Part II

BIOSYNTHESIS OF METALLIC NANOPARTICLES

Suvardhan Kanchi and Shakeel Ahmed (eds.) Green Metal Nanoparticles, (165–198)

6

Current Advances in Biosynthesis of Silver Nanoparticles and Their Applications

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Abstract

Recent advances in nanotechnology and nanoscience have resulted in more enhanced techniques on the way we analyze, treat, and inhibit numerous diseases in all facets of human life. Silver nanoparticles (AgNPs) are one of the most vital and interesting nanomaterials amongst some of the metallic nanoparticles that are elaborated in many biomedical applications. For the development of silver nanoparticles, the biomolecules from various plant constituents and microbial species have been utilized as potential agents. These AgNPs are greatly used due to their orientation, physical properties, and small size, which are reported to have influence in conversion of the performance of any other material which is in contact with these tiny particles. In addition, AgNPs can be prepared by simple chemical, physical, and biological approaches. Furthermore, biosynthesis of AgNPs has been increased substantially in many of the established countries due to their improved response of environmentally friendly technology for measurable synthesis. However, the biological method is the most emerging approach in preparation, as this technique is easier when compared to other methods used, viz., less time consuming, eco-friendly, nontoxic and cheap. Furthermore, the significance of AgNPs are broadly discussed based on their multifunctional bioapplications; i.e., as antifungal, anti-inflammatory, antibacterial, antiviral, antiangiogenic and anticancer agents, and the anticancer activity mechanism of AgNPs.

Keywords: Biosynthesis, silver nanoparticles, bacteria and algae, antimicrobial and anticancer properties, catalytic activity and toxicity, anti-biomedical applications

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6.1 Introduction

Due to recent economic developments and industrialization the environment has suffered immensely, with huge amounts of dangerous and unessential chemicals, gases or materials being released into the air. The onus is now upon us in the scientific community to learn more about the mysteries of nature and its crops, which leads to increased innovation in the synthesis methods of nanoparticles [1]. Nanotechnology applications are extremely suitable for biological molecules because of their high-class properties. The biological particles undergo greatly controlled association processes to prepare them for suitable metal nanoparticle production, which was found to be reliable and environmentally friendly [2]. A number of chemical and physical procedures have been used for the synthesis of metal nanoparticles; however, some of these existing techniques have disadvantages, i.e., use of toxic solvents, formation of hazardous products and high-energy consumption, etc. As a result, there is a crucial requirement to improve eco-friendly processes for the preparation of metal nanoparticles. The expansion of eco-friendly technologies in physical synthesis is of great importance so as to expand their application to biological systems [3, 4]. In recent years, many synthesis methods of green nanoparticles with well-defined sizes, chemical composition, and morphology have been introduced, and their applications in several innovative technological areas have been explored. Hence, green synthesis methods using different biological organisms, such as mold, yeast, bacteria, algae and plant extracts, have been established for the synthesis of nanoparticles [5]. Moreover, AgNPs have been used commercially for a wide range of coating areas with energy contact actions, electronics, and medicines. AgNPs play a key role in the commercial applications of these nanoparticles in the field of pharmaceutical and other medical sciences (Figure 6.1). In addition, AgNPs, owing to their great bioactivity against bacteria, protozoa, fungi and viruses, are measured to be the most promising of any antimicrobial agent [6–8]. A large number of microorganisms, such as fungus, bacteria, yeasts, and plants, either intra- or extracellular, which are of higher crop yields and lower costs have been revealed to be capable of synthesizing nanoparticles [9]. The high efficiency of AgNPs is essentially due to the accessibility of larger surface area to volume ratio for interactions, easing the penetration and disruption of nanoparticles into the bacterial cells, as compared to micro-sized silver ions [10]. The purpose of our study is to open new views and probe future applications of nanomaterial biosynthesis as potential antimicrobial agents.

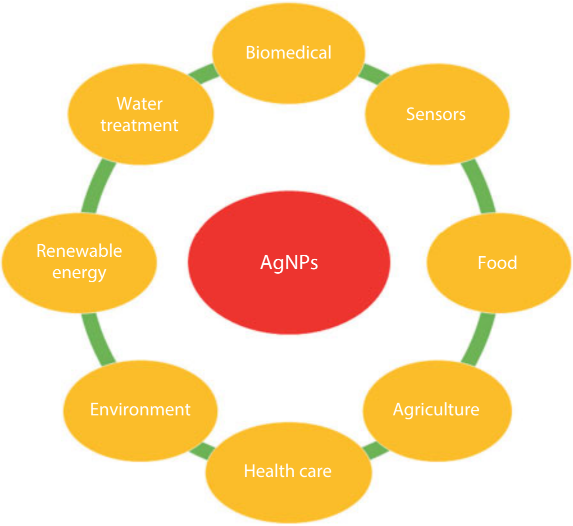

Figure 6.1 Various applications of silver nanoparticles.

6.2 Synthesis of Nanoparticles

The preparation of metallic nanoparticles mainly consists of two approches, i.e., top-down or bottom-up, by physical, chemical, and biological methods. Biogenic syntheses of silver nanoparticles are classified under bottom-up approach. The top-down method essentially works with the solid in its bulk form, and the size reduction to the nanoscale is then attained by specific ablations, i.e., thermal decomposition, mechanical milling, etching, lithography, laser ablation, and sputtering [11]. Furthermore, the "bottom-up" method is superior for the synthesis of nanoparticles, containing an identical system in which catalysts (e.g., reducing agent and enzymes) manufacture nanostructures that are organized by catalyst assets, reaction media, and conditions (e.g., solvents, stabilizers and temperature). For example, chemical reduction process is the most common artificial pathway for metal nanoparticles prepartion [12]. The top-down and bottom-up preparations are shown in Figure 6.2.

Morover, wide-ranging chemical, biological, physical and hybrid techniques (Figure 6.3) are employed to prepare the various nanoparticles [6]. Hence, the synthesis of nanoparticles is usally dependant on two methods, i.e., chemical and physical. These methods contain solvothermal synthesis, ion sputtering, sol-gel techniques and reduction. Furthermore, in

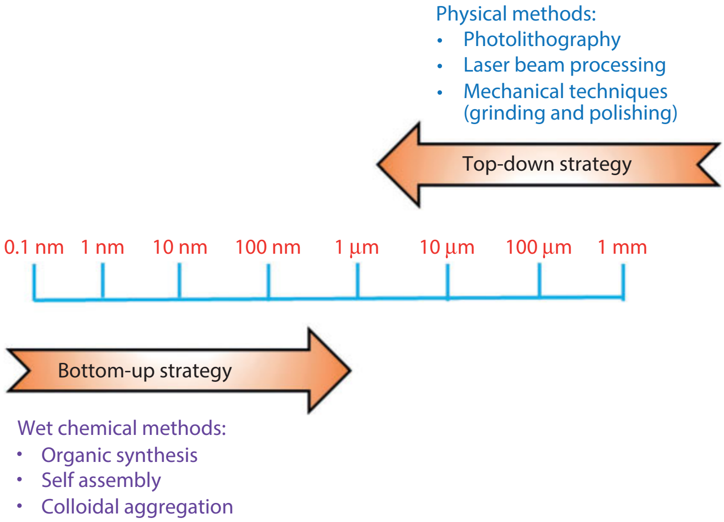

Figure 6.2 Top-down and Bottom-up synthesis approaches [13].

