pathways of nanocomponents where they enter into blood vessels or organs due to their extremely small size. In vivo studies also suggest that the major sites for the distribution of nanoparticles are the spleen, kidney, and liver, although there is no evidence to illustrate their clearance patterns in vivo [39–41,46]. It is very important to assess the cytotoxic process of nanoparticles in order to successfully interpret their associated biological activity [104]. The quality associated with the particular selection of nanoparticle dispersion depends on the utilized suspension medium, which further affects the cytotoxicity potential. Therefore, its characterization, cell viability, and accurate preparation are mandatory for cytotoxicity analysis [40]. Various studies have recorded the TiO_2 and SiO_2 nanoparticle cytotoxicity in three cell lines (3T3 fibroblasts, macrophages, RAW 264.7, and telomerase epithelial cells) [46–48]. These experiments tested the potential of cells exposed to different nanomaterials differing in shape and size after characterizing the said properties in serum containing PBS and culture media. They concluded that the target cell type, composition, and size of the nanomaterial are the critical determinants of cytotoxicity levels, responses generated intracellularly, and mechanisms

related to toxicity. Some reports also reported that out of SiO_2, TiO_2, MgO, and ZnO noncompounds tested on human Caco-2 cells, MgO was found to be safer in comparison to the other nanocomponents [47]. A study also investigated the lethal effects/impacts of SiO_2 nanoparticles on Balb/3T3 mouse fibroblasts, showing no sign of cytotoxic behavior of nanoparticles in an MTT assay. Whereas, literature [52] illustrates a greater correlation between the free intracellular Zn concentration and toxicity induced by zinc oxide nanoparticles. Similarly, an analysis reported significant cytotoxicity which was recorded as concentration dependent in nature in both HepG2 and Caco2 cells when compared to the control. However, a similar concentration increase in mitochondrial injury and oxidative loss and damage to DNA was also found.

When discussing the hepatotoxicity of nanocomponents, the spleen and liver are the main organs which are involved in the important processes of detoxification and metabolism. The main function of the liver is to flush out toxic products and elements. The high rate of blood flow to this organ generally leads to high concentration delivery of toxicants, thus making it an easy target for toxicants. Nanomaterial exposure can be facilitated by processes such as inhalation, ingestion, skin penetration, or intravenous operations. This process enables nanomaterials generally to reach the blood circulation and finally be transported to the liver. Further, nanoparticles also get entrapped by the reticuloendothelial system targeting the liver and spleen. These lethal entries of nanoparticles become entrapped as hepatotoxicants and therefore it becomes crucial to have hepatotoxicity testing to check the safety of these potential nanoelements [37]. Similarly, the kidney is also a target organ which is exposed to "nephrotoxicity" via blood-translocated nanoparticles. However, studies highlighting these areas are limited and reports show that nanoparticles could induce cytotoxicity in the kidneys also, therefore more studies are needed to describe the appropriate mechanism and reach definitive conclusions. The limited studies on the effects and impacts of nanoparticles on the immune system suggest that nanoparticles have the potential to cause "immunotoxicity." It has been observed that nanomaterials can exert/modulate cytokine production, and also induce inflammatory effects in the lungs of model animals, with increased and enhanced expression of interleukin-1 and macrophage-associated inflammatory proteins. Similarly, chemokines, colony-stimulating factors, and activation of protein kinase production are enhanced.

Further, it can lead to inflammatory responses and allergic conditions due to the increase in the oxidative stress mechanism. Genotoxicity has also been reported to be induced by nanoparticle exposure, which may result in DNA damage, oxidative stress, mutations, aberrations, formation of micronucleus complexes, etc. [49,50]. However, the data are difficult to use to provide a conclusion due to variations in the outcomes and limitations in the reports obtained through various experimental studies [51,52]. Similarly, several studies also focus on the cardiotoxic potential of nanomaterials, which can result in enhanced hematologic consequences/parameters, oxidative stress, increased myocardial enzyme concentration in serum, etc. This complexity may be directly related to the particle size and its associated damage. Furthermore, a phase of interactive toxicity is introduced by nanoparticles which can lethally interfere with the LPS content and provoke toxicity of the endotoxin LPS. Keeping in mind the increased application of nanoparticles in medical areas, the increasing LPS contamination by nanoparticles could pose a great obstacle in the medicine and pharmacological fields, thus this needs to be addressed by finding appropriate solutions.

