Journal of Controlled Release xxx (xxxx) 1–30

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Review article

Bioinspired and biomimetic micro- and nanostructures in biomedicine

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ARTICLE INFO

Keywords:
Bioinspired
Biomimetic
Biomedicine
Micro
Nano

ABSTRACT

Bioinspired and biomimetic micro- and nanostructures have a high significance in the field of biomedicine. In this review, the possible applications of these micro- and nanostructures that come across in our daily life and inspired by nature itself are presented. Also, the biomimetic and bioinspired systems related to micro- and nanostructures in biomedicine are also described. The role of bioinspired and biomimetic micro- and nanostructures in therapeutics, especially in anti-inflammatory and wound healing, development of bioinspired medical devices, tissue engineering, drug delivery, gene delivery, pressure sensors, and bioprinting are discussed. The biomimetic and bioinspired systems using carbon-based nanostructures, polymer nanocomposites, hybrid scaffolds, polymer networks,and protein nanostructures are also reviewed. The advantage of these bioinspired and biomimetic structures is derived from their high biocompatibility when compared to the synthetically derived micro–/nanostructures. By developing deeper knowledge and overcoming the associated challenges, these micro- and nanostructures present a promising solution for many unresolved problems in biomedicine.

1. Introduction

Nature is the best role model for humans from which the ocean of knowledge arises. The idea of gaining knowledge from Mother Nature is as old as human life. In the past few decades, there was tremendous progress in the biomimetic and bioinspired systems. Other suggestive names for biomimetic are bionics, biomimicry, and biognosis. The term 'Biomimetic' is derived from two Ancient Greek words 'bios' meaning life, and 'mimesis' means to imitate. Biomimetic system directly mimics the techniques or processes exhibited by the natural/biological system and on the other hand bioinspired system directly or indirectly mimics a natural/biological system. The success of this innovative approach for the generation of biomimetic and bioinspired micro- and nanostructures lies within the selection of ideas and novel principles and their appropriative applications to the different engineered systems. Different biological molecules have the ability to interact specifically with different systems or to the targeted systems of our body; from this idea, a similar/identical system can be developed which mimics the whole system. The mimicking/inspiration may range from unicellular organisms like bacteria, viruses, etc. as a carrier system to the world's most enormous creature whale from which the design of ships are inspired [1]. Both biomimetic and bioinspired technology will serve as a bridge between nature and science. Furthermore, the development of bioinspired and biomimetic micro and nanostructures (MNS) have different fields of application like drug/gene delivery, healing biological system, in textile industries (bioinspired fur from the polar bear), waterproof effect (lotus leaf), and even more the idea using micro/nanostructures must be taken into consideration because both of them have a wide variety of properties and structural characteristics which must be exploited for newer discoveries [2–4].

The leaves of lotus and petals of rose have micro/nanostructures which are superhydrophobic in nature. Rose petal surface contains a cluster of micropapillae, and each of them, in turn, has too many nanofolds [3,5]. The lotus leaves possess wax-coated nanostructures in the form of protrusions. The shape and size of the protrusions can vary according to the *species* like *Nelumium speciosum, Nelumbo komarovi,* and *Nymphaea nelumbo* in the form of hairs, tentacles and so on [6]. The butterfly wings are the most unique system, which has a number of tremendous features. Wings are covered with thousands of colored scales of micro-size; these are further modified by plate-like setae, anti-

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https://doi.org/10.1016/j.jconrel.2022.02.013
Received 22 October 2021; Received in revised form 9 February 2022; Accepted 10 February 2022
0168-3659/

fogging surface, and tile-like microstructures [3,7]. Carnivorous animal polar bears consist of thick layers of hollow hairs of white color and have the capability to keep them warm in cold conditions. Seashells are the exoskeletons of invertebrates and are mainly composed of calcium carbonate. It is enriched with well-organized bio-minerals having high thermal conductivity, the toughness from which bioinspired ceramics are developed [8]. Spiders are one of the great architectures of nature. It possesses micro-structured *spigots*, each produces a filament enriched with protein from which silk threads are produced. These threads are usually used for catching prey, it is water and light-resistant, so this can be mimicked to create different fabrics of water-resistant capacity [9]. Geckos, tree/torrent frogs have high adhesion capacity. Their paws are contained with thousands of nanopillars responsible for both wet and dry adhesion [10]. A schematic presentation of some natural structures and the derived bioinspired and biomimetic systems or applications is shown in Fig. 1.

Meanwhile, micro-and nanostructures have a significant role in biomedical applications ranging from delivery of therapeutically active moieties, tissue engineering, as cell-laden matrices, fabrication of transdermal drug delivery systems, biosensing, bioimaging, bio-inks for 3-D printing, as prebiotics, and even as artificial cells [11–16]. Microparticles are mainly used for drug delivery, scaffold building, and biofabrications. Microparticles formed from natural polymers are useful in biomedical applications, while those from synthetic polymers are useful in both biomedical and industrial applications. The micro-and nanostructures can entrap the bioactive or chemical entities without losing their activity and can deliver it to the specific sites in a controllable manner. Thus, newly developed bioactive chemical molecules can be easily entrapped and delivered with various micro-and nanostructures for future studies with less toxicity [17]. Application of biological properties on micro-and nanostructures will get the combined effect of biocompatibility and biodegradability. Furthermore, inbuilt properties of micro-and nanostructures desirable for body conditions are added advantages [18]. Thus, the development of bioinspired and biomimetic micro-and nanostructures would have impactful results in their future biomedical applications.

2. Superhydrophilic and superhydrophobic surfaces

Ultra hydrophobic or superhydrophobic surfaces are extremely hydrophobic, i.e., the surfaces that are difficult to wet. The contact angle between the water drop and the superhydrophobic surface is more than 150°; the water drops getting contact with these surfaces effortlessly roll off and this condition is often termed as lotus effect or petal effect. The researches on the development of superhydrophobic and superhydrophilic had begun from the early stages of the 1970s itself. This is mimicked by the sensors on the traffic signals, i.e. self-cleaning glasses or to develop stain-resistant fabrics. The superhydrophobic surface is also possessed by wings of butterflies, moths, flies, and so on [19]. On the other hand, superoleophobic surfaces are those with a contact angle of more than 150° along with a low contact angle for liquids with low surface tension such as oil and alcohol. This surface is more prominent in underwater creatures because they are not being affected by oil spoilage or by other polluting agents in water. Insects have a certain microscopic structure called brochosomes on their surface that shows the superoleophobic effect; which protects them from external pollution [20].

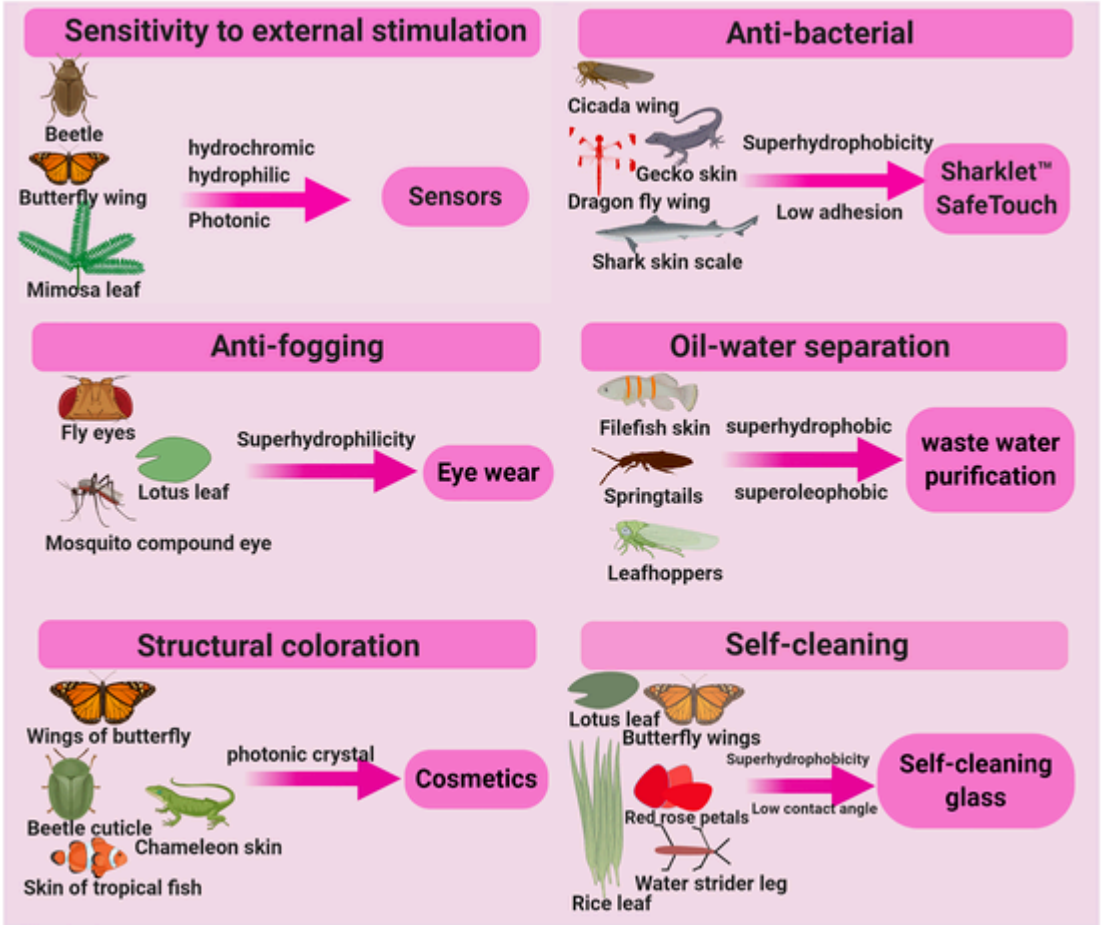

Fig. 1. Schematic presentation of some natural structures and the derived bioinspired and biomimetic systems or applications.

Superhydrophilicity (*self-cleaning*) is a condition in which the surfaces have a greater attraction to water (extremely hydrophilic) and the contact angle is equal to 0°. The superhydrophilic surface is a characteristic feature of the aquatic ecosystem, especially scales of fish, shark fins, lizard's skin, and cactus are other examples. Shark fins are mimicked to produce swimming suits [19]. In the future, this kind of surfaces can be vigilantly applied to the medical research field for the development of stain and water-resistant fabrics for medicinal applications, mainly in surgical procedures, which helps to avoid the chance of getting contaminated with microbial growth. Microbial growth is a major concern of the fabric dealing with the wet surfaces. Thus, they can serve as a platform for newer applications for future medical application. Fig. 2 illustrates various natural superhydrophilic and superhydrophobic systems.

Recently a superhydrophobic photonic composite was reported with angle-independent colors and self-healing ability. The composite was developed by attaching a photonic glass on a healable supramolecular polymer with segments of hydrophobic polydimethylsiloxane. The self-cleaning, angle-independent colors, and non-wettability properties open up applications in the field of coloring, coating and large area antifouling. The composite's self-healing ability and mechanical durability are vital in the development of wearable devices and biomimetic decorative materials [21].

3. Biomimetic syntheses of micro- and nanostructures

Biomimetic synthesis aims to synthesize nanostructures through possible reaction series to produce the desired products either mimicking or inspired by the living things or other biologically active structures in nature. Biomimetic nanostructures can be synthesized either by functional biomimetic synthesis or biomimetic process synthesis. The former type mimics the specific properties of natural substances, systems, or structures, and the later mimics the methods/process routes of natural substances/systems [1].

Chitosan/ calcium phosphate (CS/CaP) flower-like microparticles can be used as a pH-sensitive carrier in a drug delivery system (DDS) to achieve sustained release of the drug. CaP is an inorganic material found in the body with good biocompatibility and degradability. Due to its rigid and brittle nature which is not suitable for drug delivery makes CaP forms hybrids with polymers. CS can be used to make a hybrid with CaP and can avoid the brittle nature of the CaP. CS/CaP composites like hydrogels, microspheres are not suitable for drug delivery due to low drug loading capacity, inconvenience in administration, and unstable in GIT. Flower-like microparticles have a high specific surface area and good absorption. So, these CS/CaP flower-like microparticles can be used for the absorption of dye and immobilization of enzymes. Its specific surface area is about 52 m^2/g, which is greater than that of other hybrid composites of CS/CaP. Due to the large surface area, flower-like microparticles of CS/CaP have excellent adsorption than other DDS. Its biocompatibility and sustained release in intestinal pH make them suitable for drug delivery to the intestine [22].

The eggshells are considered as waste material, and it consists of 95% calcium carbonate. So, it can be used for the synthesis of calcium-rich materials for bone-related problems. Calcium hexahydroxostannate microparticles can be synthesized from eggshells by a simple approach. Cleaned eggshells were converted to fine powder. This eggshell powder (calcium source) and tin chloride ($SnCl_2$) are dissolved separately in water and sonicated at ambient temperature for 30 min. These solutions are then mixed and subjected to sonication for 2 h. The product obtained after sonication is subjected to centrifugation at 4000 rpm to obtain a precipitate. The precipitates are separated, washed, dried using a vacuum oven, and finally ground to a fine powder [23].

Polymeric microparticles are generally synthesized by emulsion polymerization. However, this technique require high energy, and the surfactants and other initiators used during the process are very difficult to remove at the end of the process. Starch molecules have self-assembling property, this nature of starch can be used for the production of spherical shaped microparticles. Glucans obtained from waxy maize starch can be used for the production of microparticles. These mi-

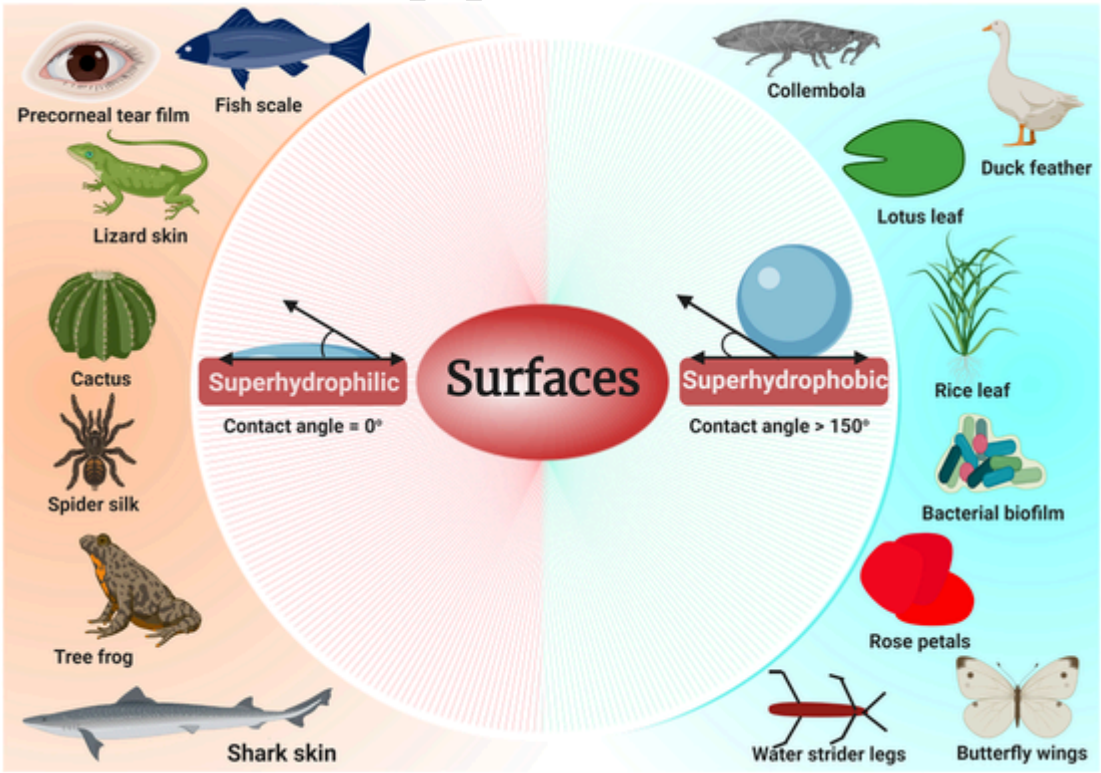

Fig. 2. Various natural superhydrophilic and superhydrophobic systems.

croparticles from maize starch glucan can be used in colon-specific drug delivery because it doesn't get digested in the intestine. Waxy maize starch was dissolved in sodium acetate buffer and heated to promote gelatinization. After cooling, to this gelatinized solution, pullulanase was added and incubated for 24 h. Then it is subjected to centrifugation for 5 min at 15000 rpm. The supernatant solution was collected, and chitosan was added to it and again incubated for 24 h at 4 °C to promote the self-assembly of polymeric microparticles. The prepared microparticles are then collected and washed with deionized water. By using this method, highly monodisperse microparticles can be produced [24].