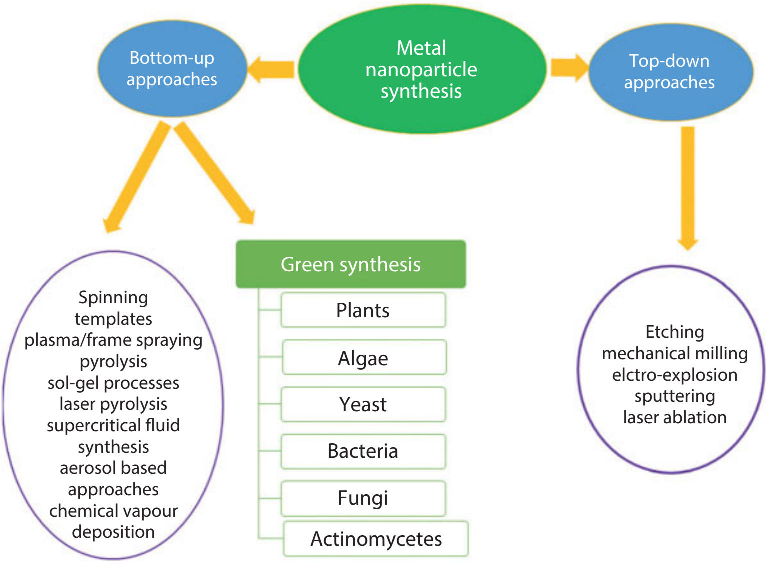

Figure 6.3 Different approaches for synthesis of silver nanoparticles.

biological procedures where the microbes and plants are used as reducing agents or protective agents these procedures can be used to synthesize the nanoparticels [14]. A lot of biological organisms that are mutually unicellular and multicultural, are known to produce inorganic materials either intra- or extracellularly, regularly of nanoscale dimensions and of attractive morphology and classified assembly. In addition, the biosynthesis of nanoparticles employs usage of biological agents like fungi, bacteria, yeast, actinomycetes, algae and plants [15, 16]. The rate of reduction of metal ions using biological agents is found to be much faster and also occurs under ambient temperature and pressure conditions. Here, we summarize some of the organisms used in the biosynthesis of nanomaterials and describe the properties that should be inherent for the production of nanoparticles with desired characteristics.

6.2.1 Green Synthesis of Nanoparticles and its Benefits

Green synthesis of silver nanoparticles includes choosing properties and materials which are cost effective and include bulk preparations. These techniques are associated with atmospheric pressure, less energy consumption, low temperature and are free of toxic chemicals [17]. Green synthesis of nanoparticles are mainly classfied into five methods: Tollens' technique, irradiation method, polysaccharide method, polyoxometalates method and biological method. Tollens' process is involved in a one-step process. In this method, the reduction of Ag^+ ions is done by introducing saccharides in the existence of ammonia, yielding silver nanoparticles with various sizes and shapes of 50–200 nm [18]. In the irradiation method, the metal nanoparticles can be synthesized by using many irradiation procedures at room temperature without the use of a dipping agent. Therefore, temperature-dependent covering agents can also be used in the irradiation process. In addition, silver nanoparticles with a distinct shape and size distribution, for example, can be found from laser irradiation of an aqueous solution of silver salt and surfactant [19]. By using the polysaccharide process, metal nanoparticles are produced by using water and polysaccharide substitutes as a stabilizing agent, a reducing agent, or both reducing and stabilizing agents. For example, the fabrication of silver nanoparticles can be achieved by using starch as a defensive agent and β-d-glucose as a reductant in a mild-heating system. Furthermore, in this way the magnetism among starch and silver nanoparticles is weak and flexible at higher temperatures, enabling the separation of the produced silver nanoparticles [20]. Polyoxometalates have the potential of manufacturing silver nanoparticles since they are soluble in water and have the ability of experiencing a stepwise, multi-electron redox process without distressing their structure [21]. Extracts from bioorganisms might perform both as reducing and capping agents in silver nanoparticles preparation. In addition, the reduction of Ag^+ ions by amalgamation of biomolecules found in these extracts, such as enzymes/proteins, polysaccharides, amino acids, and vitamins, is environmentally benign, yet chemically complex. A large volume of the literature reports include effective synthesis of silver nanoparticles using bio-organic compounds. The rate of reduction of silver ions using biological agents is said to be much faster and also occurs at ambient temperature and pressure situations. Figure 6.4 shows some of the TEM images of silver nanoparticles by various methods. Green chemistry unites a few novel approches for the synthesis, processing and uses of chemical substaences in such a way as to decrease threats to health and environment. The novel approaches are:

- Clean chemistry
- Atom economy
- Environmentally caring chemistry
- Benign-by-design chemistry

The main aim of green chemistry is to protect the envionment from pollutants. Green chemistry is the methodology to design, manufacture and use chemical products to intentionally decrease or remove chemical hazards.

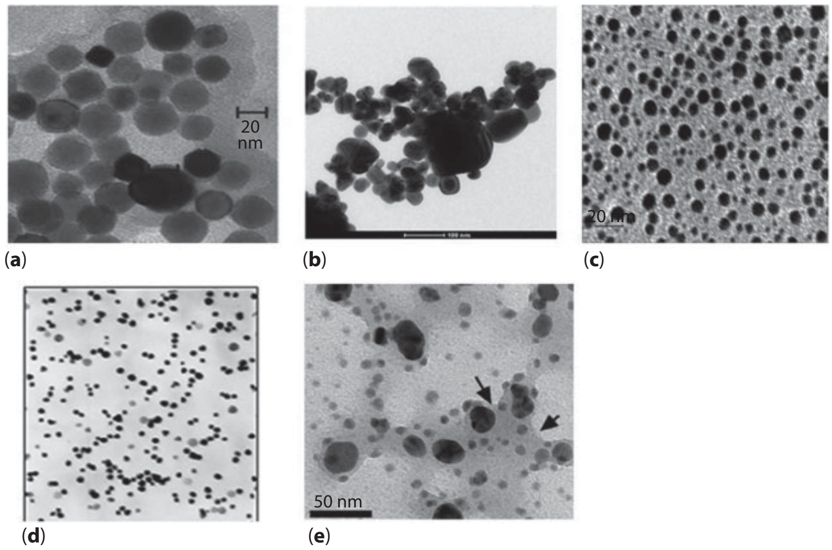

Figure 6.4 (a) TEM image of silver nanoparticles by Tollens' method [22]. (b) TEM image of silver nanoparticles by irradiation method [23]. (c) TEM image of starch silver nanoparticles by polysaccaride method [24]. (d) TEM image of silver nanoparticles by polyoxometalate method [25]. (e) TEM image of silver nanoparticles by biological method [26].