2.3 The toxic interactions: nano–bio interactions and the mechanism involved

This section demonstrates the toxicological effects of various nanomaterial features, particularly how these properties affect the toxicokinetic, cellular absorption, and toxicity processes of nanomaterials, in an effort to better understand nanotoxicity. The majority of inhaled, orally ingested, and topically applied nanoproducts are retained in the exposed organs by intricate bioenvironments and may further cause harmful effects before gradually leaving the body [53]. Humans can be exposed to manufactured nanomaterials at various phases of their life cycles and by a variety of routes, mostly by inhalation, oral absorption, skin contact, intravenous injections, etc. Furthermore, circulating nanomaterials may, regardless of the exposure route, bypass the blood–brain, blood–testis, and placental barriers to enter the central nervous system, the reproductive system, and the progeny, respectively, and have biological impacts on these organs. According to their characteristics, nanomaterials exhibit different patterns of metabolism, excretion, and degradation, most of which occur in the liver and kidney [54], while a small percentage of these nanomaterials can enter the bloodstream and/or lymphatic system via absorption [53]. Nonintravenously injected nanomaterials display more broad

and uniform dispersion throughout the body because of the delayed dosage rate and distinct absorption routes, from exposure portals to absorption sites.

They are more quickly eliminated from the bloodstream and tend to collect in organs like the liver and spleen that have a high mononuclear-phagocytic system (MPS) population [55]. It is plausible to infer from their toxicokinetic process that a number of organs, in particular the lung, colon, liver, spleen, and kidney, may be the toxicity targets of nanomaterials. Therefore, more fundamental explanations for organ/tissue toxicity are provided by nano—bio interactions at the cellular, subcellular, and molecular levels, which is helpful for the assessment of nanomaterial safety [56]. Nanomaterials can typically attach to, pierce through, embed in, and/or internalize membranes.

Numerous investigations have confirmed that liver damage and malfunction, gut and microbiota dysfunction, spleen inflammation, renal injury, and respiratory toxicity can be caused by nanomaterials. Different mechanisms by which nanomaterials enter cells can affect their intracellular location, destiny, and subsequent cytotoxicity [56]. The majority of cellular entry methods for nanomaterials use endocytosis-based pathways, including phagocytosis, micropinocytosis, clathrin- and caveolin-dependent endocytosis, and clathrin- and caveolin-independent endocytosis. The majority of endocytosed nanoparticles are initially captured by vesicles produced from the cytomembrane, and are then transported to endosomes and fused with lysosomes. Nanomaterials in the lysosome either degrade enzymatically and biochemically, exit the lysosome, or are ejected into the extracellular environment [56]. In contrast, nanomaterials are restricted in caveolae through caveolin-dependent endocytosis, which allows them to travel throughout the cytoplasm and end up in the Golgi apparatus and endoplasmic reticulum (ER). The 10 types of WPMN-proposed nanomaterials that are either in use now or will be soon are cerium oxide (CeO_2), zinc oxide (ZnO), titanium dioxide (TiO_2), gold nanoparticles (AuNPs), silver nanoparticles (AgNPs), fullerenes, multiwalled carbon nanotubes (MWCNTs), single-walled carbon nanotubes (SWCNTs), nanoclays, and silicon oxide. The chemical makeup of a nanomaterial's core is a key element in determining its potential toxicity and underlying mechanisms. It affects the nanomaterial's ability to dissolve, undergo redox reactions, ionize, and have an affinity for macromolecules.

For instance, 12 cellular models spanning various organs and systems were used in a thorough in vitro toxicity screening of typical nanomaterials

using ten separate tests for cytotoxicity, embryotoxicity, epithelial integrity, cytokine production, and oxidative stress [57]. In the majority of tissues, the order of hazards has been determined to be nano-ZnO > nano-SiO_2 > nano-TiO_2, with the exception of embryotoxic tissues, where nano-TiO_2 was shown to be weakly embryotoxic but not nano-ZnO or nano-SiO_2 [57]. In contrast to insoluble nano-TiO_2 and harmless breakdown products of nano-SiO_2, the increased toxicity of nano-ZnO is intimately associated with its dissolution into hazardous Zn^{2+}.