Poly-2 pyrrolidone (PPD) is a biodegradable and biocompatible polymer. PPD microparticles can be synthesized by ring-opening polymerization of PPD in the presence of bovine serum albumin (BSA) and iron fillers. Synthesis of these magnetic responsive microparticles does not require any solvents or other substances. PPD, BSA, and iron were stirred together for 30 min at room temperature. After 30 min, the mixture was dispersed in acetone and then filtered to remove the untreated PPD. The resultant mixture was dispersed in NaCl and filtered; then, it was washed with borate buffer and then finally with water [25].

Bio-based hybrid microparticles can be synthesized by using the combination of castor oil silylation and thermostabilized emulsion process (TEP). Castor oil/ silica hybrid microparticles can be used for the encapsulation and delivery of poorly water-soluble drugs. Silylation of castor oil was done by the use of (3-isocyanatopropyl) triethoxysilane and. it is then subjected to the TEP process. The poorly water-soluble drug was dissolved in silylated castor oil (oil phase). By using acetate buffer as the aqueous phase, an emulsion(O/W) was formed at 60 °C and 9000 rpm. To gel the aqueous phase, a temperature shift from 60 to 4 °C was applied and it is subjected to a sol-gel reaction. After the solidification of hybrid microparticles, they were washed with water, separated, and then freeze-dried [26].

Cordiamyxa leaf extract can be used for the synthesis of zinc oxide (ZnO) microstructures. This green synthesis of ZnO microstructures can be used as antifungal and antimicrobial agents. Solution combustion synthesis was used for the preparation of ZnO microstructures from this myxa leaf extract. The phenolic group present in this myxa leaf extract can act as a reducing agent for the synthesis of ZnO microstructures. Here, the leaf extract and zinc nitrate (zinc precursor) were mixed and stirred thoroughly to get a homogenous mixture and then it was subjected to calcination. The ZnO microparticles get precipitated as a white milky product. This method is low cost and environment friendly, and the produced microstructures show antibacterial property against both Gram-positive and Gram-negative bacteria [27].

The functionalization of nanoparticles or the use of a bioinspired system results in the enhanced stability of various approaches to drug delivery. Yeast microcapsules can incorporate various charged particles by electrostatic interaction. Among them, biomimetic insulin loaded yeast microcapsule is a promising approach for oral insulin delivery where the insulin is combined with yeast microcapsule by electrostatic interaction and further coated with alginate to bypass the acidic pH of the stomach. The glucan particles of the baker's yeast provide receptor-mediated uptake of the drug by phagocytic cells through M cell-mediated transport and deliver the drug to systemic circulation by lymphatic route [28]. Bioinspired supramolecular dendritic systems can be used for tumor-specific drug delivery. The dendrimers have hydrophilic and hydrophobic segments. The hydrophilic segment is shielded with polyethylene glycol (PEG) chains, and the hydrophobic part forms conjugation with anticancer drug doxorubicin. In this supramolecular dendritic system, the PEG shielding provides a longer circulation time. This is also capable of crossing various barriers present in the body. So this bioinspired system can be used for targeted delivery of anticancer drugs [29].

Lead oxide nanoparticles (PbO NPs) can be synthesized from rosemary leaves. This bioinspired synthesis of PbO NPs is a cost-effective and environment-friendly alternative for the synthesis of these NPs. Plant extracts are used as reducing agents for the NPs synthesis process. Rosemary leaves were washed and sterilized, and then they were immersed in deionized water and boiled at 80 °C. The obtained extract was filtered, and the precursor lead acetate was added to it and then acidified to get a pH of 4.6. The resultant solution was allowed to cool to room temperature, and then the PbO gets precipitated and then dried in an oven. The dried powder was then annealed in a crucible at 600 °C results in the formation of green to brown colored PbO NPs [30].

Biomolecules and other naturally occurring substances have good biocompatibility, and they can be used for the synthesis of bioinspired carbon dots. Biodots are a class of fluorophores with many biological and chemical properties. These biodots with biomimetic functions can be synthesized from proteins, nucleic acids like biopolymers, small molecules such as glucose, and also from many plants or animal extracts. Biodot synthesis involves two approaches, one is bottom-up which involves the use of small molecules such as amino acids. Thisapproach has better reproducibility than the top-down approach. The second one is the top-down approach, which involves the use of large natural biomass products. Biodots have stable photoluminescence, so this can be used in bioimaging applications due to their biocompatibility, stability, and fast cellular uptake. Some biodots exhibit pharmacological properties so that they can be used in theranostic applications. In this field, anticancer agents like doxorubicin and platinum-based drugs can be loaded into biodot for their targeted delivery. Some biodots can be used to provide beneficial health effects like anti-cancer, tumor inhibition, anti-microbial and hemostatic effects [31].

Bioinspired gold nanoparticle (AuNPs) synthesis is a cost-effective method. Natural RBC membranes can be used to coat AuNPs, which provide long circulation and photothermal effects in tumor tissues, and also it can eliminate non-targeted side effects. Leukocyte membrane coated AuNPs shows the stimuli-responsive release of the loaded drug and high site-specific drug delivery. AuNPs can also be inspired form dopamine chemistry. The catechol group present in the dopamine can easily undergo chelation with metal ions and have reduction capability. So, this property of dopamine can be used for the synthesis of AuNPs [32]. Protein inspired nanoparticles are biocompatible, improves pharmacokinetics, nonspecific adsorption, and simple synthesis. Glutathione S transferase is an endogenous protein found in humans. It is capable of incubating AuNPs with high quality and also can eliminate the use of high temperature and reducing agents for the synthesis. The formed AuNPs shows the uniform size and high imaging performance. It also exhibits a theranostic application with the use of gadolinium. It shows good targeting property without systemic toxicity and low immunogenicity (Fig. 3a) [33].

Bioinspired synthesis of gold NPs (Au NPs) can also be achieved by using plant extracts. These synthesis methods are non-toxic, renewable, and inexpensive. AuNPs can be synthesized from oil palm leaf extract without the use of any additional reagents. Here, gold chloroauric acid was used as a precursor and was mixed with the leaf extract. The leaf extract act as stabilizing and reducing agent in this bioinspired synthesis results in the formation of spherical shaped AuNPs for drug delivery and other applications (Fig. 3b) [34]. The biomimetic synthetic nanoparticle can be developed from natural mammalian cells for drug delivery. Natural killer (NK) cells provide immunosurveillance for cells that are stressed or diseased. This NK cell inspired NKsome can be developed, and it is a fusogenic liposome for providing targeted drug delivery, especially for tumor tissues. The surface of NKsome contains NK cell-associated protein and shows a greater affinity towards tumor tissues. So NKsome can be used for the targeted delivery of anticancer agents [35].

Biomimetic bovine serum albumin-based nanoparticles can load hydrophilic (indocyanine green) and hydrophobic (gambogic acid)

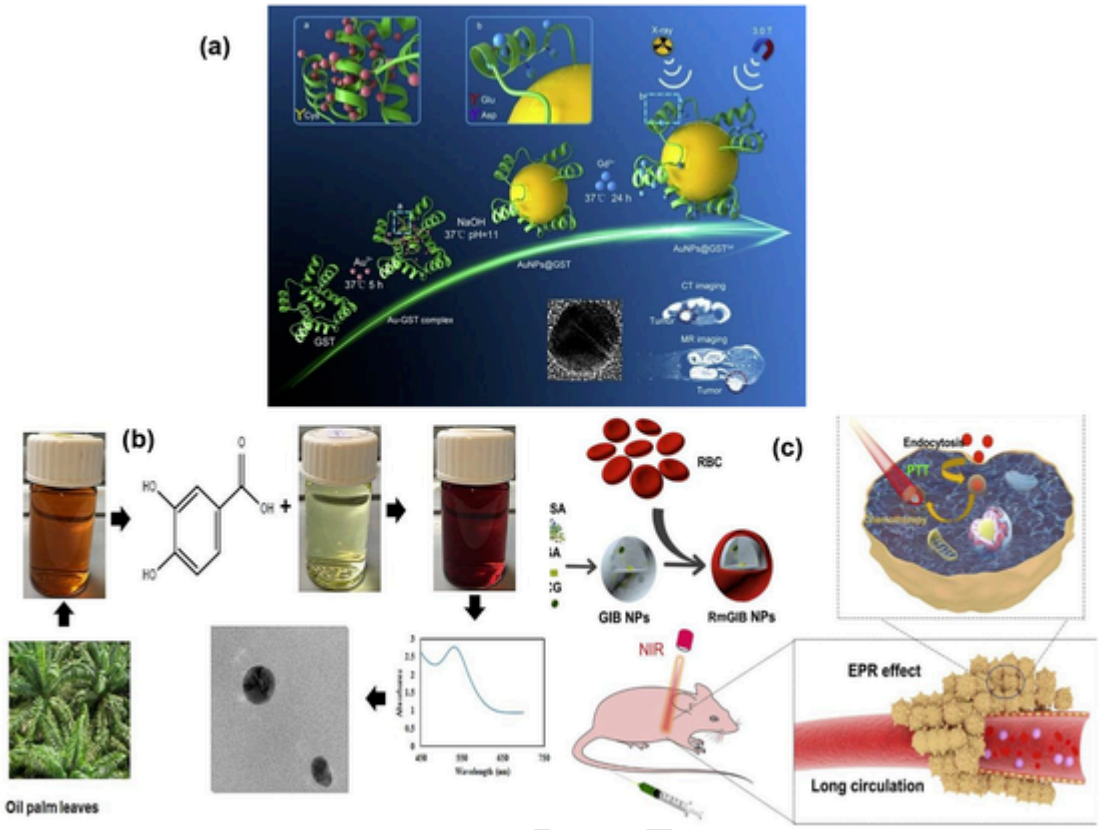

Fig. 3. Schematic representation of biomimetic syntheses. a) Glutathione S inspired AuNP for targeted delivery. Reproduced with permission from Ref. [33]. Copyright 2018, Elsevier. b) Bioinspired synthesis of gold nanoparticles for drug delivery. Reproduced with permission from Ref. [34]. Copyright 2017, Elsevier. c) Biomimetic bovine serum albumin-based nanoparticle for cancer therapy. Reproduced with permission from Ref. [36]. Copyright 2020, Elsevier. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

agents. These nanoparticles are further coated with red blood cell (RBC) membranes to enhance circulation time and also to eliminate the premature release of the drug from the NPs by the immune system. The RBC coated NPs have a high affinity towards both hydrophilic and hydrophobic agents and thereby exhibit high drug loading efficiency. These NPs shows a greater accumulation rate in the tumor site and low toxicity. So, these bioinspired RBC coated NPs can be used for cancer therapy due to their high loading capacity and low toxicity (Fig. 3c) [36].

High-density lipoproteins (HDL) are naturally occurring nanoparticles, having good biodegradability, biocompatibility, and low immunogenicity. This HDL can circulate for a longer period and transport substances like proteins, lipids, and RNA to the target sites. Its targeting property makes them more suitable for drug delivery. Inspired by this, reconstituted HDL (rHDL) nanoparticles with similar properties that of HDL can be prepared and can act as a good carrier for drugs by eliminating all the barriers in drug delivery. The stability of the nanoparticles gets enhanced, and the half-life gets increased. It can achieve the delivery of drugs and other agents through all the membrane barriers to the targeted site [37].

Physicochemical properties of stimuli-responsive polymers can change with changes in the surrounding environment. The layer by layer technique can be used to modify the surface of biomaterials. This technique can be used to prepare stimuli-responsive polymer coatings using elastin-like recombinamers responsible for the special sequences to change physicochemical properties. This makes them more suitable for many biomedical and biological applications [38]. Copper nanoparticles are used for the treatment of microbial infections due to their antimicrobial properties and can be developed by using fungal based synthesis. This bioinspired synthesis is cost-effective, easily scalable, and environment friendly as compared to the conventional synthesis procedures. Here, copper sulfate was added to fungal filtrate (*Aspergillus niger)* and incubated for 24 h at room temperature. This method involves a single step, and the resultant copper NPs can be used as anticancer, antidiabetic, and antibacterial agents [39].

The silver nanoparticles (Ag NPs) are active against multidrug-resistant pathogens. Bioinspired synthesis of Ag NPs from medicinal plant extracts or microorganisms became important because there are no harmful/ toxic chemicals and materials required, and the plant extract itself acts as a stabilizing agent. Bioinspired synthesis consists of eco-friendly reactions, non-harmful chemicals, and easily available and low-cost materials for synthesis. Bioinspired synthesis of Ag NPs is carried out by using the medicinal plant extract of *Gardenia resinifera.* Plant leaves are washed, dried, and the methanolic extract of the leaves is prepared. This extract is added dropwise to silver nitrate solution at 200 rpm and at room temperature to carry out the reduction of Ag^+ to Ag. The solution changes color from green to brown, indicating the formation of Ag NPs. It is then collected and centrifuged at 10000 rpm and dried at 40 °C. These Ag NPs synthesized are more effective against *Escherichia coli* and *Staphylococcus aureus* [40]. The small intestinal submucosa which is rich in collagen and other growth factors has been used for the purpose of repairing the damaged tissue. The disadvantages like poor mechanical properties limit its application. In a recent study, a biomimetic small intestinal submucosa has been prepared using chitosan and elastin. This system offers better mechanical properties, and also it improved viability and fibroblast proliferation. The chitosan and elastin were added to improve the properties like antibacterial activity and biodegradability. The studies revealed that they can be used for repairing walls of the abdomen [41].

Calcium is an essential mineral for life. Being rigid and its brittle nature, it is incongruous for drug delivery. So this problem can be solved by converting to hybrids using various micro-nano structures of biological origin or introducing biosynthetic substitutes, more precisely calcium produced from biomaterials of the human body, and this will be helpful in the deficiency conditions also. This will also pave the way for the future development of delivery systems, especially the drugs which are difficult to deliver alone. Various biomimetic syntheses of micro and nanostructures are given in Table 1.

4. Bioinspired researches on therapeutics

4.1. Antibacterial surfaces

The greatest challenge behind the utilization of antibiotics is the development of bacterial resistance. If the resistance is more, it will be difficult to treat; thus, huge research is ongoing with an intent to prevent bacterial infections. The success of the study will be a generation of an antibiotic that can destroy the bacteria completely. The method will be costlier, or higher dose antibacterial agents has to be prescribed. So, an alternative method is sought by the scientists for the development of antibacterial agents from nature. It was observed that certain plant and insect surfaces have antimicrobial surfaces, which can protect themselves from pathogenic bacteria. Dragonfly wing, gecko skin, cicada wing, etc., are some of them. These naturally occurring bactericidal surfaces have nanopillars of 50–250 nm diameter. Also, superhydrophobic surfaces are also found to be non-sticky to microbes; thus, they prevent bacterial growth, while hydrophilic surfaces allow bacterial proliferation [42]. The surface of the wings of the insect Cicada has antibacterial activity against *Pseudomonas aeroginosa.* Even though their wings are superhydrophobic in nature, microbes can adhere to the wing surface. They undergo some morphological changes and microbes were killed within 5 min. However, Cicada wings are effective against Gram-negative bacteria but not against Gram-positive, because of their thick peptidoglycan cell wall [43].