Advantages of green syntheses include:

- Energy efficiency
- Economical
- Less waste
- Fewer accidents
- Lower cost of production and regulation
- Competitive
- Safer products
- Healthier work places and communities
- Protects human health and the environment
- Compatible for pharmaceutical and other biomedical applications
- Can be used for large-scale production of nanoparticles and external experimental conditions like high energy and high pressure are not required, leading to substantial energy saving processes.

6.2.2 Synthesis of Silver Nanoparticles by Bacteria and Fungi

The first silver nanoparticle synthesizing bacteria were prepared using the *Pseudomonas stutzeri* AG259 strain that was isolated from the soil of silver mines. In this synthesis, some microorganisms that can survive high metal ion concentrations, can also develop under those environments, and this occurrence is due to their resistance to that metal. These elaborating mechanisms in the resistance are efflux organisms, which modify solubility and toxicity through oxidation or reduction, bioaccumulation, biosorption, extracellular composite development or precipitation of metals, and absence of definite metal transportation systems. After that, many syntheses procedures were established, i.e., green synthesis of silver naoparticles using 30 cyanobacteria was examined [27]. Cyanobacterial aqueous sources were then subjected to silver nanoparticles synthesis at 30 °C. The results are primarily confirmed by UV, in this case scanning of these aqueous extracts with silver nanoparticles in UV-visible range exhibited a single peak. SEM micrographs of silver nanoparticles from cyanobacterial extracts showed that though preparation of nanoparticles followed in all strains, their reaction time (30 to 360 h), shape, and size (38 to 88 nm) varied (Table 6.1). Moreover, extracellular green synthesis of silver nanoparticles using *Pseudomonas aeruginosa* [28] and *Escherichia coli* [29] were described. Fungi and other microorganisms are superior candidates

Table 6.1 Fungal and bacterial green synthesis of silver nanoparticles of different sizes.

Producer organism	**Size (nm)**	**Ref.**
Candida albicans	50–100	[31]
Fusarium sp.	12–20	[34]
Trichoderma harzianum	19–63	[35]
Fusarium solani	5–30	[36]
Cunninghamella phaeospora	12.2	[27]
Aspergillus versicolor	15.5	[37]
Colletotrichum sp.	20–50	[38]
Aspergillus clavatus	25–145	[39]
Aspergillus niger	25–175	[39]
Aspergillus flavus	45–185	[39]
Aspergillus fumigatus	5–95	[39]
Trichoderma viride	15.5	[40]
Penicillium expansum	14–25	[41]
Aspergillus terreus	10–18	[41]
Cyanobacteria aqueous	38–88	[27]
Nocardiopsis valliformis	5–50	[42]
Bacillus pumilus, B. persicus	77–92	[43]
Pilimelia columellifera	12.7	[44]
Bacillus safensis	5–30	[45]
Corynebacterium glutamicum	15	[46]
Pseudomonas mandelii	1.9–10	[47]

in the preparation of metal nanoparticles (Figure 6.5) with dissimilar sizes (Table 6.1), due to their capability to discharge a large amount of enzymes. Many reducing agents are emitted by microbes (Figure 6.6). For example, Salvadori *et al.* [30] described a biological method that used dead biomass of the fungus *Hypocrea lixii,* as a new, effective and eco-friendly bioprocess for the synthesis of nanomaterials. Biological synthesis of silver nanoparticles was initiated to be between 123–195 nm size [9], 50–100 nm using the fungus *Pestaloptiopsis pauciseta* [31] and 20–80 nm using *Candida albicans* [32]. While in comparison with bacteria, fungi can produce superior amounts of nanoparticles, as they can secrete larger amounts of proteins which simply translate to higher production of nanoparticles [6]. In

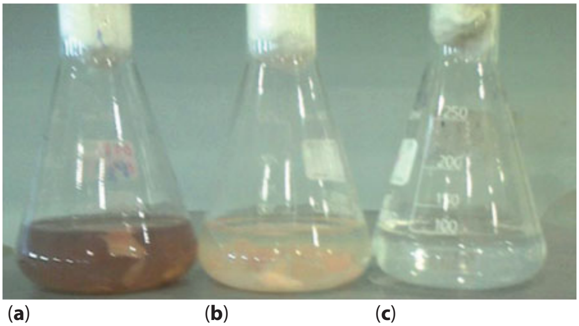

Figure 6.5 Conversion of silver nitrate to silver nanoparticles: (a) silver nitrate solution inoculated with biomass of *Fusarium moniliforme*, (b) distilled water immunized with biomass of *F. moniliforme*, (c) silver nitrate solution without biomass of *F. moniliforme* [33].

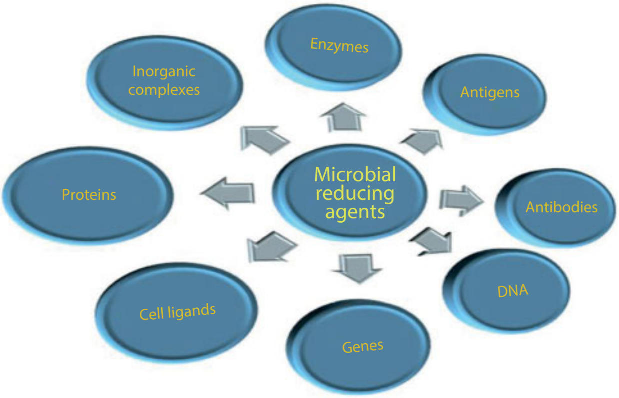

Figure 6.6 Reducing agents within microbial synthesis of silver nanoparticles.

addition, the mechanism of silver nanoparticle manufacture by fungi is known to follow the following steps: trapping of Ag^+ ions at the surface of the fungal cells and the subsequent reduction of the silver ions by the enzymes present in the fungal system. However, although the exact mechanism for elaborating silver nanoparticle construction by fungi is not fully understood, it is thought that the above-stated occurrence is responsible for the procedure. The main disadvantage of using microbes to synthesize silver nanoparticles is that it is a very sluggish procedure in comparison to plant extracts. Therefore, the use of plant extracts to synthesize silver nanoparticles represents a choice that is more plausible.

6.2.3 Synthesis of Silver Nanoparticles by Algae

Sinha *et al.* [48] described a method in which silver nanoparticles (size of 34.03 nm) were produced within a few minutes of silver ions coming in contact with the algal extract of *Pithophora oedogonium*. Patel *et al.* [49] describe silver nanoparticles manufactured by various strains of microalgae, including *Botryococcus braunii, Coelastrum* sp., *Spirulina* sp. and *Limnothrix* sp. exhibited diameters of 15.67, 19.28, 13.85 and 25.65 nm, respectively, silver nanoparticles of sizes between 15 and 47 nm were biosynthesized using aqueous extract of *Chlorella vulgaris* as reducing agent [50]. Later, Abdelghany *et al.* [27] estimated the antitumor efficiency of several concentrations of silver nanoparticles biosynthesized by the blue green algae *Anabaena oryzae, Nostoc muscorum* and *Calothrix marchic* on Ehrlich-Lettre ascites carcinoma *in vitro*. These procedures provide appropriate evidence for cellular internalization and biotransformation of silver nanoparticles in *Chlamydomonas reinhardtii*, which are very functional for accepting the performance and fate of silver nanoparticles in an aquatic environment. AgNPs were synthesized using *Spirulina platensis* (average size of most particles was 11.5 nm) and *Nostoc* sp. (average size of most particles was 20.3 nm) at room temperature and were calculated by Abdelghany *et al.* [27].