In more recent research, the toxicity profiles of 29 rare earth and transition metal oxide nanoparticles in several types of liver cells were examined [58]. It was discovered that REOs caused pyroptosis in Kupffer cell and other macrophages, but pro-oxidative TMOs caused apoptosis in hepatocytes. Other essential nanomaterials, such as nano-CuO, nano-Ag, and quantum dots, can disintegrate into poisonous ions, posing serious risks to biological systems [59]. Stable metallic nanoparticles, such as AuNPs, exhibit more favorable biocompatibility compared with dissolvable metal/metal oxide-based nanomaterials. For example, it has been observed that AuNPs are not harmful to RAW264.7 macrophages, which decrease ROS and do not cause the release of proinflammatory cytokines [60]. The low toxicity of mesoporous silica nanoparticles (MSNs) is partially due to their special surface silanol groups, which can either form hydrogen bonds or dissociate into SiO to interact electrostatically with a variety of biomolecules, leading to the disruption of cytomembranes, lysosomes, mitochondria, etc. [61].

Liposomes are another illustrative nanomaterial with good biocompatibility; they have been used in the clinic as drug carriers (e.g., Doxil and AmBisome) to reduce the toxicity and enhance the pharmacokinetics of active pharmaceutical ingredients.

In addition, the domains of biomedicine, energy, food safety, and environment science have shown a great deal of interest in a library of nanomaterials known as "nanozymes" that have the ability to mimic enzymes in a special way. Although pro-oxidant nanozymes, such as iron-based nanozymes, can exhibit peroxidase-mimicking activities to produce harmful hydroxyl radicals, their substrates, such as H_2O_2, and catalytic conditions, such as acidic pH, frequently exist in disease conditions, such as tumor cells, giving them the ability to kill tumor cells specifically rather than healthy tissues [62]. Intentional material design techniques like surface coating/grafting and element doping can affect the toxicology of nanoparticles in addition to the chemical composition of the core nanomaterials.

A limited percentage of foreign atoms, primarily metal atoms, are inserted into pure nanomaterials during the functionalization process, which is referred to as element doping.

By changing the Fermi energy level and bandgap of nanomaterials, doping can modify their electrical, magnetic, optical, and redox properties. Numerous experimental, theoretical, and computational studies at the cellular level have demonstrated that size-dependent cellular entrance is the predominant channel for nanomaterials. Although the explicit tiny size effect is still being investigated, it is thought that small nanoparticles can directly pass through the cell membrane and move to the cytoplasm.

The primary cellular absorption methods for large nanoparticles are diverse endocytic processes [63]. The primary channels for nanomaterials of tens or several hundred nanometers are caveolin- and clathrin-dependent endocytosis, which produce 50—100 nm caveolae and 100—500 nm intracellular vesicles, respectively, after nanomaterial entrapment.

Smaller nanomaterials typically exhibit higher toxicity than their larger counterparts, which can be due to their increased surface area, exposed surface atom ratio, and elevated catalytic activity [64]. Additionally, a size reduction may harm the structured crystal plane and the electronic configuration, resulting in more reactive surface sites and, ultimately, more harmful effects [2]. Furthermore, surface characteristics have a direct impact on how cytotoxicity is induced. According to research by Manshian et al. heightened autophagy induction and increased cell membrane damage are positively correlated with higher degrees of surface hydrophobicity [64]. According to Liu et al. various surface charges and ligands can interfere with cellular metabolism in different ways. Positively charged PEI-Au NRs were significantly more hazardous to A549 cells than PDDAC-Au NRs because they significantly disrupted pathways for oxidative stress, hexosamine biosynthesis, choline metabolism, and energy metabolism [65]. Studies have, however, also documented increased toxicity following agglomeration. For instance, at the same concentrations, rope-like agglomerated CNTs showed a higher level of cytotoxicity than asbestos fibers and well-dispersed CNT bundles. This is likely because agglomerated CNTs are larger, stiffer, and more solid, which causes more significant damage to the cell structures [66]. Biofate, biokinetics, and nanomaterials are all significantly impacted by biocorona [67]. The resistance of nanomaterials to the sequestration of MPS cells often rises with the rich absorption of desoponins, such as albumin and apolipoprotein (Apo), which results in their prolonged blood circulation and even accumulation throughout the body.