Several artificial surfaces mimic these natural surfaces were developed, which shows excellent bactericidal activity. These artificial and bio-inspired surfaces to include black silicon, diamond nanocone and diamond coated black silicon, titania nanowire array, structured polystyrene surface, Au nanostructured surface, etc. Another example shows the antibacterial surface prepared from silicon-based micro/nanostructures. Silicon mimics natural bactericidal surfaces by reproducing the geometric features and surface chemistry of the wings of Cicada and Dragonfly, and leaves of lotus and taro plants. Black silicon surfaces were developed by using reactive ion etching of silicon; its bactericidal activity mimics the dragonfly wing, however it is more effective active against both Gram-positive and Gram-negative bacteria than dragonfly wings.

Titania is a material with high biocompatibility, chemically inertness, and mechanical stability. Titania nanostructured surface is fabricated by the alkaline hydrothermal process. Their activity was found to be against motile bacteria than non-motile. Titanium nanopatterned arrays were developed by the chemical hydrothermal process at high temperature, and it mimics the dragonfly wing and shows bactericidal activity against *Pseudomonas aeroginosa* and *Staphylococcus aureus.* Polymethyl methacrylate (PMMA) fabricated with periodic nanostructures using nanoimprint lithography, which possesses hydrophobicity and bactericidal activities [42]. Natural and bioinspired antimicrobial surfaces, their composition, and activity are given in Table 2.

4.2. Antibacterial activity

Biomimetic antibacterial structures are developed with the help of different polymers. Chitosan is a natural, biodegradable, and non-toxic polymer obtained by deacetylation of chitin. The studies proposed that

Table 1
Biomimetic synthesis of various micro and nano structures and their applications.

Bioinspired micro and nanostructures	Biologically active structures used	Applications	References
Chitosan calcium phosphate flower-like microparticles	Calcium phosphate	• pH sensitive drug delivery system • absorption of dye • Immobilization of enzymes	[22]
Calcium Hexahydroxostannate microparticles	Egg shells	• Calcium-rich materials for bone-related problems	[23]
Polymeric microparticles	Maize Starch	• Colon-specific drug delivery	[24]
Poly-2 pyrrolidone microparticles	bovine serum albumin	–	[25]
Castor oil/ silica hybrid microparticles	Castor oil silica	• Delivery of poorly water-soluble drugs	[26]
zinc oxide microstructures	*Cordiamyxa* leaf extract	• Antifungal and antimicrobial agents	[27]
Yeast microcapsules	yeast	• Incorporate various particles by electrostatic interaction • Receptor-mediated uptake of the drug	[28]
Lead oxide nanoparticles	rosemary leaves	• Cost-effective • Environment-friendly synthesis	[30]
Biodots	proteins, nucleic acids like biopolymers, and small molecules such as glucose	• Theranostic applications • Anti-microbial and hemostatic effects	[31]
Gold nanoparticles	RBC membranes	• Long circulation time • Photothermal effects in tumor tissues	[32]
	Dopamine	• Stabilizing and reducing agent	[32]
	Glutathione S transferase	• Eliminate the use of high temperature and reducing agents for the synthesis • Uniform size and high imaging performance	[33]
	Oil palm leaf extract	• stabilizing and reducing agent	[34]
NKsome	NK cells	• Targeted drug delivery	[35]
RBC coated BSA nanoparticles	RBC BSA	• Eliminate the premature release of the drug • Longer circulation time • Hydrophilic and hydrophobic drug loading	[36]
Reconstituted HDL (rHDL) nanoparticles	High-density lipoproteins	• Longer circulation time • Transport of substances like proteins, lipids, and RNA to target sites	[37]

(*continued on next page*)

• Table 1 (*continued*)

Bioinspired micro and nanostructures	Biologically active structures used	Applications	References
Copper NPs	*Aspergillus niger*	• Single step synthesis • Anticancer, antidiabetic, and antibacterial applications	[39]
Ag NPs	plant extract of *Gardenia resinifera*	• Effective against *Escherichia coli* and *Staphylococcus aureus*	[40]

chitosan has a bacteriostatic effect on all bacteria, except *Salmonella typhimurium,* and their oligomer has bactericidal activity against all bacteria [60]. A quarternized chitosan/polyvinyl alcohol (PVA) having a 60 nm diameter shows excellent antibacterial activity than chitosan. PVA also possesses antibacterial activity because of its hydrophilicity. 8- hydroxyl quinoline immobilized chitosan shows antibacterial and antimycotic activity [61]. Another compound is nisin, which shows antibacterial activity. Nisin is a peptide that has broad-spectrum antibacterial activity, especially against food spoiling bacteria, and thus this is used as a food preservative. Nisin loaded poly-L-lactide nanoparticles are prepared by GAS precipitation technique and which shows antibacterial activity for a long time. This is used as a food preservative and pharmaceutical preservative [61]. Another example is silver nanoparticles and their antibacterial activity. These nanoparticles efficiently cross the cell membranes of the bacterium causing the destruction of the cell contents as well as lysis of the cell membrane. The main reaction is in between the sulfur-containing proteins of the bacterium and silver ions. Both have a high affinity to each other, which makes the silver ions bind, causing the disruption of the entire system including respiratory, and multiplication to stop later cell death [62,63].

Metal nanoparticles like AgNPs can be prepared by using *Bacillus* species. Now it can be prepared from *Pseudomonas aeuroginosa* biomass extract. The AgNPs can be captured within the graphene oxide (GO) sheets to provide a high surface area. So, this AgNP-GO shows a synergistic effect on antimicrobial activity, especially against *E. coli* [64]. The biomass extract of *Pseudomonas aeruginosa* has the capacity to form nanoparticles because of the presence of terpenoids and alkaloids within it. The AgNPs on graphene sheets were synthesized by using this microorganism. They show higher toxicity against pathogenic microorganisms. Then the studies revealed their capacity to inhibit the growth of both Gram-negative and Gram-positive bacteria like *Escherichia coli* and *S. aureus,* respectively [64]. The antibacterial activity of nanoparticles like chitosan, silver, gold, nicin, etc., which can be used in the food, medicines, and water purification as well as during the manufacturing stage to restrict the bacteria from its multiplication.

4.3. Anti-inflammatory activity

The inflammatory response is a complex process involving many cells and chemical modulators for protection from infection. The common inflammatory disorders include rheumatoid arthritis, pneumonia, gastritis, psoriasis, etc. Immune cells are mimicked for the development of bioinspired nanoparticles for targeting inflammation. Liposome surface was conjugated with a targeting ligand, I domain of Lymphocyte Function Associated Antigen-1 (LFA-1), and is directed towards inflammatory sites, which is less toxic and are localized in the inflammatory areas. Biotinylated-SLex conjugated on avidin modified PLGA microspheres and were targeted towards selectin, this stimulates leukocyte adhesion. Similarly, leukocyte membrane proteins such as LFA-1, macrophage adhesion molecule-1(Mac-1), P-selectin glycoprotein ligand-1(PSGL-1), etc. were also coated on liposomes to form a proteolipid vesicle and is targeted towards inflammatory vasculatures [65].

Table 2
Natural and bioinspired antimicrobial surfaces, their composition, and activity.

Nano/micro structures	Composition	Activity	References
Natural antimicrobial surfaces			
Gecko skin	Dome shaped scales arranged in a hexagonal patterning.	Active against *Porphyromonas gingivalis* (Gram-negative bacteria)	[44]
Cicada wing	Nanopillar arrays	Mechanical rupture of *Pseudomonas aeruginosa*	[45]
1. Megapomponia intermedia 2. Ayuthia spectabile 3. Cryptotympana agulia	Nanopillars of different scale	Active against *Pseudomonas fluorescens*	[46]
The wings of *Tibicen tibicen* (dog day annual cicada)	Hexagonally close-packed arrangements of spherically capped cones	Active against *Saccharomyces cerevisiae*	[47]
The wings of *Magicicada septendecim* (brood II periodical cicada)	Hexagonally close-packed hemispherical bumps	Active against *S. cerevisiae*	[47]
The wings of *Progomphus obscurus* (common sanddragon)	Hexagonally close-packed arrangements of spherically capped cylinders	Active against *S. cerevisiae*	[47]
Bioinspired antimicrobial surfaces			
- Diamond nanocone surfaces - Inspired from cicada wings	More varying cone dimension, sharp tipped nanocone nonuniform arrays	Active against *P. aeruginosa*	[48]
- Black silicon - Inspired from the wings of the dragonfly Diplacodes bipunctata	Nanoprotrusions on the surface	Effective against Gram-negative and Gram-positive bacterias and endospore	[49]
- Diamond coated black silicon	Nano-protrusions, such as spikes or needles	Lethal to both Gram-negative and Gram-positive bacteria at high rates	[50]
- Ion etched Silicon wafer super surface - Inspired from the wings of dragonfly	Nanopillars with random inter-pillar spacing.	Active against both gram negative (*Escherichia coli*) and gram positive (*Staphylococcus aureus*) strains	[51]
3D nanostructured titanium	3D-nanopillared substrates	Reduce the adhesion and growth of *S. aureus*	[52]
- Titania (TiO2) nanowire arrays - Inspired by cicada wing surfaces	Bactericidal nanopillar patterns	Selectively bactericidal against motile bacteria	[53]
- Titanium nano-patterned arrays - Inspired by dragonfly wings	Hydrothermal etched nano patterened surface arrays	It can kill 50% of *P. aeruginosa* cells and about 20% of the *S. aureus* cells	[54]
- Polydimethylsiloxane elastomer - Inspired from the skin of fast moving sharks (Sharklet AF™)	Microscale topography	Lethal to *Ulva linza* zoospores	[55]

(*continued on next page*)

1. Table 2 (*continued*)

Nano/micro structures	Composition	Activity	References
- Nanopatterned PMMA films - Inspired from cicada wings	Nanopillars	Nanopillars adversely affect *E.coli* morphology	[56]
- Au nanostructured surfaces - Inspired from cicada wings	Nanopillars Nanorings Nanonuggets	All are Active against methicillin-resistant *S. aureus*	[57]
- Nanostructured medical sutures	Lamellar nanopattern	Prevent bacterial attachment and biofilm formation	[58]
- Surface modified polystyrene - Inspired from the skin of fast moving shark (Sharklet AF™)	Lamella-like textured surfaces	inhibit *S. aureus* adhesion	[59]

Cell membrane inspired nanomaterials can block natural cell responses during infectious diseases. A bioinspired anti-inflammatory nanocapsule (BANC) is a bioinspired nanosystem. It is coated with a cytokine receptor containing macrophage membrane coated with lipopolysaccharide. It has a gold nanocage in which the M2 polarization inducer is loaded. This BANC is capable of blocking cytokines and enhances the polarization of macrophages and thereby participates in bone tissue repair. Neutralization of cytokine and macrophage polymerization makes the BANC suitable for bone tissue repair as a bioinspired anti-inflammatory agent (Fig. 4a) [66].

The lubrication of all the natural joints is due to the hydration lubrication of articular cartilage. Phosphatidylcholine is a cartilage matrix, and it has zwitterionic charges. Inspired from this, a nanosphere poly (methacryloyloxyethyl phosphorylcholine) mesoporous silica nanosphere can be prepared, and it can enhance lubrication due to the presence of a hydration layer around the polymer and can deliver many anti-inflammatory drugs locally. These bioinspired nanospheres enhance lubrication and also the sustained release of the loaded drug. This can be used as effective nanomedicine for the treatment of osteoarthritis (Fig. 4b) [67].

Cellulose acetate scaffolds loaded with anti-inflammatory dexamethasone were developed by electrospinning, which delivers the drug by a biphasic release pattern, i.e., initial rapid release followed by controlled release. This is used for implant-related acute inflammation in osteoarthritic patients [68]. Chondroitin sulfate functionalized biomimetic collagen scaffolds are implanted subcutaneously into the affected area of arthritis and which up-regulates the genes involved in the apoptosis of inflammatory cells [69]. Sepsis is a serious inflammatory condition which even leads to death. The pathology of sepsis is mainly activation of leukocytes, and it will lead to multiple organ dysfunction such as cardiovascular instability, renal dysfunction, and lung injury. Thus, a biomimetic membrane device was designed to capture the activated leukocytes, especially neutrophils. Selective Cytopheretic Device (SCD), a cartridge containing polysulfone hollow fiber can bind and sequestrates activated neutrophils. During the process, blood is anticoagulated in that region to reduce the concentration of ionized calcium, and which also inhibits neutrophil activation [70].

The mechanism of SCD can be used in combination with various blood replacement therapies. Various medical conditions like acute kidney failure and heart problems need replacement of blood. The conjugation of the SCD with anticoagulation solution can provide more information about the critical pathways which causes fatal consequences.

4.4. Thrombosis

Thrombosis is a medical condition in which the formation of blood clots inside the blood vessels obstructing blood flow through the circulatory system. The condition is taken into consideration at the time of injuries. Usually, the body uses its own defense mechanism to prevent the blood flow by forming clots with the help of thrombocytes and fibrin to prevent blood loss. The excessive production of thrombocytes leads to the emergency condition like thrombocytosis. The most recommended prevention of thrombosis is the administration of low molecular weight heparin (LMWH). The main side effect of heparin includes heparin-induced thrombocytopenia, which provided inspiration from nature to develop a cure from nature itself. Pitcher plants are carnivorous plants having modified leaves called *pitfall traps,* which is a prey-trapping mechanism enriched with slippery digestive fluid e.g. *Nepenthes distillatoria, Drosera, Pinguicula, Heliamphora,* etc. They trap insects either by using their sliding structures or by slippery structures. Each of the plants has its own mechanisms to trap its prey.

Most of the plants possess a layer of three-dimensional waxy platelets of micro-size responsible for creating a slippery effect inside the *pitfall trap* and pays a way to the digestive fluid. Inspired by these plants, researchers exploited a sophisticated idea of creating a slippery, liquid-infused, porous surface (SLIPS). This versatile technology creates an anti-adhesive slippery surface by using a thin layer of liquid perfluorocarbons or otherwise tethered liquid perfluorocarbon (TLP). The creation of anti-thrombogenic surfaces can be made helpful to coat in different medical devices and utilized mainly intensive care units and other surgeries to prevent thrombosis without using any anti-thrombotic drugs [71,72]. The biomimetic modification of polyvinyl alcohol has been done. The surface functionalization of polyvinyl alcohol with the extracellular matrix of proteins and peptides increase the attachment to the cell. Their thrombotic activities were analyzed by incubating plasma, which is rich in platelets. The ex-vivo studies also revealed that it is a promising approach for reducing bleeding by using antiplatelet monotherapy [73].

Modification of SLIPS technology can be used in the future to create non adhesive anti thrombogenic surfaces for clinical application. The coating of anti adhesive slippery surface can be used artificial hearts and ventricular assist devices. The coating will be able to prevent thrombosis or bacterial infections. Coating with bioinspired materials will help them to mimic the physical and chemical properties as that of biological surfaces.