6.2.4 Synthesis of Silver Nanoparticles by Plants

In recent years, nanoparticle preparation has been one the most attractive scientific areas of interest, and attention has been evolving to producing nanoparticles using plant extracts. The main benefit of using plant extracts for silver nanoparticle preparation is that they are easily available, safe and nontoxic in extreme cases, have a wide-ranging variety of metabolites that can aid in the reduction of silver ions, are faster than microbes in synthesis and have significant phytochemicals that can be used as reducing agents for silver nanoparticles synthesis (Figure 6.7). Table 6.2 shows the names of the plant extracts used to prepare silver nanoparticles, as well as the shape and size of the nanoparticles. The main mechanism measured for the procedure is plant-assisted reduction, due to phytochemicals. Green synthesis of silver nanoparticles was attained using extracts from sixteen usually accessible plants by sonication method [51]; and an antibacterial evaluation of the effects of biosynthesized silver nanoparticles against bacteria (*E. coli, Salmonella paratyphi, S. aureus* and *B. subtilis*) was carried out, which revealed outstanding antibacterial activity. Moreover, synthesis of silver naoparticles has been established using extracts of *Chrysophyllum*

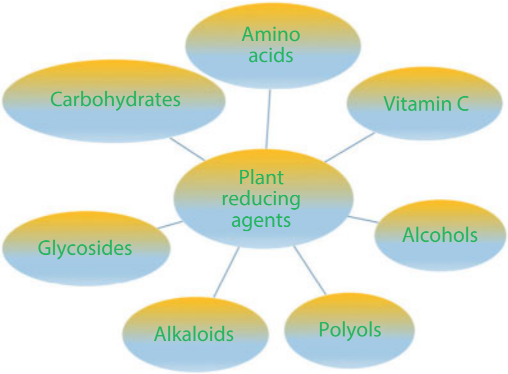

Figure 6.7 Bioreductant phytochemicals.

oliviforme, reducing aqueous silver nitrate [52]. In addition, the silver nanoparticles were prepared over a green route with the use of *Momordica charantia* leaf extracts equally with reductant and stabilizer [53].

6.2.5 Need for Green Synthesis

Nature has invented numerous processes for the preparation of nano- and micro-length scaled inorganic materials, which have contributed to the enhancement of this moderately new and largely unexplored area of research based on the biosynthesis of nanomaterials. Moreover, synthesis using bio-organisms is compatible with the green chemistry principles. "Green synthesis" of nanoparticles makes use of eco-friendly, nontoxic and safe reagents. Nanoparticles synthesized using biological methods or green technology have diverse natures, with greater stability and suitable sizes, since they are manufactured using a one-step procedure. Furthermore, green synthesis of nanoparticles is a careful bottom-up approach where the key reaction arising is reduction/oxidation. The biosynthesis of designed nanoparticles is costly in terms of the physical and chemical methods needed. A lot of chemical synthesis processes lead to the existence of some of the toxic chemicals engaged on the surface, which may have adverse effects in medical applications [74]. This is, however, not an issue when it comes to biosynthesized nanoparticles via the green synthesis route [75]. Therefore, in the examination of cheaper pathways for nanoparticle synthesis, scientists have used microbial enzymes and plant extracts (phytochemicals). Their antioxidant or reducing properties are regularly responsible for the reduction of metal compounds into their individual nanoparticles. Green synthesis offers innovation over chemical and physical techniques,

Table 6.2 Bionanoparticles synthesized using botanicals with their size, shape and references.

Plant	**Parts used**	**Metal/ alloy**	**Size/shape**	**Ref.**
Pelargonium graveolens	Leaves	Ag^+	16–40 nm/ quasilinear superstructures	[54]
Aloe vera	Pulp	Ag^+	25 nm/ spherical	[55]
Eclipta	Leaves	$AgNO_3$	-	[56]
Cycas	Leaves	Ag^+	3.29	[56]
Jatropha curcas	Latex	Ag^+	-	[1]
Cinnamomum zeylanicum	Bark	Ag^+	-	[57]
Black tea	Leaves	Au^{3+} Ag^+	-	[58]
Desmodium triflorum		Ag^+	5–20 nm/ spherical	[59]
Murraya koenigii	Leaves	Ag^+	20 nm/ hexagonal and nearly spherical	[60]
Citrus limon		Ag^+	-	[61]
Coriandrum sativum	Leaves	Ag^+	26 nm/ spherical	[62]
Gliricidia sepium	Leaves	Ag^+	27 nm/ spherical	[63]
Hibiscus rosa sinensis	Leaves	Ag^+		[64]
Jatropha curcas	seeds	Ag^+	15–50 nm	[1]
Capsicum annuum	Leaves	Ag^+	10–12 nm	[65]
Medicago sativa	Leaves	Ag^+	2–20 nm/ spherical	[66]
Quercetin	Leaves	Ag^+	Radius 1–1.5 mm	[67]
Rice paper plant stem	-	Ag^+	Below 100 nm	[54]

Aloe vera	Leaves	Silver, gold	Triangular, spherical	[68]
Emblica officinalis	Leaves	Silver, gold	10–20 nm, 15–25 nm	[69]
Azadirachta indica	Leaves	Ag^+ gold	Ag core–Au shell Polydisperse, flat, plate-like, spherical, peculiar core–shell structure 5–35 nm diameter, 50–100 nm	[70]
Cinnamomum camphora	Leaves	Silver, gold	Triangular, spherical 55–80 nm	[71]
Capsicum annuum	Leaves	Silver	-	[72]
Pelargonium graveolens	Leaves	Silver	16–40 nm	[73]
Brassica juncea	Leaves	Silver, gold, copper	-	

as it is cost-effective, eco-friendly, easily scaled up for large-scale synthesis, and in this process there is no need to use high energy, pressure, temperature and toxic chemicals.