In contrast, when opsonins (such as immunoglobulins, fibrinogens, and complements) are absorbed in large amounts, MPS cells are better able to phagocytose nanomaterials, which causes them to be quickly eliminated from the blood and accumulate in the liver and spleen [68]. Many in vitro toxicological studies overlook the effects of biomolecule absorption on interactions between nanocells. Studies conducted in vivo, particularly those that administer nanomaterials via nonintravenous injection routes, frequently overlook the impact of biocorona formation and evolution on the toxicokinetics of nanomaterials. Additionally, the biocorona component should not be limited to proteins but rather broadened to include all types of biomolecules, particularly for the gastrointestinal and pulmonary biocorona. Furthermore, despite the use of effective systems toxicology techniques, it remains problematic to interpret subtly changed biomolecules, making it impossible to acquire a comprehensive understanding of the mechanisms underlying nanomaterial toxicity. Thankfully, the aforementioned issues have received a lot of attention and may be resolved with careful experimental planning, cutting-edge in situ analytical techniques, and bioinformatics methods.

2.3.1 Interactions of nanoparticles with biological systems

2.3.1.1 Surface functionality of nanoparticles and membrane perturbation

NPs can trigger structural remodeling and phase transitions in the lipid bilayer of the cell membrane. Direct contact of surface-functionalized NPs with cells can compromise membrane structural integrity, with the level of leakage dependent on the NP surface chemistry [69]. Rotello et al. established in early research on NP toxicity that a cationic mixed monolayer protected cluster (MMPC1) had greater cytotoxicity than its anionic equivalent (MMPC2), highlighting the importance of surface charge in NP cytotoxicity [70]. Similarly, due to strong electrostatic interactions with the negatively charged lipid bilayer, MMPC1 ruptured anionic phosphatidylcholine/phosphatidylserine vesicles more effectively than MMPC2. Similarly, Holl et al. demonstrated that alkylamine-functionalized NPs with 2 nm gold centers disrupted supported lipid bilayers (SLBs) [71]. These NPs aggregated on the anionic mica substrate after expanding preexisting flaws inside the SLB. The degree of SLB disruption, according to Zhu and Jing, is dependent on the surface chemistry with carboxylate-functionalized polystyrene NPs of varied diameters ($d = 28$, 62, and 140 nm) [72]. These findings were confirmed by simulation/modeling investigations

utilizing a mesoscale thermodynamic model [69]. Mukherjee and Rotello et al. studied the effects of NP surface charge on cell membrane potential further. Four gold nanoparticles (NPs) with different surface charges (cationic, anionic, zwitterionic, and neutral) were treated with cells [73]. When compared to other NPs, positively charged gold NPs depolarized the membrane potential in a dose-dependent way across distinct cell types. Furthermore, cationic NPs quickly elevated intracellular Ca2 concentration, [Ca2]i, through activating plasma membrane Ca2 inflow and endoplasmic reticulum Ca2 release, with simultaneous suppression of the proliferation of human bronchial epithelial cells (BECs) and human airway smooth muscle cells (ASM) [74]. Positively charged NPs, when combined, cause cell membrane disruption via structural reconstruction and lipid bilayer phase change. Furthermore, by altering the membrane potential and raising [Ca2]i, they cause cytotoxicity and/or cell death via intracellular signaling [75].

2.3.2 Surface functionality of nanoparticles and genotoxicity

NPs can influence gene regulation and genotoxicity either directly or indirectly by boosting endogenous oxidative stress and inflammation. Rotello et al. studied mixed monolayer protected gold clusters (MMPCs) that had been functionalized with tetraalkylammonium ligands that might interact with the DNA backbone [76]. T7RNA polymerase was inhibited in vitro by this complementary electrostatic interaction with DNA (37 mer). A further research discovered that the amounts of glutathione (GSH), which regulates the intracellular redox milieu, can alter the MMPC−DNA interaction [77]. Although the connection between MMPC and DNA changes depending on the monolayer covering used, up- or downregulated transcription resulting from NP interaction can induce cellular DNA damage and genotoxicity. ElSayed et al., for example, found that 30 nm gold nanoparticles containing arginine glycine-aspartic acid (RGD) and nuclear localization signal (NLS) peptides cause DNA damage and cytokine arrest in human oral squamous cell carcinoma cells (HSCs) [78]. Chen et al. also found that cationic amine-modified polystyrene NPs slowed the G0/G1 phase of the cell cycle while decreasing the production of cyclin D and cyclin E [79]. Hussain et al. also discovered that the surface charge and functionality of gold nanoparticles affected gene expression in apoptosis, cell cycle, and DNA repair [80]. In addition to surface charge, NP surface hydrophobicity is important in cytotoxicity and subsequent DNA damage. Rotello et al. created gold nanoparticles (2 nm core) with quaternary