4.5. Wound healing

Wound healing is a complex natural restorative process involving the extracellular matrix (ECM), blood cells, cytokines, parenchymal cells, etc. Natural and synthetic polymers mimic these biological structures. Natural polymers such as gelatin, collagen, and synthetic polymers such as polyurethane, polyvinyl alcohol are used as bio-inspired wound healing agents. They have a high porosity, which helps in gas permeation; a large surface to volume ratio enables drainage of exacerbated exudates from the wound, hemostatic effect, and close structural resemblance with ECM. Among these, gelatine is widely used to mimics the structure and components of ECM, which enhances tissue growth. Gelatin improves hemostasis, cell adhesion, and cell proliferation during wound healing. Poor mechanical strength and thermal stability is the main problem associated with gelatin, which can be overcome by cross-linking with suitable agents. Gelatin is cross-linked with 3-(glycidyloxypropyl) trimethoxysilane (GPTMS) by green electrospinning technique to form gelatine cross-linked nanofibres having 200–300 nm size. Then it is doped with antibacterial agents, gentamycin sulfate, and silver nanoparticles. This electrospun gelatine nanofiber is effective against Gram-positive and Gram-negative bacteria and helps in rapid wound healing [74].

Sericin obtained from the cocoon of the silkworms is mainly used for the repairing of the skin. The polyvinyl alcohol was mixed with the sericin and $AgNO_3$, which results in the formation of silver nanoparticles within sericin/PVA hydrogels. It has good mechanical properties,

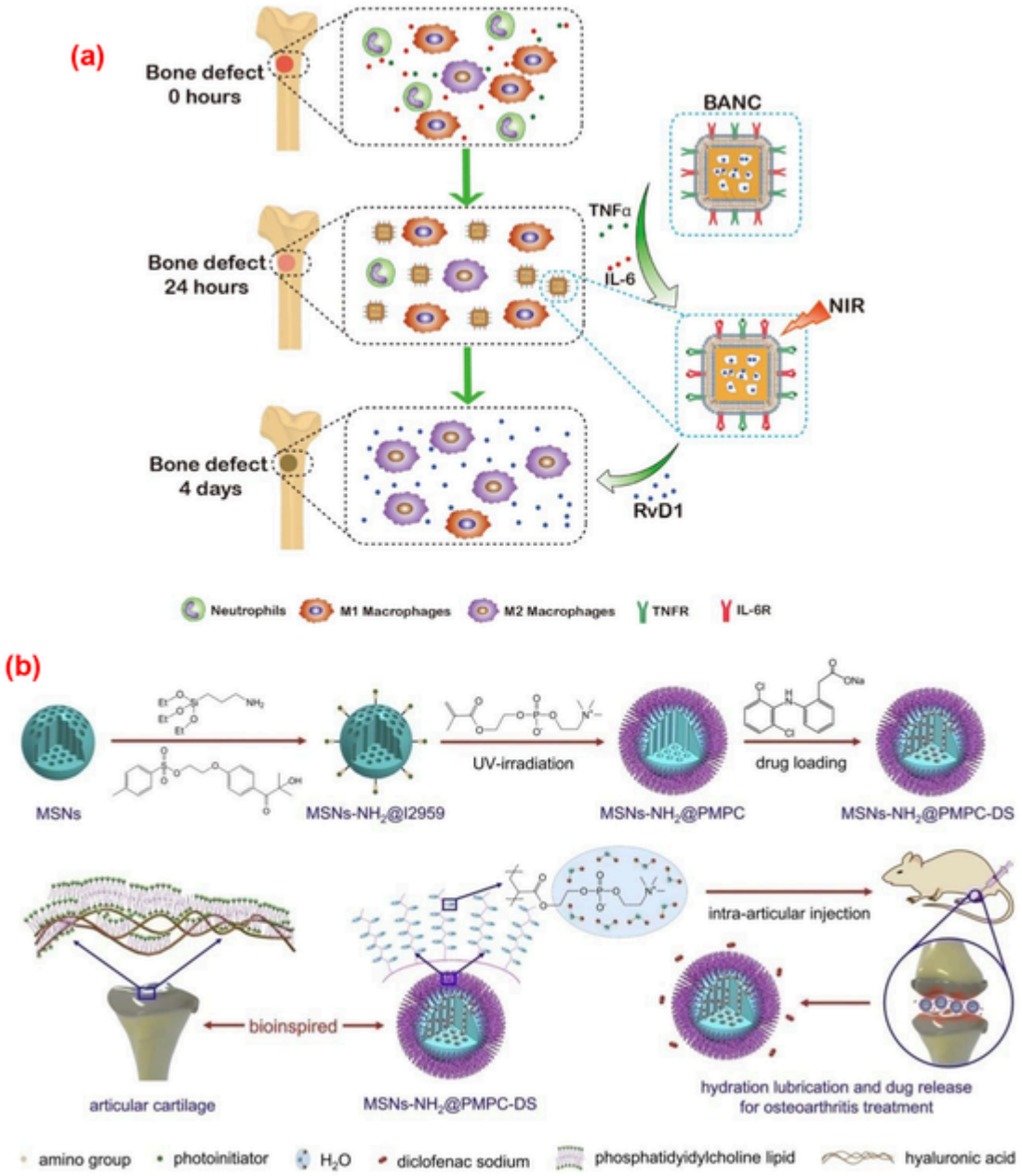

Fig. 4. Schematic illustration of the synthesis of the various bioinspired systems having anti-inflammatory activity. a) bioinspired and anti-inflammatory nanocapsule for bone tissue repair. Reproduced with permission from Ref. [66]. Copyright 2019, Elsevier. b) bioinspired poly(methacryloyloxyethylphosphorylcholine) mesoporous silica nanosphere for osteoarthritis. Reproduced with permission from Ref. [67]. Copyright 2020, Elsevier.

biocompatibility, and hydrophilicity. It has the ability to heal the wound; hence it has been used as an alternative to wound dressing [75]. Chemokine loaded biomimetic hydrogel can act as a good reservoir to stimulate the requirement of bone marrow mesenchymal stem cells to produce rapid wound healing. This biomimetic hydrogel has a porous structure, with high swelling rate and moisture retention rate. The loaded chemokine gets released and reaches the bone marrow mesenchymal stem cells. This biomimetic hydrogel is biocompatible and biodegradable and does not produce any harmful effects on the skin [76]. A schematic representation of the preparation and use of bioinspired or biomimetic systems for wound healing is shown in Fig. 5.

Modification of gelatin by conjugation or coating can alter the surface characteristics as wound healing agents. Modifying the surface characteristics of gelatin can helps to target a particular site without changing its properties. Good biocompatibility and low immunogenicity will make gelatin a promising material in wound healing applications.

4.6. Adhesion

Adhesion is a property of dissimilar surfaces/particles to stick to one another. In biomimetic and bioinspired research, more interest is in wet adhesion and dry adhesion, inspired by various living organisms in the ecosystem. These will lead to the development of new innovative ideas and other biomedical applications. Geometry-based nanowire coating adhesives are developed for better mucoadhesion, i.e., silicon nanowire coated beads produced from micro-nano structures (MNS) found in the living organisms (lizards, spiders, insects, tree, and torrent frogs) that can mimic the adhesion property for better mucoadhesion. Tree/torrent frog's toe possesses an attachment pad, which is believed to have high wet adhesion under shear. The microscopic examination reveals that

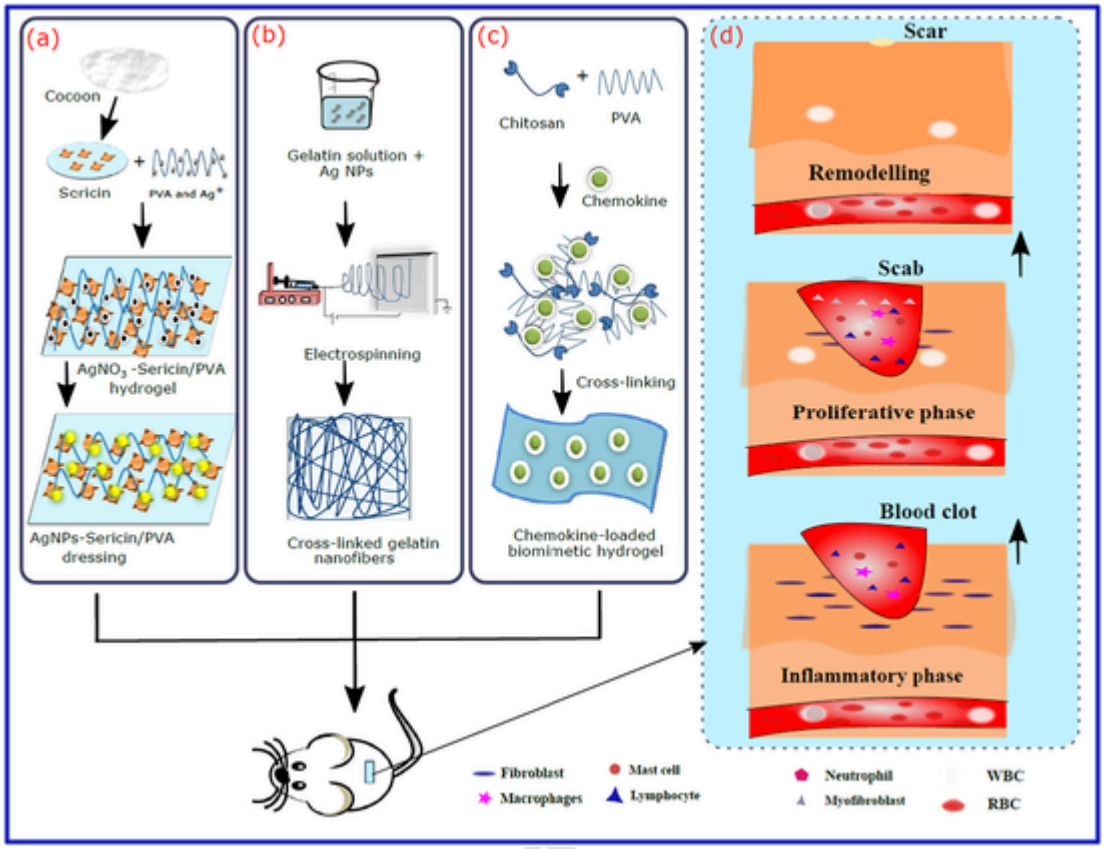

Fig. 5. Schematic illustration of the preparation and use of bioinspired or biomimetic systems for wound healing. (a) In situ synthesis of AgNPs in sericin/PVA hydrogel to promote wound healing effect. (b) Improving the wound healing properties of gelatin by cross-linking with suitable agents using the electrospinning technique. (c) Preparation of porous chemokine-loaded biomimetic hydrogel which stimulates requirements of bone marrow mesenchymal stem cells to produce a rapid wound healing effect. (d) Phases of wound healing in mice after application of biomimetic systems.

the presence of arrays of *nanopillars,* which is of a submicron size having structural and physical properties equivalent to silicon wires, was the reason for their adhesive property even at highly slippery or flooded areas.

When considering the small intestine, it is coated with a mucus layer which in turn containing microvilli to increase the surface area. So the primary strategy behind the development of mucoadhesive nanowires is developing a device that could mimic the geometry of the microvilli by decreasing the surface area of the device to a nano-level that can easily cross the mucus layer and strongly adhere to the epithelial membrane. The interaction of microvilli and the nanostructured device can be detected by using Caco-2 models as an in vitro model. If the device is developed to adhere only to the intestine, it should be designed in such a way that it could bypass the inconvenient area, so the enteric coating is preferred [10]. Dry adhesion is another property that can be inspired. Spiders and Geckos have the largest surface area compared to other insects. The microscopic studies on these two organisms show that their feet are covered with millions of small hairs called setae and are clustered to form a large number of spatula of both micro/nanosize ranges. Moreover, the adhesive property depends on the size, shape, and geometry of the micro/nanostructures. Mimicry of these micro/nanostructures found to be useful in re-usable adhesive tapes,toys, etc. [77]. Another example includes, development of the mucoadhesive system can be by mimicking the components of flagella and fimbria by imitating their adhesion mechanism on the human mucous membrane. This enables the adhesion of carriers on cell even in a large volume of fluid [78].

Bioinspired dry adhesives can be prepared using polydimethylsiloxane and multiwalled carbon nanotubes, which show good thermal stability and good pull-off adhesion property at high temperatures. The replica modeling technique was used for their preparation in the reported study [79]. Marine mussels can adhere to many surfaces under wet conditions. This property of mussels is due to the presence of foot proteins (Lysine amino acids and dihydroxyphenylalanine). This mussel foot protein inspired chitosan-based copolymer shows greater adhesion. Also, it is highly biodegradable and non-toxic. It can offer adhesion of soft and bone tissue and also act as adhesive for hemostatic and metallic materials [80].

Functional coatings to implants result in increased biocompatibility and bioactivity. Mussels have secretion of adhesive proteins rich in dihydroxyphenylalanine (DOPA) to adhere to any surface under wet conditions. Two bioinspired polypeptide DDDEEK-G_4-$(DOPA)_4$ and WR-WRWR-G_4-$(DOPA)_4$ were used to coat an implant material surface. Among this DDDEEK is inspired by salivary acquired pellicle in dental plaque film for bone cell adhesion and also has the capacity for the formation of biominerals. WRWRWR has antibacterial property and can sterilize multidrug resistance bacteria by respiration blocking and destruction of cell wall integrity. When these two polypeptides are mixed, then the coating can not only exhibit antibacterial activity, but also can promote the synthesis of the bioactive compound to exhibit cell adhesion. So, this polypeptide coated dental implant exhibit 2 to 3-fold antibacterial, osteogenic activity than implant without coating [81].

Adhesive materials for the wet environment have many applications in biomedicine. These biomimetic adhesive materials are inspired by the adhesive mechanism by natural organisms in underwater. For example, wet adhesives can be prepared inspired by the coacervate mechanism by the organisms like sandcastle worm. The coacervation mechanism is responsible for the formation of adhesion glue in this worm and inspired by this mechanism, a polyacrylate adhesive is prepared with positive amine and negative phosphate groups. This bioinspired adhe-

sive material can adhere to any surface underwater [82]. *Octopus vulgaris* arms are covered by suckers, and a round-shaped protuberance is found inside the entire suction cup. Compression of this protuberance against any surface results in the attachment of this cup on to that surface. Octopus suction cup inspired patches are made by using polyurethane acrylate polymers. These suction cup inspired materials are cell compatible and can be used as tissue adhesive [83]. The development of a mucoadhesive system that mimics the adhesion mechanism of flagella and fimbria enables the adhesion of carriers on cells, can be developed in the future. Bioinspired and biomimetic adhesives are illustrated in Fig. 6.

4.7. Sustained release of single paracrine factors

Proteins are synthesized from one cell and are diffused out to induce smaller changes in neighboring cells. This is called paracrine interaction, and the diffusible proteins are called paracrine factors. Growth factors and cytokines are natural paracrine signaling molecules. Micro and nanoparticle (MNP) delivery systems mimic the local paracrine release of growth factors and cytokines, and they give the signal to adjacent cells to respond correspondingly. It enables the sustained release of factors for several minutes to days, sometimes for months. Vascular endothelial growth factor (VEGF) is delivered via MNP for angiogenesis and to treat ischemia. IL-10 is delivered for inflammatory bowel diseases and Glial cell line-derived neurotrophic factor (GDNF) for nerve regeneration and to treat spinal cord injuries. Bone morphogenetic protein (BMP) was delivered for osteogenesis in bone therapy [84]. A delivery system that mimics the release of paracrine signaling molecules can be developed. This delivery system release signal to the adjacent cell and will helps to sustain their release. Such a delivery system can be used for the treatment of various diseases.

4.8. Sustained release of multiple paracrine factors

The synergistic therapeutic effect can be achieved by multiple deliveries of paracrine factors. Lyophilised VEGF and platelet-derived growth factor (PDGF) were successfully incorporated inside poly-L-lactic acid co- glycolic acid microparticles. This nanosystem releases VEGF for the first week and then PDGF for four weeks. This sequential release of factors promotes vascularisation in wound healing and the treatment of ischemia. These factors are also co-delivered by using alginate –PLGA microspheres [85].