6.3 Biomedical Applications of Silver Nanoparticles

Green synthesis nanoparticles having numerous medical applications, i.e., antifungal, antibacterial, chemotherapy, drug carrier and antiviral. The main mechanism of action is silver nanoparticles entering the human body via the respiratory tract, gastrointestinal tract, skin and female genital tract through direct exchange of materials with the environment, creating an eco-friendly environment [76]. In addition, green synthesized silver nanoparticles act as reducing agents and stabilizers; silver nanoparticles are stabilized with proteins, bacteria, fungi, carbohydrates, plants and algae. For example, Naik *et al.* prepared silver nanoparticles from peptides with average size of 60–150 nm, these silver nanoparticles are combined with peptides to form a combinatorial phage-display peptide library [77]. The combinatorial peptide phase interacts with aerobic and anaerobic bacteria to produce the bacterial cellular proteins and these block the microbial respiratory chain system. Furthermore, the respiratory system forms a thin layer with peptidoglycan within the cytoplasmic membrane and outer membrane [78]. These layers interact with silver nanoparticles and enhance the cytoplasm, and bacterial activity. Silver nanoparticles have larger surface area, and due to the larger surface area easily interact with bacteria and fungi, which may create free radicals and induce oxidative stress, thus further enhancing their bactericidal activity [79]. In addition, silver nanoparticles are used for treatment of wounds and burns or as a contraceptive and marketed as a water disinfectant and room spray. The use of silver nanoparticles is becoming more and more popular in medicine and associated applications.

6.3.1 Antibacterial Properties

Silver nanoparticles have a wide range of antibacterial impact on a range of Gram-positive and Gram-negative bacteria as well as antibiotic-resistant bacteria strains. The antibacterial efficiency of silver nanoparticles mainly depends on their size, concentration and shape. Moreover, the silver nanoparticles have greater antimicrobial properties, and therefore are regularly used in coating of bone prostheses, surgical devices, distillation methods and dental composites [80]. Silver nanoparticles are known to possess oligodynamic properties and can destroy antibiotic-resistant microbes while applying partial cytotoxicity against mammalian cells. Gram-negative bacteria easily retain the color of the stain even after washing with any alcohols or acetone and include genera such as *Escherichia, Acinetobacter, Salmonella, Pseudomonas* and *Vibrio*. *Acinetobacter* types are related to nosocomial contagions, i.e., infections that are the result of treatment in hospitals or at healthcare service units, but secondary to the patient's original condition [81]. Gram-positive bacteria are those which lose the color of the stain after washing with alcohol or acetone, and include many well-known genera such as *Listeria, Enterococcus, Clostridium, Bacillus, Staphylococcus* and *Streptococcus*. The mechanisms of silver nanoparticles which caused cell death were observed in *E. coli* through the leakage of reducing sugars and proteins. In addition, silver nanoparticles are capable of terminating the permeability of the bacterial membranes via the bacterial membranes through the generation of several depths and gaps, signifying that silver nanoparticles might damage the structure of the bacterial cell membrane [82]. The activity of silver nanoparticles can thus be changed by numerous factors, and also by the characteristics of the nanoparticles (size, shape, coating); or attributable to the medium (presence of light, oxidative species, presence of other potential ligands for silver, ionic strength). Hence, these limitations will have an influence on many phenomena that can easily increase or decrease the antibacterial activity via complex pathways, as shown in Figure 6.8. Due to their large surface area to volume ratios, truncated triangular silver nanoplates show the strongest antibacterial activity.

6.3.2 Antimicrobial Activity

The risk posed by the potential outbreak of antibiotic-resistant microbes is increasing universally and demands a production outline of unique progressive stages for the study and expansion of additional effective antimicrobial agents against multidrug-resistant strains. Moreover, silver nanoparticles prepared by using *Abutilon indicum* leaf extract have revealed extremely powerful antibacterial activity on *Bacillus subtilis* (18.3 mm), *Staphylococcus aureus* (16.8 mm), *Salmonella typhi* (14.5 mm), and *Escherichia coli* (17.2 mm) [84]. In addition, the impregnation of *Ipomea carnea* silver nanoparticles with a cellulose acetate membrane to form a designed antimycobacterial membrane exhibited a 14 mm zone of inhibition on *Mycobacterium smegmatis* [85]. In many cases, the exact mechanisms behind these activities cannot be assumed. The mechanisms of antimicrobial effects of silver nanoparticles are still not completely

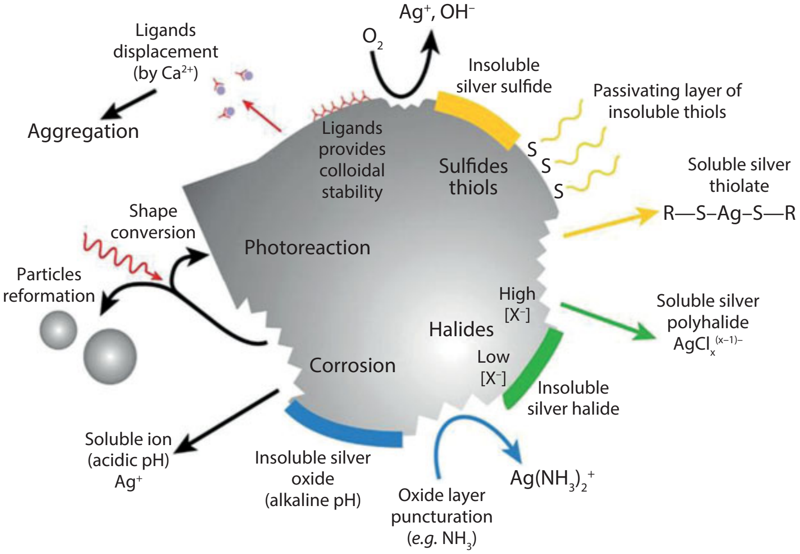

Figure 6.8 Graphical illustration of several phenomena affecting silver nanopartcles dissolution [83].

understood, but some studies have exposed that silver nanoparticles may be attributed to the adversely charged bacterial cell wall and separation, which leads to denaturation of protein and finally cell death, as shown in Table 6.3. Several studies propose that:

1. silver nanoparticles can be assigned to the surface of the cell membrane, disturbing penetrability and inhalation functions of the cell. Bactericidal action depends upon the surface area of the nanoparticles. For example, smaller silver nanoparticles having a large surface area accessible for interaction would give more bactericidal effect than the larger silver nanoparticles.
2. It is also possible that silver nanoparticles not only interact with the surface of membrane, but can also penetrate inside the cell wall of the bacteria.
3. silver nanoparticles synthesized with disaccharides, maltose and lactose, have a higher antibacterial activity than those synthesized using monosaccharides, glucose and galactose
4. Sodium dodecyl sulfate (SDS) and Tween 80 has the ability to modify antibacterial activity. Hence, they can easily

Table 6.3 Applications of silver nanoparticles in pharmaceutics, medicine and dentistry.

Pharmaceutics & Medicines	Treatment of dermatitis; inhibition of HIV-1 replication
	Treatment of ulcerative colitis & acne
	Antimicrobial effects against infectious organisms
	Remote laser light-induced opening of microcapsules
	Silver/dendrimer nanocomposite for cell labeling
	Molecular imaging of cancer cells
	Enhanced Raman scattering (SERS) spectroscopy
	Detection of viral structures (SERS & Silver nanorods)
	Coating of hospital textile (surgical gowns, face mask)
	Additive in bone cement
	Implantable material using clay layers with starch-stabilized silver nanoparticles
	Orthopedic stocking
	Hydrogel for wound dressing
Dentistry	Additive in polymerizable dental materials Patent
	Silver-loaded SiO_2 nanocomposite resin filler (dental resin composite)
	Polyethylene tubes filled with fibrin sponge embedded with AgNPs dispersion

bind to constituents of the bacterial cell and disturb the usual functions of the cell. Additional possible mechanisms involve the release of Ag cations, which are antibacterial, from silver nanoparticles [86].