ammonium functionality and a systematically varied hydrophobic alkyl chain [81]. In HeLa cells, increasing the hydrophobicity of the NP surface resulted in increased cytotoxicity and accompanying ROS generation. However, comet experiments employing NP-HEX revealed a lower percent Tail DNA and Tail length, indicating less DNA damage with increased particle hydrophobicity, most likely due to upregulation of the autophagic mechanisms under oxidative stress [82]. As a result, surface functioning is critical in both DNA damage and ROS generation, with potentially hazardous effects [83].

2.3.3 Nanoparticle surface functionality for therapeutic applications

2.3.3.1 Surface functionality of nanoparticles in delivery strategies

As previously stated, the surface characteristics of NPs determine their cytotoxic reactions. As a result, surface functionalization can aid in the development of NPs with enhanced therapeutic effectiveness. Furthermore, the functional diversity of NP monolayers makes them an ideal platform for delivery vehicles. Rotello et al. employed a gold nanoparticle functionalized with photocleavable o-nitrobenzyl ester moieties to control the release of the anticancer medication 5-fluorouracil in cancer cells [84]. The zwitterionic ligand on the surface of the NPs enhanced solubility while restricting intracellular absorption in this study. Noncovalent drug conjugation onto the NP surface monolayer offers an alternative to covalent conjugation, perhaps resolving prodrug problems. Rotello and colleagues established an effective method for encapsulating anticancer medicines inside the hydrophobic monolayer of gold nanoparticles, allowing subsequent release in cancer cells [85].

The surface characteristics of nanoparticles can influence NP penetration in tissues as well as medication delivery/release. Cationic NPs provide the drug payload to the majority of cells in a tumor model, whereas anionic NPs carry medications deeper into the tumor model [86].

2.3.4 Beyond carriers

2.3.4.1 Nanoparticles as therapeutics

NPs offer excellent drug-loading efficiency, minimal toxicity, an enhanced pharmacokinetic profile, and high cellular uptake. NPs, on the other hand, can be designed to be cytotoxic in order to be used as possible treatments in their own right [87,88]. Rotello et al. for example, reported the utilization of cationic gold nanoparticles as therapeutic agents by regulating their

cytotoxicity [89]. The cationic NPs containing a terminal diamino hexane moiety interact strongly with cell membranes and subcellular compartments, causing membrane rupture and cytotoxicity. However, combining NP-NH2 with cucurbit [7] uril (CB [7]) complex lowers the particles' capacity to break endosomal membranes and hence helps in decreasing toxicity. The host–guest complex on the particles can be destroyed intracellularly by the orthogonal guest molecule 1-adamantylamine (ADA), which has a high affinity for CB [7,90].

2.3.5 Influence of the surface, size, and shape of nanoparticles on immunological responses

Aside from their usage as drug carriers, AuNPs have the potential to be used as vaccination platforms. Subunit vaccines, in which an antigen alone is connected to a powerful immunogen, such as proteins or virus-like capsules, have been the focus of recent attempts to develop effective and safe vaccinations. However, the antigen–protein combination produces antibodies specific for both the antigens and the protein carriers, rendering repeated immunizations ineffective due to carrier-specific antibody exclusion. Synthetic carriers are interesting possibilities for preventing antibody formation against the carrier itself [91]. AuNPs have been deployed as antigen carriers for subunit vaccinations with no anti-AuNP antibodies produced. AuNPs have been shown to be excellent antigen carriers for a variety of viruses [92,93].