4.9. Tissue engineering

Tissues are clusters of cells, and the in-vivo and in-vitro tissue synthesis depend on cell-cell adhesion and the internal cytoskeleton. Tissues are cultured on laser patterned substrate, the commonly used substrate being Si, and are synthesized in the absence of chemotropic factors and extracellular matrix (ECM). Neural cells and fibroblasts are cultured on hydrophilic laser engineered hierarchically structured Si rough surfaces for tissue development [86]. The recent introduction of biomimetic and bio-inspired nanoscale structures in the field of tissue engineering has brought remarkable advancement, especially in the case of cardiac diseases such as myocardial infarction (MI). The feasible use of biomimetic nanostructures can improve the performance of injured tissues and repair them. Currently, the application of various nanoparticles like carbon nanotubes, gold nanoparticles, gold nanorods, graphene oxide, iron oxide nanoparticles, mesoporous silica nanoparticles, and polymeric carriers as such or incorporating them with biomimetic scaffolds and hydrogels can mimic the cardiac morphology and electrophysiological nature. This enables the successful restoration of the structural and functional ability of cardiac tissues. A mussel-inspired conductive cryogel based cardiac tissue patch was designed to repair the myocardium. The mussel-inspired dopamine is used as a crosslinker to integrate the ingredients of the cryogel. The patch exhibited better adhesion and restoration of the myocardium in MI. (Fig.

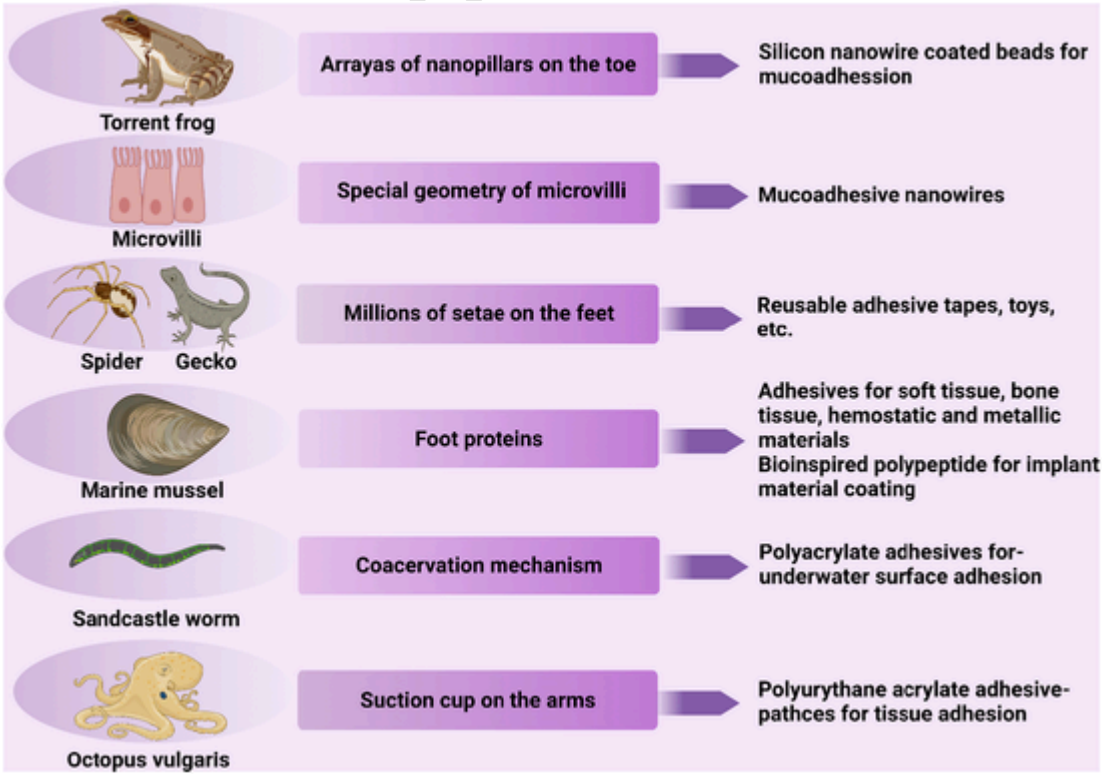

Fig. 6. Various bioinspired and biomimetic adhesives.

7) [87]. The cell-specific adhesion with tissue engineering scaffolds, implants, and other drug delivery systems is made efficient by the customized surface modification with biomimetic polymers. A biomimetic scaffold generated from PVA and carrageenan is highly efficient in imitating the microenvironment of the natural cartilage extracellular matrix and can be an effective strategy in cartilage tissue engineering [88].

Biomedical implants are used for orthopedic treatment procedures to provide mechanical support to the bone during joint pain and bone fractures. The major drawbacks of these implants are microbial infection and poor interaction with the bone tissue. This can be overcome by the use of bioinspired implants in tissue engineering. They mimic the physiological process in bone formation and functioning. This can be achieved by inspiration from the structural and mechanical properties of bone. A biomimetic coating to the implants results in the formation of a bioinspired implant. For example, coating with calcium phosphate, growth factors, components of bone tissue, etc. These biomimetic implants provide long time integration with patient bone tissue [89].

4.10. Biomedical equipment

Bioinspired metals have taken a huge place in the field of therapeutics. When compared to the other naturally occurring polymers, ceramics and minerals, metals have several advantages over these materials like superconductivity, ductility, resistance to corrosion, superhydrophobic nature, which makes them a good candidate for making biomedical equipment. Metals like iron, gold, silver, magnesium, cobalt, copper, tin, etc., in their pure form as well as their alloys like an alloy of tin, an alloy of iron, etc., are used. Cardiovascular diseases are a class of diseases that involve the heart and its related blood vessels prevailing in the world's population. Only 75% are curable by drugs established risk factors are avoided. The remaining will need the help of surgeries and medical devices. Typical cardiovascular devices have been developed and in the past few years using bioinspired metals. Pacemakers, coronary stents, implants, and mechanical valves have become popular [90]. Manganese, titanium, and their alloys are popular choices among the other metals for making orthopedic implants and dental implants because of the advantages like corrosion resistance and high metallic content. The micro/nanostructures on the titanium implants will provide higher surface area and mechanical strength, which makes them a suitable candidate for making dental implants. Stainless steel is another alloy useful in making hip sockets, cranial plates in dentistry, temporary crowns, needles, and other dental implants. The stainless steels are common to use or can be used daily by autoclaving [91–93].

5. Bioinspired and biomimetic drug delivery systems

5.1. Design of bioinspired and biomimetic systems

The opportunities of bioinspired and biomimetic systems can be applied to the field of drug delivery. Unlike the other resources, here researchers could use a minimum number of resources to get an efficient carrier-mediated drug delivery system. The biomimetic and bioinspired drug delivery system works by mimicking structure, shape, locomotion, appearance, and surface.

5.1.1. Locomotion

Since the locomotion/movement of a drug carrier is very difficult through the physiological matrix, the movement of a living cell is mimicked. Ionic electroactive polymer, PEG hydrogel, and silicon dioxide are transformed into mini-robots to mimic movements of octopus, myriapods, spermatozoids, or bacterial flagella under electric and magnetic fields [94]. Superhydrophobic systems can move through the oil/water interface. The self-beating systems such as heartbeat, brain waves can be recreated by using ADP/ATP conversion or Krebs cycle redox reactions [95].

5.1.2. Shape and appearance

Nanocarriers are small spherical particles; they are targeted to the cells by mimicking the shape and texture of the cell. Polymeric particles can change their shape in response to stimuli. In certain conditions,

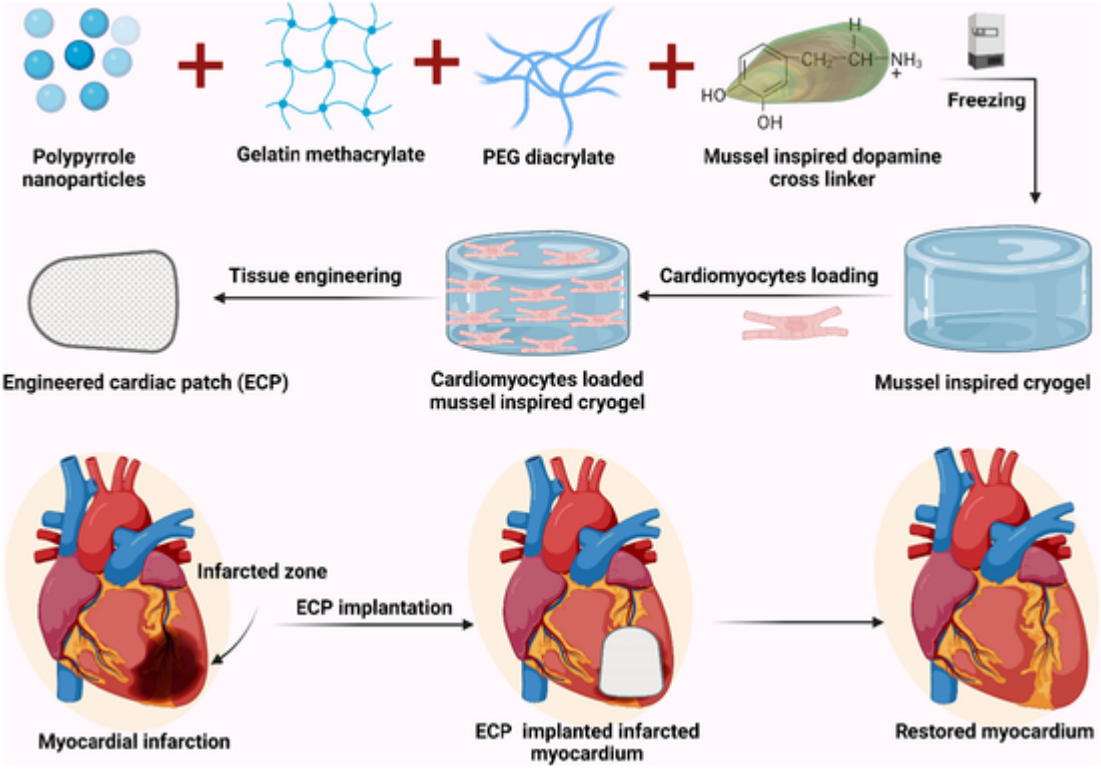

Fig. 7. Fabrication and application of engineered cardiac patch for infarcted myocardium.

peptides and copolymers can self-assemble. The association leads to functionalization, and the dissociation causes inactivation. Usually, nanocarriers are developed by self-assembly of the lipid bilayer because it can mimic the phospholipid bilayer of the cell membrane. And thus, they can transport the contents from the nanoparticle core. Another strategy to improve drug release from the nanoparticle is by incorporating an ion channel into the bilayer, so the molecules can easily travel out of the core. The biological ion channels can be mimicked by using synthetic polymeric domains. One of the great successful ideas was artificial receptor development by molecular imprinting technology. Innovative receptors can be developed by mimicking biological structures like antibodies and enzymes. They are prepared by molecular imprinting. It is a technology to design functional materials capable of recognizing biological and chemical agents. It can be prepared by template-directed synthesis, this includes the addition of a monomer to a template. And then imprinted cavities are formed by the reversible breakdown of framework bonds [96]. Disc-like flexible drug nanocarriers designed from erythrocytes by anti-phagocytosis CD47 coating to load therapeutic agents inside or to conjugate on their surface [97]. Various studies reveal that the shape of micro or nanoparticle has an unavoidable effect in phagocytosis. Phagocytosis is inhibited by cells with high aspect ratios (the relationship between height and width) (>20). Some bacteria can change their shape from rod to coccus or rod to filament etc.; these shape-changing bacterial MNPs are good candidates for drug delivery. This is mimicked by polymers; some polymers can change their shape in response to certain stimulations such as temperature, pH, or chemicals, such a shape-changing can modulate the phagocytic interactions by the cells. Elliptical disc-shaped particles are less affected by phagocytosis by macrophage [85]. In the case of artificial antigen-presenting cells (aAPC), non-spherical particles show 20 folds stronger T-cell response than spherical aAPC. Moreover, they have a strong in vivo antitumor effect than spherical particles. Ellipsoidal nanoparticleaAPC has a 15-fold stronger T-cell activity. The nonspherical nanoparticles have great drug delivery potential as they mimic viral functions, and they can avoid clearance by the reticuloendothelial system [98].

5.1.3. Size

To prepare a biomimetic micro or nanostructure, the size of the material is very important. The closer the particles to the cellular size, the more potent the effect on the target cell. Thus a material with a similar size of the cell is developed for better results [99]. As the size of the particle decreases, it can easily penetrate through the microvasculatures and barriers in the body. Particles having a 1–5 μ size mimic the size of bacteria, and they can travel through blood vessels without embolism. Smaller virus-sized particles can even cross even the blood-brain barrier, and the therapeutic efficiency is increased. Phagocytosis occurs for the particles having 2–3 μ in diameter [85]. In short, the interaction of MNP with other cells depends on their size.

5.1.4. Material selection

Materials synthesized from polymeric or inorganic metal precursors are found to be not better biomimetic. Thus, biomimetic substances are prepared from materials better mimic the natural biological properties of the cell. To mimic at cellular levels, the material with a low compressive modulus is selected and is achieved through the hydrogel-based particle. The hydrogel can mimic the compressibility of red blood cells, and thus they can squeeze through small channels. By adjusting the percentage of crosslinker, hydrogel with different rigidity varying from 7.8 kPa −63.9 kPa can be produced [99]. Mechanical stiffness of nanoparticles affects phagocytosis [85].

Bioinspired nanocarriers are used for drug delivery in various diseases such as cancer, cardiovascular disorders and are very effectively targeted to the sites. They act by mimicking the chemical composition, the 3D surface of protein presentation, and membrane fluidity inside the biological system. It includes bacteria inspired, virus inspired, fungus inspired, sponge inspired, cell inspired, and mammalian cell inspired systems [100]. The polymers which change shape in response to temperature, pH, or chemical have the capacity to modulate phagocytosis, can be designed in the future to modulate phagocytic reactions to drug delivery systems. The development of particles in elliptical shape also will results in decreased phagocytosis of that particle by the macrophages. Different carriers for biomimetic and bioinspired drug delivery systems are given in Table 3.

5.2. Drug delivery systems

5.2.1. Bacteria inspired

Bacterial cells are used as a carrier for cancer therapy since they are suitable for penetrating a tumor cell and can colonize in hypoxic and necrotic areas. The bacterial cell is modified to carry drugs, proteins, andgenes. Bacteria are utilized for their ability to act as tumor markers, deliver specific anticancer agents, and oncolytic therapy. With their capacity for strong tissue penetration and generation of specific proteins that are antitumor agents proves to be better candidates for tumor targeting. Anaerobic bacteria gets accumulates in the necrotic/hypoxic cells and kills the tumor cells [116]. The intrinsic ability of the bacterial cells to get colonize in the tumor cells and also to act as an effective vector makes them ideal candidates for tumor targeting. The bacteria mediated tumor therapy is getting highly significant due to its effective tumor-targeting potential [117]. Recent studies have proven that *Clostridia* spores are efficient in bacteria-mediated tumor targeting and to induce the antitumor effect; also the *S. typhimurium* can target both aerobic and anaerobic tumor-specific regions. The bacteria inspired systems include recombinant bacteria, microbot, bacterial ghost [118,119]. Fig. 8 represents the diagrams Schematic representation of different bacteria-inspired biomimetic systems (bacterial ghost and microbot) for tumor therapy.

Table 3
Different carriers for biomimetic and bioinspired drug delivery system.