6.3.3 Anticancer Activity of Silver Nanoparticles

Conventional plans for combating cancer interference include surgery, radiation therapy and chemotherapy. While several chemotherapeutic agents are now being used on various types of cancers, the side effects are huge, and administrations of chemotherapeutic agents by intravenous infusion is often a deadly process [87]. Hence, it is essential to develop technologies to avoid systemic side effects. Silver nanoparticles perform well as cancer therapeutics as they can interrupt the mitochondrial respirational chain, which makes the generation of reactive oxygen species

(ROS), and ATP synthesis, which can induce DNA damage [88], useful. Moreover, at this stage, numerous researchers are interested in developing nanomaterials as a substitute tool to create preparations that can target tumor cells directly. Some research laboratories have used many cell lines to address the chances of discovering a new molecule to fight cancer. For example, Gopinath *et al.* [89] examined the molecular mechanism of silver naoparticles and found that automatic cell death was concentration-dependent. Furthermore, they detected a synergistic effect on apoptosis using uracil phosphoribosyltransferase (UPRT)-expressing cells and non-UPRT-expressing cells in the presence of fluorouracil (5-FU). Under these investigational conditions, they identified that silver nanoparticles not only induce apoptosis but also alert cancer cells. Furtehrmore, the usage of nanoparticles as a carrier is extremely developed. However, a different feature of nanoparticles that needs close attention is their impressive property of acting as a drug by themselves. The major demand that arises when such features are put into focus is the mechanism by which the nanoparticles avoid the cancer cells. This response is yet to be revealed. Numerous attempts have been made to use silver nanoparticles as an anticancer agent and they have all turned up positive. In addition, the next milestone will be the detection of the mechanism of action. Figure 6.9 displays the possible mechanism by which silver nanoparticles target cancer cells.

6.3.4 Antidiabetic Activity of Silver Nanoparticles

Diabetes is one of the most common and interesting diseases whose prevalence is increasing globally. Type-I diabetes, which is the total deficiency of insulin secretion and related autoimmune damage of pancreatic β-cells, is expected to be widespread among relatives of those with the disease. However, Type-II diabetes, which accounts for 90% of cases, is initiated by the combination of resistance to insulin action and decreased insulin secretion [90]. The aptitude of silver nanoparticles produced using stem extract of *Tephrosia tinctoria* to regulate blood sugar levels was calculated. Silver nanoparticles searched out free radicals, lowered levels of enzymes that catalyze the hydrolysis of composite carbohydrates (α-glucosidase and α-amylase), and improved the consumption rate of glucose [91].

6.3.5 Wound Healing Activity of Silver Nanoparticles

Silver nanoparticles find remarkable use in topical ointments as well as creams used to inhibit wounds, burns and infections. Silver nanoparticles

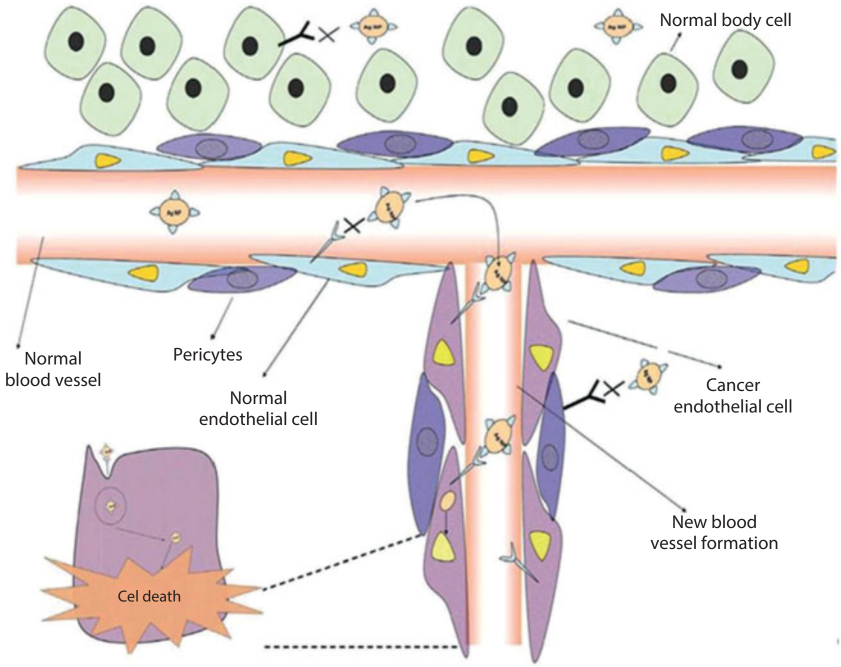

Figure 6.9 Possible mechanism for targeted delivery of silver nanoparticles in cancer therapy.

are extensively used in medical devices and implants. Furthermore, they are also added to consumer products, such as colloidal silver gel and silver-embedded materials, which are now available in generous amounts [92]. Silver nanoparticles manufactured *in situ* within the system of peptide fibers using UV radiation inhibited bacterial growth of *Pseudomonas aeruginosa, Escherichia coli* and *Staphylococcus aureus*. Silver nanoparticles-based hydrogels on HDFa cells did not display any important effect on cell viability. Silver-coated implants, biomedical devices [93] and textile fibers are being actively used for the treatment of wounds or burns, in addition to glass windows and other exterior parts, to preserve cleansing and hygienic conditions. In addition, metallic silver nanoparticles are active microbicides; therefore, they have garnered important attention in many products extending from paints to textiles. Silver nanoparticles synthesized extracellularly using the fungus *Aspergillus niger* are useful in controlling and elaborating cytokines in wound healing, as shown in a rat model [94]. An important reduction in cytokines was detected in wound healing in an average time of 3.35 days for the silver nanoparticles fused onto the cotton fabric and bandages; bacterial clearance was also increased from diseased wounds with no adverse effects [95]. Silver nanoparticles utilize antimicrobial properties, producing reduction in wound irritation and modulation of fibrogenic cytokines. For example, some of the excised tissues were marked for histological analysis and wound area measurement using an H&E stain, which is shown in Figure 6.10. The epithelial tissue, which can be seen at the wound edge, signifies the migration of keratinocytes from the surrounding tissue to the wound bed. Epithelial and dermal tissues were redeveloped from under the wound bed, and cell movement from both sides of the wound margin to the central area of the wound was