Several recent studies have found that AuNPs can stimulate immunological responses such as antibody and cytokine production [94,95]. As a result, understanding the effects of nanoparticles on cytokine release is critical for their future use as vaccine adjuvants. Maysinger and colleagues [96] discovered that the inflammatory response in microglial cells is AuNP shape dependent. Rotello and colleagues [97] discovered a link between nanoparticle surface hydrophobicity and immunological response. Niikura et al. [98] evaluated the adjuvant activities of CTAB-coated spherical (20 and 40 nm in diameter), rod (40 10 nm), and cubic (40 40 40 nm) nanoparticles. According to Gole and Murphy [99], the nanoparticles were coated with poly(4-stylenesulfonic acid-co-maleic acid) before being electrostatically coated with West Nile virus envelope (WNVE) protein. These scientists discovered that large spherical nanoparticles (40 nm) outperformed other forms (cube and rod) or smaller spheres as a platform for antibody synthesis (20 nm). These findings suggest that, in addition to surface features, the size and shape of AuNPs should be taken into account when developing successful

nanoparticle-based vaccinations. Furthermore, in future investigations on the use of AuNPs as adjuvants, the effects of antigen immobilization chemistry on immune responses should be addressed.

2.3.6 Nanoparticle–DNA binding in medical biotechnology

Many conventional technologies for illness diagnosis and therapy now confront cost, efficiency, and sensitivity problems due to the biodetection systems and devices employed. The development of cost-effective, portable detection devices with great sensitivity is critical. Using DNA markers, new techniques based on nanoparticle technology have been created for the early and accurate detection of sickness, cancer, and bioterrorism. AuNPs can boost Raman scattering signals by orders of magnitude, allowing for single-molecule detection [100]. The addition of AuNPs improved surface plasmon resonance (SPR) sensitivity by 1000-fold [101]. Updated research into nanoparticle-based DNA binding approaches that make use of their distinctive size and optical features will result in well-established assays for a wide range of biological applications. Engineered AgNPs are often utilized to detect antibacterial/antiviral and enhanced catalytic activity, as well as to improve SERS [102]. The unique binding ability and properties of AgNPs make them appealing for their growing use in medical diagnostics. The use of oligonucleotide-modified nanoparticles can improve DNA detection and transport efficiency through sequence-specific identification. Covalent nanoparticle–DNA binding, on the other hand, complicates DNA release for targeted treatment. As a result, noncovalent binding appears to be essential for efficient DNA and siRNA transport [103].

3. Conclusions and future challenges

Nanotechnology is increasingly being used in the human environment and in consumer items.

Human exposure to nanoparticles is predicted to rise in the future. As a result, widespread human exposure to nanoparticles has become a public health concern. As a result, better tools for assessing the safety of nanoparticles are required. The current state of knowledge about the impacts of nanomaterials on humans is quite limited. According to the present literature, nanoparticles encountered in the human environment have the potential for toxicological consequences. The present literature on the toxicological consequences of nanomaterials, on the other hand, is mixed. The current data come from studies that have not been harmonized. Distinct in vitro and

in vivo test models, different sources of test nanomaterials, diverse nanomaterial characterization methodologies, and different experimental settings have been used in this research. As a result, the results are difficult to comprehend. There is a need for more research on nanomaterial characterization, biological interactions, toxicity, and health effects.

The potential risk of nanoparticles in the human environment, like that of many of their larger counterparts, is a challenge. Aside from the data gaps mentioned above, there is scientific uncertainty about aspects of risk assessment, such as: (a) the different characteristics of the nanocomponent that may impact toxicity; (b) the ultimate destination and translocation through the environment; (c) the exposure routes and the severity of the exposure mechanism; (d) the translocation pathway and mechanisms of transportation to different parts of the body; and (e) the disease and toxicity relationship and mechanisms.

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Antiviral and Antimicrobial Coatings Based on Functionalized Nanomaterials

Design,Applications, and Devices

Antiviral and Antimicrobial Coatings Based on Functionalized Nanomaterials: Design, Applications, and Devices is the first book on functionalized nanoparticles-based coatings that encompasses the majority of aspects of antimicrobial and antiviral coatings. The use of functionalized nanoparticles has revolutionized all fields of science and engineering, and this book provides the reader with a fundamental, interdisciplinary look at this emerging field. It focuses on the most advanced coating systems being utilized by various industries including a discussion of the current challenges to be considered during manufacturing.

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- Evaluates functionalized nanoparticles-based antimicrobial and antiviral coatings as prime options for sustainable and transformational opportunities
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