Strategy for drug delivery	Applications	Reference
Bacteria-inspired		
Recombinant bacteria	• Gene delivery • Vaccine delivery	[101]
Microbot	• Gene delivery • Protein delivery • Tumor targeting • Microsensor • Microactuator	[100,102]
Bacterial ghost	• Vaccine delivery • Peptide delivery • Gene delivery • Drug delivery	[103–105].
Salmonella inspired	• Tumor targeting • Gene delivery	[106,107]
Virus inspired		
Viral gene vector	• Imaging • Cancer therapy • Gene delivery	[101,108]
Virus-like particles	• Vaccine delivery • Drug delivery	[109,110]
Virosomes	• Vaccine delivery • Gene delivery • Drug delivery	[101,108]
Fungus inspired	• Immunochemotherapy • Cancer therapy	[111]
Sponge inspired	• Tissue engineering • Hormone delivery • Gene delivery	[112]
Mammalian cell inspired	• Tumor targeting	[113,114]
Cell inspired	• Tumor targeting • Tumor imaging	[115]

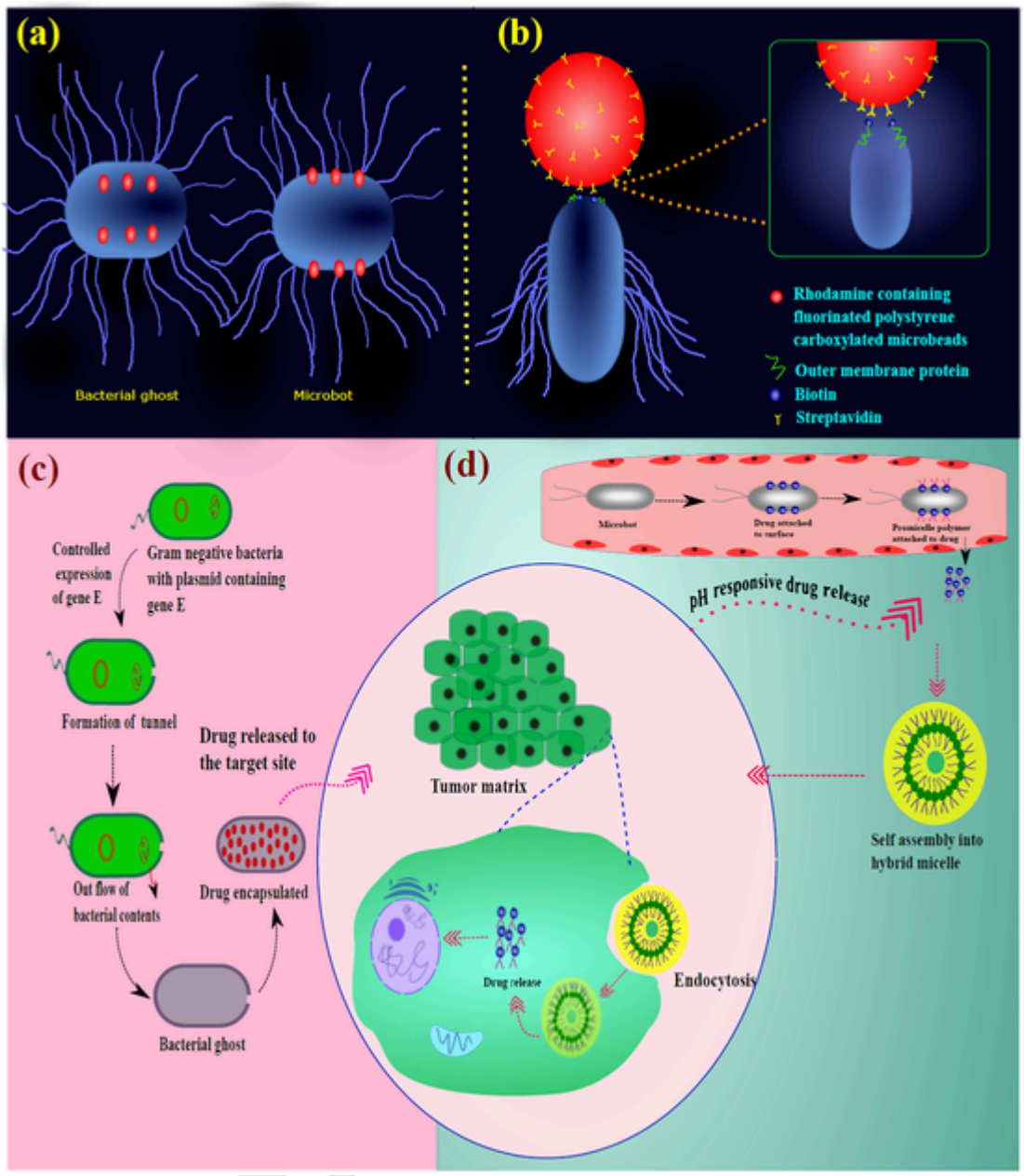

Fig. 8. Schematic representation of different bacteria inspired biomimetic system for tumor therapy. (a) Drug loaded bacterial ghost and microbot. Bacterial ghost encapsulates the drug while the microbot delivery system carries the drug on its surface. (b) Microbot is attached to the rhodamine containing fluorinated polystyrene carboxylated microbead through interaction between biotin and streptavidin on the bacteria surface. (c) Preparation of bacterial ghost by the expulsion of cytoplasmic contents and their targeted delivery to tumor matrix. (d) The drug attached microbot passes through the bloodstream and diffuse to the tumor cell. In response to tumor cell pH, the drug is released, and self assembles into hybrid micelle which enables tumor-specific drug delivery.

The intrinsic tumor targeting and penetration ability of bacterial cells can be used in cellular imaging. Bacterial cell entrapped imaging agents can be targeted to the tumor cell for efficient tumor cell imaging. Co-encapsulation of drug and imaging agents can provide the benefits of chemotherapy and imaging, together with the tumor-targeted ability of the bacterial cell. Hyperthermia induced agents can also encapsulate in the bacterial cells for targeted destruction of tumor cells.

5.2.1.1. Recombinant bacteria. These are bacteria inserted with plasmid vectors. This recombinant bacterium could produce the desired protein encoded by the human genome; moreover, due to the presence of a full complement of RNA polymerase, they can deliver protein at the targeted site. Engineered *Lactobacillus acidophilus* was designed to secrete the protective antigen of *Bacillus antracis* [101]. The causative agent for gas gangrene and gastroenteric diseases are *Clostridium perfringens. C. perfringens*alpha-toxin (CPA) is the disease-causing factor. Recombinant *E. coli* with the expression of CPA toxin is injected into the sheep for the production of the CPA vaccine [120].

Glucose production from cellulose is done by using the simultaneous enzyme production and saccharification process. This process requires the supplementation of β-glucosidase. Glucosidase gene is obtained from *Thermoanaerobacter brockii,* and this gene was expressed into recombinant bacteria *E. coli*. These recombinant bacteria are then applied to the simultaneous enzyme production and saccharification process to avoid the continuous supplementation of β-glucosidase. This can be a cost-effective approach for glucose production by the saccharification process [121].

5.2.1.2. Microbot. Microbots or bacteriobots are delivery systems containing a nanoparticle on the bacterial surface, which in turn loaded with drug particles for delivery into the cell. The bacteria, due to their specific invasive property, can colonize the hypoxic regions of the tumor. The main uses of microbots are gene and protein delivery. Bacteriobots are one of the most innovative ideas for tumor targeting by using a bacterial strain of *Salmonella typhimurium* to directly driven paclitaxel-loaded liposomal micro cargo. The robots are directly delivered into the bloodstream. The results showed a better therapeutic effect; i.e., they act by destroying the tumor without affecting the normal cell, which indicates that the development of reaches on microbots can annihilate the miseries of chemotherapy [100]. They can act as a combination of microsensors, microactuators, and a therapeutic agent. Highly motile bacteria *S. typhimurium* display biotin on their membrane protein, and the bacteria are attached to the rhodamine containing fluorinated polystyrene carboxylated microbeads through high interaction between biotin and streptavidin on microbead surface. These bacterialbots can move towards solid tumors than normal cells. The recombinant bacteria-based microrobot shows effective tumor-targeting capacity was found to be an innovative approach for active drug delivery [102].

A novel microbot has been developed which delivers the hybrid micelles and produce an antitumor effect. *Escherichia coli* Nissle with promicelle polymers was used as a carrier for drug loading. These microbots pass through the bloodstream and diffuse into the tumor cell. In response to the acidic pH of the tumor cell, the drug is released from the microbot. This system enables synergic treatment efficacy by the delivery of hybrid micelles [122].

The negative charge of the microbot can be exploited for the effective conjugation of positively charged metal-based nanoparticle for tumor-targeted drug delivery and imaging. The inherent ability of bacterial cells can effectively direct the conjugated particle to the tumor site, without affecting healthy cells. Quantum dots based microbot preparation is possible and can be used for tumor cell imaging.

5.2.1.3. Bacterial ghost. Bacterial ghosts (BG) are empty bacterial envelops derived from Gram-negative bacteria by protein *E*-mediated lysis and are devoid of genetic material and cytoplasmic content. This inducible expression of gene E leads to fusion of outer and inner membrane and an intermembrane tunnel was formed, through which the cytoplasmic contents are expelled. They are non-cytotoxic and safer than attenuated bacteria. They are good delivery platforms for vaccines, peptides, drugs, or DNA [103–105].

BG is used as an immunizing agent against Gram-negative bacterial infections. Bacterial ghost of *Actinobacillus pleuropneumoniae (APP)*, a respiratory tract infectious agent was developed and was protective against aerogenic infection by preventing colonization of bacteria in lings and tonsils. Their adjuvant property to induce specific humoral and cellular immune responses in animals was also studied. Since the bacterial ghost cytoplasm is empty, approximately 250 FL space is available, which can be successfully loaded with drugs. BG derived from *Mannheimia haemolytica* used as a carrier for doxorubicin to human colorectal adenocarcinoma cells. This BG was targeted to Caco-2 cells and doxorubicin was released, which shows 2 fold high cytotoxicity and anti-proliferative activity than doxorubicin alone. The reduced side effect and higher stability of bacterial ghosts make them more advantageous than bacterial cells [100]. Antigens are presented either inner or outer membrane of BG. Bacterial ghost vaccine developed from *E. coli* loaded with OmpA-HbcAg-149 Protein-based antigen elicit significant Ag- specific humoral immune response in mouse [123].

Another *E. coli* O2:K1 BG vaccine developed to fight against avian colibacillosis by using bacteriophage PhiX 174 lysis gene E. This vaccine helps to stimulate immune responses and thereby prevent avian colibacillosis [124]. Using *Salmonella enteritidis* ghosts *Neisseria gonorrhoeae* DNA was developed, which offers both antibody and cellular immune responses [125]. BG loaded with major outer membrane protein and macrophage infectivity potentiator. DNA vaccines have been developed to control *Chlamydia psittaci* infections which produced immune responses better than vaccination with naked DNA vaccine alone [126].

Bacterial ghost has large innerspace that can be used for the entrapment of drug-loaded nanoparticles and its innerspace allows for high loading efficiency. A sustained-release effect can be given to the bacterial ghost and it could offer an efficient, sustainable release of entrapped drugs/genes/proteins/ nanoparticles. The entrapment of hyperthermia-induced agents can be used to kill cancer cells.

5.2.1.4. Salmonella inspired. A certain obligate or facultative anaerobic bacterium has antitumor activity by multiplying selectively in tumors and inhibits tumor growth. And some bacteria are capable of therapeutic gene delivery to tumor cells. Salmonella, a facultative anaerobic bacterium is used as a gene delivery vector, antitumor immune activator, and tumor cell death inducer [106]. Salmonella mediated tumor therapy can be modified by using Salmonella proteins instead of using bacteria itself. This can improve safety problems [107]. Sip-A protein of Salmonella interacts with transport protein P-gp and leads to multidrug resistance to tumors through the activation of a protease enzyme, caspase – 3. Thus, Sip-A is only available to extracellular space. Later, a new strategy was developed to deliver this protein into the cancer cell by conjugating gold nanoparticles with Sip-A. But this was also failed to show a therapeutic effect. By incorporating doxorubicin to this, the antitumor effect was observed [127].

5.2.2. Virus inspired

Viruses are highly infectious microorganisms, smaller than bacteria, and consist of nucleic acid inside a protein coat. Adenovirus, adeno-associated virus, lentivirus, and retrovirus are commonly used as viral vectors. Virus-inspired drug or gene delivery system includes viral gene vector, virus-like particles, and virosomes [108,109].

5.2.2.1. Viral gene vector. The viral gene is replaced with a therapeutic desired gene and it is transferred to the host cell. The transfection and self-replicating properties of the virus are utilized here. The application of nanotechnology in gene delivery improves the effect of tumor targeting. Hyperthermia inducing gold nanoparticle is conjugated with Adenovirus via covalent linkage for targeting tumor-associated carcinoembryonic antigen. The introduction of a targeting ligand to the viral vector improves the therapeutic effect to a high extent [100]. Dendritic cell targeting ligand CD40 L is used for Adenovirus accumulation in the target cell, which shows 10,000-folds high activity than a non-targeted virus. But the major side effect with viral vector is safety issues and limited loading capacity. The safety issue can be overcome by replacing the viral protein with chimeric protein and this is called pseudo doping [101]. And the introduction of a drug to the targeted viral vector gives a synergistic effect.

5.2.2.2. Virus-like particles. These are non-infectious, multiprotein nanostructures that lack viral genetic material. The expression of proteins like capsids leads to the self-assembly of virus-like particles (VLP), ensuring tissue-specific targeting. The main aim of VLP production is that its advantages which can be exploited in the development of the vaccine. Also, it is useful in other fields like microbiology, virology, and immunology [108,128]. In another study, a drug-DNA adduct was encapsulated in albumin to form an artificial virus or virus-like particle, which was subsequently coated with poly(L-lysine) and poly (D/L-glutamic acid) to result in a pH-responsive tumor-targeted drug release (Figs. 9, 109].

Conjugation of targeting ligand on the multi-protein nanostructures of virus-like particles can enhance the therapeutic effect. Entrapment of drugs with imaging agents can render the VLP to an efficient theranos-

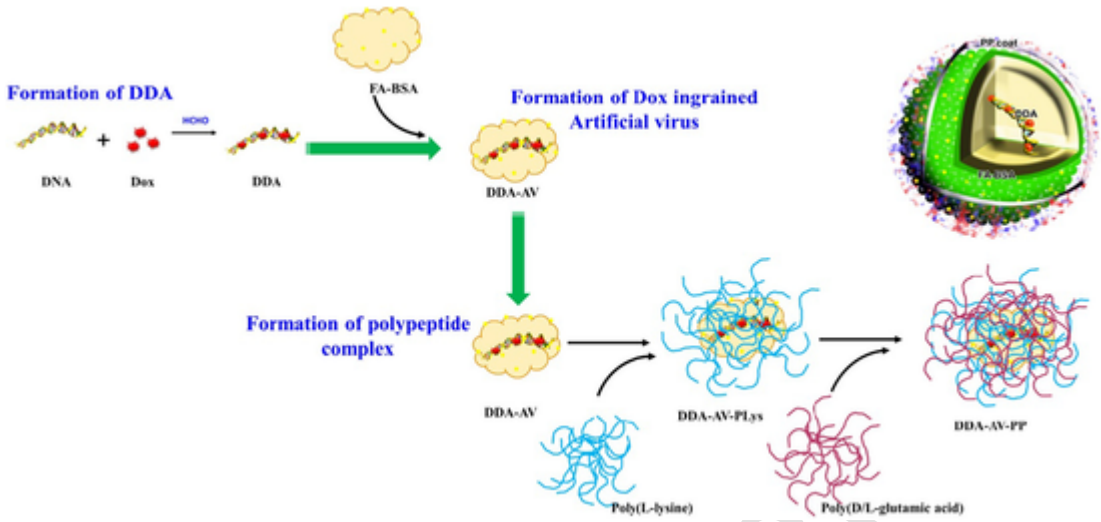

Fig. 9. Schematic diagram of a bioinspired artificial virus system for pH-responsive tumor-targeted drug delivery. Reproduced with permission from Ref. [109]. Copyright 2018, Elsevier.

tic agent. In viral encephalitis, VLP based on the causative organism can be used as a vehicle for therapeutic agent due to its ability to cross the cell BBB.