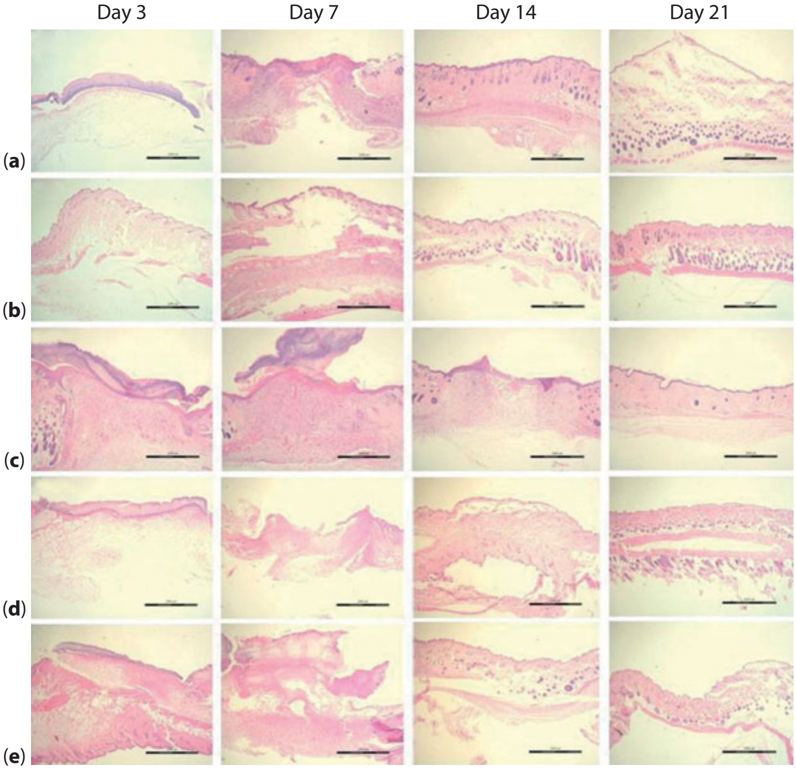

Figure 6.10 CS-AgNPs and AS-AgNPs ointment-stimulated wound closure under histological examination. Wounds were treated as follows: (a) not treated; (b) Silmazin® 1% cream; (c) Vaseline®; (d) CS-AgNPs ointment; and (e) AS-AgNPs ointment. The photomicrographs are representative of sections taken from wounds, which were stained using H&E. CKX41 microscopy (Olympus, Japan) was used at a 40× magnification. Scale bars represent 2000 μm [96].

identified. After 21 days, the skin morphology was somewhat normal, displaying an adequate thickness of the epidermal layer and the dermal layer in the Silmazin® 1% cream, chondroitin sulphate silver nanoparticles ointment (CS-AgNPs), and acharan sulphate silver nanoparticles ointment-treated groups (AS-AgNPs).

Figure 6.11 shows that the high collagen installation was observed along the granulation area in the CS-AgNPs and AS-AgNPs ointment-treated mice. After three days, no newly formed collagen deposition was observed in any group of mice due to the start of the inflammation phase.

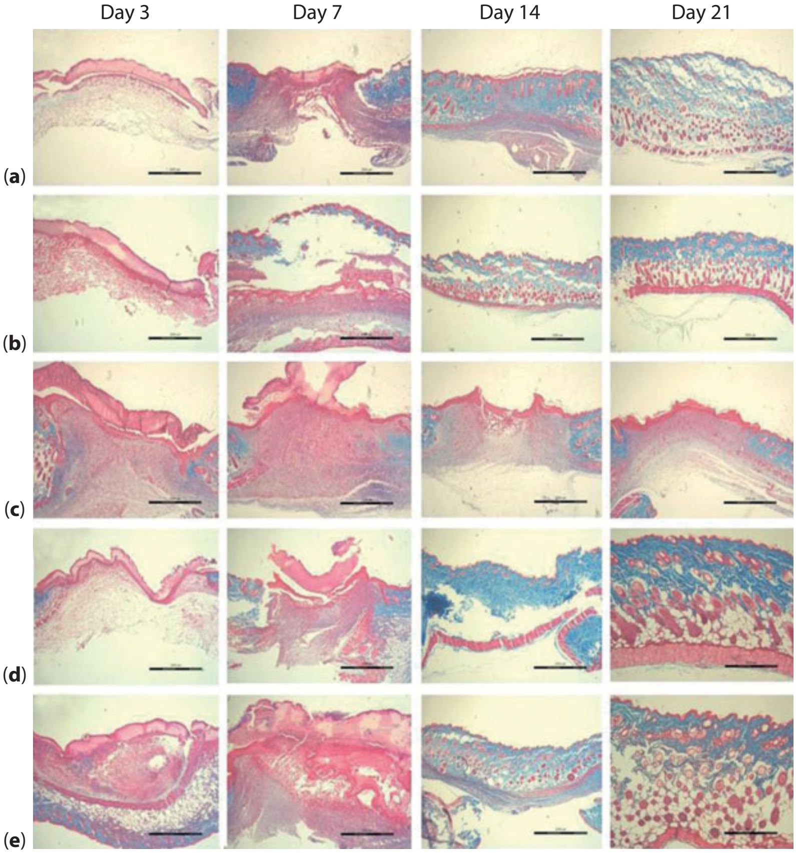

Figure 6.11 The CS-AgNPs and AS-AgNPs ointments accelerate granulation tissue and collagen deposition in the wound area. Wounds were treated as follows: (a) not treated; (b) Silmazin® 1% cream; (c) Vaseline®; (d) CS-AgNPs ointment; and (e) AS-AgNPs ointment. The photomicrographs are representative of sections taken from wounds, which were stained using Masson-Trichrome. CKX41 microscopy (Olympus, Japan) was used at 40× magnification. Scale bars represent 2000 μm [96].

6.3.6 Diagnosis and Imaging Activity of Silver Nanoparticles

Green synthesis was stimulated by scientists to develop new and advanced nanomaterials to offer improved biomolecular diagnosis, imaging and therapy. Silver nanoparticles are prominent for their exclusive and remarkable visual properties (intense color and high scattering of light), which are initiated due to localized surface plasmon resonance (SPR); for example, the mutual oscillations of free electrons at a metal dielectric interface when the frequency of instance light intersects with the frequency of electron oscillation. Moreover, these optical assets of silver nanoparticles are based on many limitations, such as their size, shape, composition and surroundings, along with the three-dimensional (3D) arrangement of elements. The size-reliant absorbance of silver nanoparticles was calculated to expose how the size and composition of nanoparticles can be active in changing the optoelectronic properties [97]. Based on these properties (excitation wavelength), Nie and Emory explained how the size and shape of silver nanoparticles and these nanoparticles are easily enhanced by signals in the region of 1014 to 1015 [98]. These enhancement signal properties were standardized and the results strongly recommend the idea of size-dependent localized SPR subsidizing surface-enhanced Raman signals, which are strong and sufficient to observe single molecules. The plasmonic properties of silver nanoparticles contribute to the large forces which were observed in the surface-enhanced Raman spectroscopy (SERS). Moreover, by using SERS, the Raman signal of a biomolecular analyte can be significantly increased by its being adsorbed onto hot-spot areas of the silver nanoparticles, such as gaps and intersections, primarily due to an increase in signal, which is strong and sufficient to allow even single biomolecule detection. In addition, conjugation of silver nanoparticles to proteins has more applications in imaging, catalysis, biosensing, drug delivery, therapy and control of protein assembly and activity. Walkey *et al.* calculated the interaction of serum albumins with silver nanoparticles, representing a two-fold increase in hysteresis results due to exposure of aggregated silver nanoparticles and the conformational change of serum albumins, signifying that this hysteresis system might be suitable in the bio-detection and bio-analysis applications of silver nanoparticles [99].