5.2.2.3. Virosome. Virosomes are unilamellar phospholipid monolayer or bilayer membrane vesicles. Virosomes are devoid of capsid proteins as well as genetic material. The prospect of virosomes in the therapeutic field is interesting. They can act as a system for drug delivery or as a mechanism for vaccine delivery to deliver the same in the targeted site [108]. These are virus-like particles, and they are similar to the native virus only in terms of morphology and characteristics of cell entry. They have a reconstituted viral envelop without the genetic material of the original virus [129]. Virosome can be used as a vehicle for tumor-targeted drug delivery. Conjugation of targeting ligand can enhance the efficiency of the targeting. Drug loaded virosome can be used in the drug delivery to the brain, mainly in viral encephalitis.

5.2.3. Fungus inspired

Advancements in the research field open a sophisticated pathway for fungus inspired delivery systems, which will lead to breakthrough changes in the field of biomedicine. Fungi species like *Agaricus blazei Murill and Shiitake lentinulaedodes* mycelium produce immunomodulating substances like lentinan and β-glucans, which found to be effective in treating cancer patients and virus-mediated infections [130]. Carnivorous fungi groups are those grow in the living things like feathers of birds, hairy back of animals, scales of aquatic creatures, and their life cycle will depend on these creatures. A major carnivorous fungus belongs to the genus *Arthrobotrys* which usually feeds on nematodes. Nanostructures contained in these types of fungi possess an excellent anticancer activity [111]. *Cryptococcus neoformans*is a type of immunocompetent fungus (yeast) spread by airways. The spores of these fungi on inhalation will cause meningitis. The researchers are working on these yeast cells to identify the exact mechanism that how they cross the blood-brain barrier which becomes a complicated puzzle for them to solve. If we get the correct access to the mechanism, that will pay tremendous pathway in the field of biomedicine especially in the field of brain tumor targeting. *C. neoformans* fungi can cross the BBB and can cause meningitis. Coating of therapeutic agents with the fungal mycelium can be used for the treatment of brain targeted drug delivery.

5.2.4. Sponge inspired

By mimicking sea sponge, Leuconoid sponge, mechano-responsive ceramic-based macroporous scaffolds were developed for regenerative medical applications. The sea sponge can control the entry of water into and out of the sponge, and this property was imitated. They can be used as tissue engineering scaffolds for bone and cartilage. Drugs can be loaded for controlled release, especially anti-osteoporosis drugs, parathyroid hormone, and even miRNA. The movement of the body is utilized as a source for mechanical stimulation(Fig. 10) [112]. The absorption of water into and out of the system is an intrinsic property of the sponge. This property can be exploited for the preparation of cleaning aids used in surgery.

5.2.5. Mammalian cell inspired

Although the nanoparticulate drug delivery offers great progress in the field of nanotechnology, the rapid clearance from circulation and the need of overcoming various physiological barriers is becoming a great challenge for satisfactory drug delivery, particularly for tumor targeting. The applications are mainly derived from the applications of the cells themselves. A diagrammatic presentation of the applications of different cell-based systems is given in Fig. 11.

A leukocyte derived biomimetic tumor-targeting nanocarrier system has been developed to get the required physiological response as it can simply cross the different barriers that are encountered while tumor-targeting [114]. Another biomimetic nanoparticle strategy with a tumor-specific peptide coating that targets the clotted plasma proteins at the tumor cells has been developed. This provides the facile accumulation of the peptide-coated biomimetic nanoparticles at the tumor sites with their unique self-amplifying tumor homing capability [113].

Not only mammalian cells but also mammalian cell membranes are also mimicked for drug delivery applications. Various cell membranes from red blood cells, Leukocytes, platelets, macrophages, immune cells, stem cells, and natural killer cells are used for designing nanoparticles for various purposes, including drug delivery and tumor imaging [131]. Cancer cell membranes were also used as a carrier, and are easily obtained by in-vitro cell culture as they can proliferate at a fast rate. PLGA core containing an upconversion nanoprobe, indocyanine green (ICG) was cloaked with the cancer cell membrane by DSPE-PEG hybridization. NIR fluorescence emission property of the probe was utilized for tumor imaging. Similarly, doxorubicin loaded into a gold nanocage cloaked with 4 T1 breast cancer cells were used for simultaneous phototherapy and chemotherapy [115].

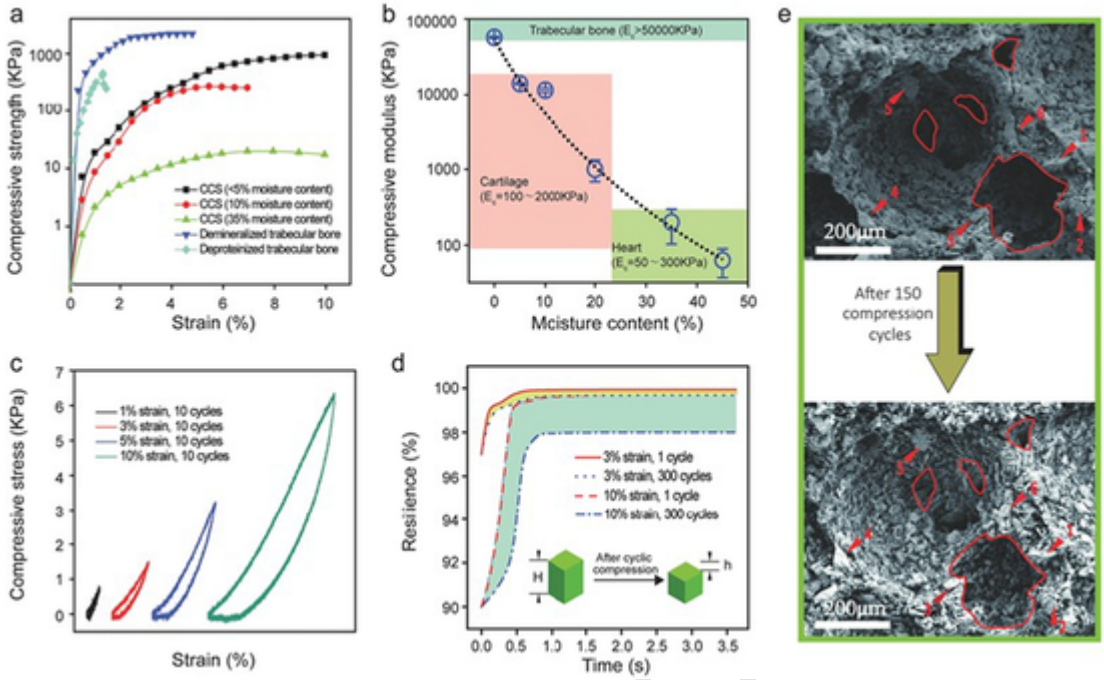

Fig. 10. Moisture dependent mechanical properties of ceramic composite sponges (a) Compressive stress-strain relation (b) moisture dependent compressive modulus (c) Compression – decompression loops (d) resilience versus recovery time relation. Reproduced with permission from Ref. [112]. Copyright 2017, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

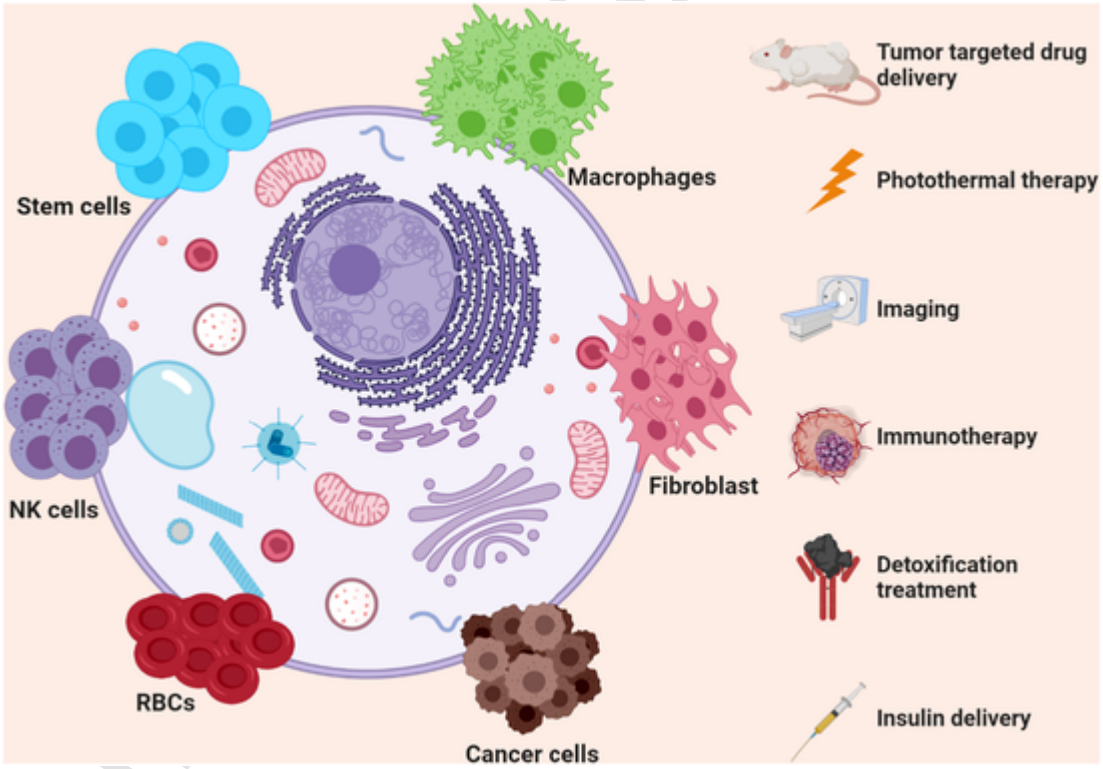

Fig. 11. Diagrammatic presentation of different cell-based systems and their applications.

To reduce the immunogenicity and to increase the circulation time in blood, cell-membrane camouflaged nanoparticles are used as drug carriers. These properties promote enhanced permeation retention (EPR) effect for tumor targeting. The poly (lactic-*co*-glycolic acid) core containing doxorubicin was cloaked with the RBC membrane was designed for tumor targeting. RBC membrane and PLGA were linked by an extrusion process. This was the first cell-membrane camouflaged nanoparticle system for tumor targeting, which enhances the circulation time in blood. Gelatin nanogel loaded with doxorubicin and is camouflaged with stem cell vesicles by extrusion, which offers efficient tumor targeting.

A NIR responsive RBC mimetic nanoparticle system was developed to obtain a synergistic chemo/photothermal therapy. Paclitaxel loaded thermos sensitive hybrid polymeric nanoparticles are coated with an

RBC membrane integrated with a NIR responsive dye. Light-induced hyperthermia results in the rapid release of the drug. Besides the prolonged blood circulation, macrophage camouflaged nanoparticles can cross the vascular barriers and molecular recognition ability on cancer cells. Macrophage cloaking technology is effective for drug delivery, photothermal therapy, tumor imaging, and diagnosis. Intrinsic cell adhesion molecules on the membrane give a circulating tumor cell and niche-targeting property to monocytes and neutrophils. Neutrophil membrane coated nanoparticles are designed to prevent tumor metastasis and treatment. On comparing with RBC camouflaged nanoparticles, leukocyte camouflaged nanoparticles not only improves the circulation time but also it can actively target the inflammatory sites of cancer cells [132].

Limitless replication potential, immune escape, and homologous targeting are the peculiar properties of the cancer cell. Various cancer cell camouflaged nanoparticles are designed for tumor targeting, diagnosis, and treatments (Fig. 12). Doxorubicin encapsulated gold nanocage camouflaged with a 4 T1 breast cancer membrane created for the synergistic effects of chemo-photothermal therapy. Various camouflaged nanoparticles for tumor targeting and metastasis prevention are also developed from the platelet membrane based on the close interaction between tumor metastasis and platelets [115].

Camouflaged nanoparticles with hybrid cell membranes also showed specific targeting and biocompatibility (Fig. 12). Sorafenib loaded copper sulfide nanoparticles modified with anti-VEGFR antibodies. This nanoparticulate system is then coated with cancer cell-macrophage hybrid membrane and is used as a chemo-photothermal therapeutic agent in hepatocellular carcinoma through immune escape, homotypic cell targeting, and tumorigenic signaling pathways [133].

Nanoparticulate systems can cross certain biological barriers like BBB; hence they have potential application in the treatment and diagnosis of brain disorders [134]. Blood cell camouflaged nanoparticles can be used as a vehicle for the easy crossing of BBB. Drug-loaded RBC, leukocyte, and platelet or their cell membrane camouflaged nanoparticles can be used to treat brain disorders. Blood cells can easily pass through the blood and can cross the BBB without any hesitation.

Nanoporous silica nanoparticles having a positive charge cloaked with purified leukocyte cell membrane have a negative charge and are

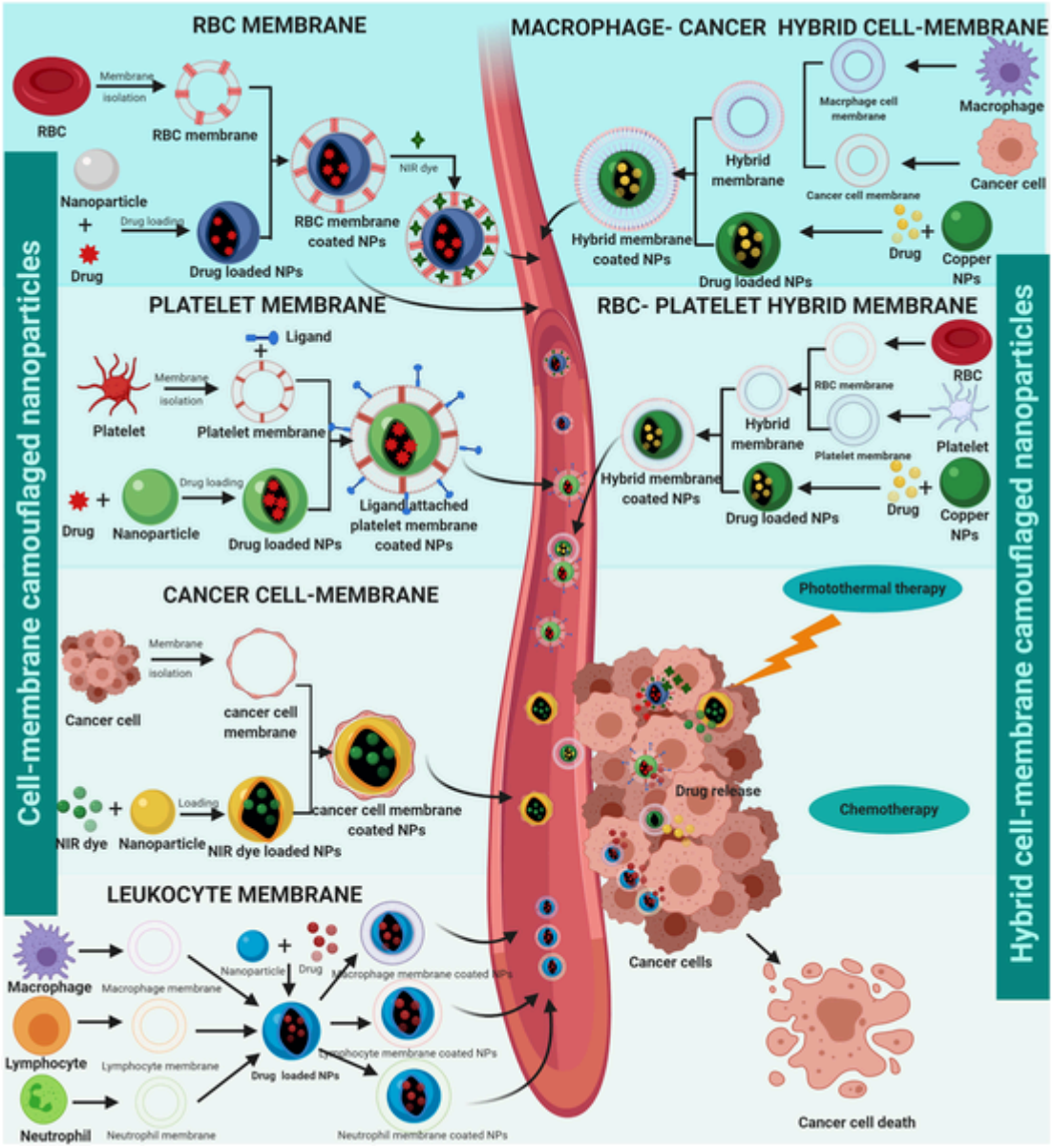

Fig. 12. Schematic illustration of the scheme of preparation and anticancer activity of various cell-membrane camouflaged nanoparticles, and hybrid cell membrane camouflaged nanoparticles.

used for targeting the tumor and inflammatory sites. The silica core and membrane were combined with electrostatic and hydrophobic interactions because of their opposite charges. The hybrid obtained is called Leukolike Vector (LLV) [135]. Doxorubicin-loaded nanoparticle cloaked with platelet membrane containing Tumor Necrosis Factor (TNF) related apoptosis-inducing ligand shows excellent antitumor activity [136].