6.3.7 Medicinal Textile and Device Activity of Silver Nanoparticles

Green synthesized silver nanoparticles using *A. indica* and *A. dubius* leaf extract were fabricated on cotton cloth and moisture pad samples, which displayed high resistance towards *Corynebacterium,* a sweat bacterium. Moreover, the antibacterial action of gauze cloth discs combined with silver nanoparticles manufactured by green mature thalli of *Anthoceros* exhibited antimicrobial activity against *Pseudomonas aeruginosa*. Based on these antibacterial activities, silver nanoparticles are widely used in medical and functional textiles, such as antibacterial fabrics which claim to prevent infection or deodorize [100]. Furthermore, the use of nanosilver in similar textiles, like home-cleaning textiles, gloves, sportswear, socks, and anti-odor clothes, have been reported.

6.3.8 Catalytic Activity of Silver Nanoparticles

Generally, high surface area and large surface energy evident from metal nanoparticles are necessary for the existence of effective catalytic medium. Developing small particles of silver nanoparticles have been perceived to be more active catalysts than constant colloidal nanoparticles. Silver nanoparticles are of specific interest in the present research of nanotechnology due to their exclusive properties, which can be combined in a broad range of applications such as catalysis, antiseptic agents in the medical industry, cosmetics, food packaging, bioengineering, electrochemistry, and environmental uses. In addition, when compared to their bulk materials, these noble nanoparticles have shown many catalytic activities. Nanocatalysis has generated much attention, giving rise to many new methods. For example, gold, silver, platinum and metal ions are well-known catalysts in the process of decomposition of H_2O_2 to oxygen [101]. Guo *et al.* explain the catalytic potential of silver nanoparticles compared to the gold and platinum nanoparticles in the emission system of chemiluminescence from luminol–H_2O_2 [102]. In this comparison, silver nanoparticles showed higher catalytic response than gold and platinum nanoparticles. Moreover, catalysis of the reduction of dyes by sodium borohydride ($NaBH_4$) can be enhanced by using silver nanoparticles immobilized on silica spheres. In the absence of silver nanoparticles as catalysts, the rate of reaction was almost stationary and it was shown that very little or even no reduction of the dyes occurred. Figure 6.12 shows more catalytic applications.

6.3.9 Toxicity of Silver Nanoparticles

Usually, silver nanoparticles can be regarded as an ideal candidate for numerous applications in many fields. This is particularly true for the biomedical industry, where they are used for diagnosis, cell imaging, drug delivery and implantation, even though some studies have reported that

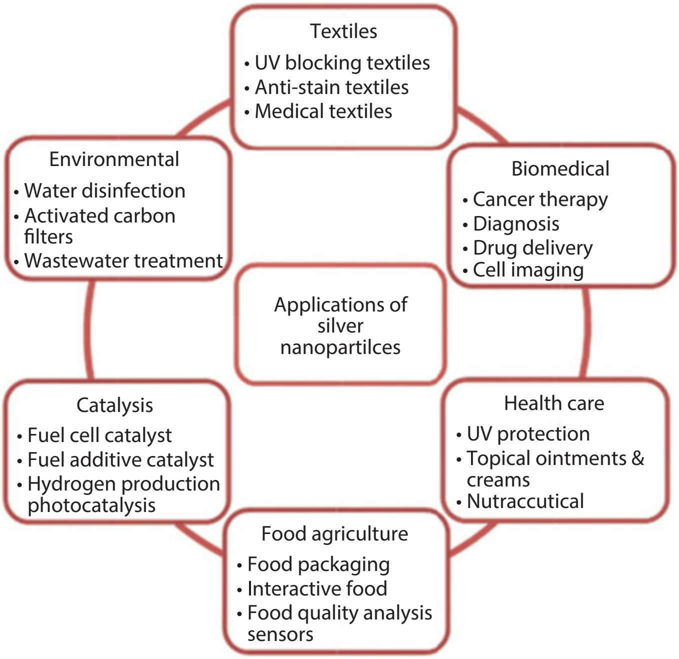

Figure 6.12 Applications of silver nanoparticles.

silver nanoparticles have an adverse effect on humans as well as the environment. One toxicological study on silver nanoparticles showed an *in-vitro* toxicity assay in rat liver cells, which confirmed that silver nanoparticles caused oxidative stress and cessation of mitochondrial function even at low level of exposure to silver nanoparticles (10–50 μg mL^{-1}). Yet, at higher doses (> 1.0 mg L^{-1}), silver nanoparticles revealed an important cytotoxicity and produced abnormal cellular shrinkage, cellular morphology, and attainment of an irregular shape. However, the above-mentioned studies tend to suggest that silver nanoparticles can adversely affect living beings, whilst comparatively less in *in-vivo* toxicology studies. Therefore, further study is essential to assess the toxicity effect of silver nanoparticles in *in-vivo* conditions for estimating their exact toxicity to humans and animals.

6.4 Conclusions

The main advantage of green methodology in the synthesis of nanoparticles over microbes, algae and plants is that the procedure can overcome the time-consuming system of culturing microbes and putting in appropriate safeguards against losing the potentiality of synthesis of nanoparticles. These green synthesized silver nanoparticles are cost efficient, easy to synthesize, and focus on greener methodologies. Therefore, increasing awareness of green chemistry and use of the green route for preparation of silver nanopartcles leads to a desire to improve eco-friendly methods. Moreover, in spite of the fact that many biological substrates have been used for the manufacture of silver nanoparticles, the use of plants, algae and yeasts for the facile robust synthesis of silver nanoparticles is largely due to their ready availability, nonhazardous nature, variety of choices available, and the advantage of quicker synthesis over other techniques. Essentially, the green synthesis of metal nanoparticles using plant extracts have different uses, such as in therapeutics, pharmaceuticals, ecological and renewable energy as well as other commercial products; and have an estimated effect on diagnosis and action of numerous diseases with precise side effects. In addition, silver nanoparticles have a widerange of bioactivities which make them favorable agents not only in aggressive infections but also in attacking malignant tumors and, particularly, multidrug-resistant cancer cells. Silver nanoparticles are also used in cancer diagnosis and treatment monitoring. Numerous anticancer studies are underway in *in-vitro* analysis and a few *in-vivo* studies. Hence, this is an exposed area for several novel studies in cancer treatment with silver nanoparticles. Currently, the application of silver nanoparticles has been growing in many areas such as molecular diagnosis and imaging, drug delivery, cancer therapy, cure of vascular diseases and wound curing; and extended to include novel medical devices such as catheters with antimicrobial properties. Similarly, these silver nanoparticles would offer a potential solution to the present energy crisis by discovering their use as energy-driven devices.

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