Erythrocyte membrane bioinspired optical nanocarrier can be made by the integration of RBC membrane vesicles with infrared persistent luminescence nanophors (PLNPs). Here the RBC membrane vesicle is biomimetic to make the nanocarriers to resist uptake by macrophages and systemic clearance. Along with the membrane lipids and proteins, the RBC membrane vesicles make the nanocarrier to mimic the cell properties. These PLNPs based biomimetic nanocarriers show long circulation in the body, making them suitable for therapeutic and diagnostic applications [137].

5.2.6. *Biomimetic hydrogel/nanogel systems in drug delivery*

The fabrication of nanogel systems that offers a well-optimized delivery of the therapeutic agent in response to the targeted biological environment remains the most remarkable advancement in nanotechnology. This hydrophilic 3D polymeric material has a highly versatile drug encapsulation and stimuli-controlled drug releasing capability [138]. The protein hydrogels formed by chemical or physical cross-linking of proteins are having extensive biological applications. These self-assembled protein hydrogels are exhibiting sol-gel transition and have great potential in tissue engineering and regenerative medicine [139]. The polyvinyl alcohol (PVA) hydrogels have a great future ahead in regenerative medicine and tissue engineering. Surface modification of hydrogels with different functionalities can make significant changes in their physicochemical properties [140].

Bioactive cell hydrogel is the living cell limited hydrogels. These hydrogels can increase the in vivo release time of drugs without affecting the immune system. This can also provide self-control by creating a microenvironment for the controlled release of drugs in the immobilized cells [141].

A biomimetic hydrogel can be prepared by the inspiration from the wound healing characteristics of the oral mucosa for the fast and scar-free wound healing. Within the oral mucosa, the microenvironment and the growth factors are responsible for the rapid wound healing. These properties are considered during the production of biomimetic hydrogel for wound healing. The hydrogel was loaded with many functional compounds to mimic the wound healing properties of the oral mucosa. This biomimetic hydrogel shows rapid wound healing with less amount/free of a scar than the normal hydrogel [142].

6. Gene delivery

Plasmid DNA encoding β gal gene complexed with lipofectamine to form a DNA- lipoplex and is co-precipitated into biomimetically nucleated apatite. This DNA- lipoplex within the biomimetic apatite coat shows high transfection efficiency than DNA-lipoplex adsorbed to the mineral surface and they are used for bone regeneration [143].

Pinecones are ordered cone scales separated by ordered cavities, and thus they have a high surface area. Bioactive glasses are inorganic biomaterials composed of SiO_2, CaO, and P_2O_5. They were prepared by mimicking pinecones, which can act as a vector for mRNA and drug carriers. The mesoporous bioactive glass was prepared by the sol-gel process and loaded with mRNA. It can protect the gene from degradation and which shows low immunotoxicity. Since viral and nonviral vectors cause intravascular and extracellular cytotoxicity, mesoporous bioactive biomimetic glasses are the best candidates for gene delivery. Not only genes but also drugs can be delivered, doxorubicin-loaded bioactive mesoporous glass was successfully targeted to the cell [144]. Biomimetic drug carriers produced by genetic engineering contain fusogenic peptides H5WYG and Gp41. These nanocarriers have good DNA binding capacity and provide protection from the nucleases. So the gene delivery can be improved [145]. Further, mesoporous bioactive biomimetic glasses (mimics pinecones) can act as vectors for gene transfer. They have a large surface area and can protect genes from nucleases. Hence mesoporous biomimetic glasses can be used for carrying multiple genes for multifactorial genetic disorders.

7. Bioinspired protein nanostructure

Self-assembling proteins and peptides with their eminent design flexibility for different nanobiological have made innovative developments in the field of nanotechnology. The generated nanotubes, fibrous scaffolds, and helical ribbons from the self- assembled proteins are exhibiting great potential for tissue repair and regenerative medicine [146]. The mono and multi-enzyme assemblies derived biomimetic nanoenzyme is manifesting high catalytic efficiency and substrate specificity. Certain protein assemblies having interior cavities are having immense potential as protein nanocarriers and are used for biomedical therapy and diagnosis. Such an application is shown by albumin binding proteins, which can promote penetration through BBB. Paclitaxel can be encapsulated into this protein nanostructure to allow its penetration through BBB against tumor growth [147].

Self-assembled proteins are widely accepted as nanomedicines. The virus capsids and hollow proteins are having wide application as nanocontainers for the purpose of genetic material encapsulation and transport of ions. The bacteriophage MS2 viral capsid is a protein nanostructure with accessibility for even large organic molecules and exhibits tissue targeting capability [148]. The stimulus-responsive biomimetic protocells designed from proteosomes are having multifaceted applications. They can be used for gene-directed protein synthesis, guest molecule encapsulation, and membrane gated enzyme catalysis [149]. Bioinspired minimalistic pseudopeptides having the ability to mimic the complex biomolecules exhibit the potential for catalytic activity, the formation of more ordered structures, and to participate in recognition and transcription of information events in molecular devices [150].

Meanwhile, viral capsids can be used as nanocarriers. The capsid from bacteriophage MS2 was used as an effective protein nanocarrier. In this current scenario for the development of the drug against COVID-19, a new attempt can be tried. Viral capsid isolated from coronavirus can be used as a nanocarrier for an antiviral drug against COVID-19, and this capsid-drug complex may expect high affinity towards virus in the body, and thus targeted drug release can be achieved.

8. Biomimetic polymer networks

The polymer derived biomimetic networks find great opportunity in the field of biomedicine. These biocompatible polymers are designed to specifically recognize and bind to significant biomolecules. A biomimetic polymer network generated is having a tailored affinity and capacity to target the molecule Glucose-D and utilized for micro and nano-scale biosensors and in diagnostic devices. Various strategies were developed in order to incorporate silicon substrates into this biomimetic network and to find accessibility into the micro-device platforms [151]. The biomimetic polymer networks can mimic the biological recognition pathways, and this system finds a great potential ahead [152]. The surface modification of medical implants, scaffolds, and other nanostructures in tissue engineering by incorporating the biomimetic polymers is highly beneficial, enabling the cell-specific adhesion and thus offering more optimized drug delivery [153].

The highly selective blood-brain barrier of the central nervous system is highly responsible for the various impeded therapies targeting the brain. A long circulating drug delivery system invented is composed of zwitterionic polymer poly (2-methacryloyloxyethyl phosphoryl-

choline) and is surface modified with a biomimetic structure in order to obtain the long-circulating mechanism. Also, studies proved the minimal immune response with this system and the efficient blood-brain barrier penetrating capability [154]. Surface modification of medical implants with biomimetic polymers can offer advantages in tissue engineering. This concept can be adapted for developing less antigenic artificial organs, which may be more acceptable.

9. Bioinspired strong polymeric materials

Naturally occurring biological materials such as nacre, bone, teeth, wood, and spider silk have high strength and toughness. Various technologies were developed for the fabrication of polymeric nanomaterials having similar strength and toughness to that of these biological materials. Nacre like strong polymer composites was developed based on micro/nanoscale sheets such as graphene oxide and its derivatives, aluminum oxide platelets, etc. The spider silk has the high tensile strength and thermostability (up to 350 °C) because of well-organized hydrogen bond β sheet crystals confined within a semi-amorphous protein matrix. To mimic this spider silk, scientists fabricated by introducing artificial β sheet crystal graphene oxide quantum dots (GODs) to polyvinyl alcohol (PVA). This GOD-PVA composite film shows high tensile strength and toughness [155]. Polymers from various biological organisms find a wide range of applications in the biomedical field, polyesters, for example, polyacid(3-hydroxybutyrate) or APHB synthesized by bacteria is highly utilized in the fields of medicine and agriculture.

Bioinspired thiolated polymers can increase the residence time of many drug delivery systems. These polymers have high versatility and flexibility, which makes them more suitable for drug delivery systems. These have high mucoadhesive properties, so they can also enhance the absorption of drugs from the mucus membrane [156]. A biodegradable nanosystem can be made from bioinspired polymers like hyaluronic acid and polyarginine. These bioinspired polymers are non-toxic, biodegradable, and biocompatible. These polymers can easily recognize membrane glycoproteins like CD44 receptors overexpressed due to cancer cells. Nanoparticles prepared by using this polymeric material shows better targeting property, and the cytotoxicity can also be reduced [157].

Lignin is a polymer of aromatic origin. Lignin-inspired polymeric nanocarrier systems can be used for drug delivery. These bioinspired polymeric materials are inexpensive, easily available, and capable of the formation of self-assembling structures. All these properties make them suitable for drug delivery. Fibers of lignin can reduce the occurrence of colon cancer. Lignin absorbs the carcinogenic materials from the colon and thereby reduces the contact time of carcinogens with the colon. It also has reactive oxygen species scavenging property which is another mode against cancer development [158]. Further, lignin-based nanoparticles can be developed to carry colonic anticancer drugs, and this system can expect a better effect in the future for colon cancer therapy, as lignin itself has carcinogen absorbing capacity.

In addition to the above mentioned bioinspired polymers, a plethora of polymer-derived bioinspired and biomimetic structures are also available. They also provide opportunities in biomedical applications. A list of the recently reported such systems is presented in Table 4.

10. Biomimetic hybrid scaffolds

The biomimetic hybrid scaffolds greatly influence the present biomedical scenario. In the field of regenerative medicine, the evolution of multi-phasic scaffolds could bring tremendous developments. This will boost multiple tissue integration and cell/tissue integration. The biomimetic hybrid scaffolds for engineering human tooth-ligament interfaces offer high potential in resolving defects in the neogenesis of osseous and ligamentous interfacial structures [168].

Table 4
Polymers for biomimetic and bioinspired structures and their applications.

Sl. No.	Scaffold/ structures	Polymers used	Application	[Ref.]
1	Reduction-sensitive polymer-drug conjugate	Phenylboronic Acid, Polyethylene Glycol, Disulphide, Polycaprolactone	Cancer therapy	[159]
2	Peptide imprinted polymeric nanogel	Acrylamides, methacrylates	Peptide recognition elements	[160]
3	Artificial polymer membrane	Poly(4-vinyl-N-Methylpyridine iodide),poly(4-vinylpyridine),Poly (acrylic acid),Poly(allyl glycidyl ether),Poly(butylenes),poly(benzyl methacrylate),Poly(caprolactone), Poly(dimethyl siloxane),Poly(ethyl ethylene),Poly(L-hlutamic acid), Poly(isoprene),Poly(lactic acid),Poly (methacrylicacid),Poly(styrene),poly (propylene oxide),Poly(sarcosine), Poly(vinyl alcohol)	Artificial organelles, artificial and active surfaces	[161]
4	Marine inspired medical adhesive	Polyethylene glycol-catechols, Polypropylene – polyethylene glycol,Polyacrylamide, Polymethacrylate,	Alternative to sutures or staples	[162]
5	Light responsive block copolymer with spiropyran	Poly (methyl acrylate), L- lactide	Building blocks for the preparation of biomimetic nanostructures	[163]
6.	Polychaete jaw inspired semi-interpenetrating networks	2,6-bis(1′-methyl-benzimidazolyl)-4-hydroxypyridine, Poly(ethyleneglycol methacrylate,	Development of smart materials	[164]
7.	Cryogels	2-(Dimethylamino)ethyl Methacrylate/(2-Hydroxyethyl) Methacrylate	Bone repair	[165]
8	Biosilicate nanoparticles	Polyethyleneimine	Biosensors	[166]
9	Core–shell protein-based delivery system	poly(2-methacryloyloxyethyl phosphorylcholine)	Drug delivery platform for CNS related disease therapy	[154]
10	Hydrogel ink	Acrylamide and N-isopropylacrylamide	soft robotics, hydrogel actuators, and tissue engineering.	[167]

The endothelium remodeling is a major hurdle in the fabrication of tissue-engineered vascular grafts, which are mostly used in bypassing the damaged blood vessels. The hybrid scaffolds with their integrated properties could highly assist the endothelium remodeling and studies were conducted in order to uncover the underlying mechanism. The biomimetic hybrid scaffolds fabricated from the bioactive gelatin methacrylamide (GelMA) and poly-ε-caprolactone (PCL), was used to reveal the vascular endothelial cell responses on them. The success of tissue-engineered vascular grafts is decided by the bioactivity and mechanical strength of the hybrid scaffolds, and this is having a great influence on vascular endothelial remodeling [169]. A functionally graded scaffold having the ideal mechanical and morphological requirements for osteochondral defect repairing is also reported. This biomimetic hybrid scaffold generated for osteochondral tissue repairing has great potential in cell proliferation and bone differentiation [170]. The nano- and microstructured biomimetic calcium phosphate mineralized organic-inorganic hybrid scaffolds have been generated to substitute the natural bone materials in tissue engineering, and it mimics the properties of the extracellular matrix. These biomimetic mineralized hybrid scaffolds are intended to be the potential candidates for bone tissue engineering [171].

The construction of a biomimetic scaffold eliminates the problem of meeting the specific structural requirement of osteochondral tissue in the field of tissue engineering. The chitosan and gelatin used for the preparation of this scaffold act as the binding sites for the cells, and after degradation, they will not produce any harmful chemicals. The growth of the cells in this scaffold is improved [172]. A porous scaffold has the ability to mimic the bone. This mimicking property of scaffold can be used for tissue engineering purposes. Biomineralized scaffolds are the combination of inorganic and organic molecules and provide support and protection to the skeleton. These biomimetic scaffolds have good mechanical strength and biocompatibility [173]. Biomimetic nanofibrous scaffolds have the same matrix and provide an environment to attach to it. These scaffolds can regenerate cells and tissue. These are prepared by the electrospinning method and they have interconnected fiber networks for mimicking the nerve branching. Neurons in the scaffold made synapses with other neurons to communicate with them and enhance neuronal growth [174].

The bioactive gelatin methacrylamide (GelMA) and poly-ε-caprolactone (PCL), incorporated biomimetic hybrid scaffold, can highly assist in the fabrication of tissue-engineered vascular grafts and can be effectively used to bypass damaged blood vessels. This biomimetic hybrid scaffold is having a great influence on endothelium remodeling, and this circumvents the major hurdle in the construction of tissue-engineered vascular grafts.

The micro and the nanostructured biomimetic calcium phosphate mineralized organic-inorganic hybrid scaffolds in bone tissue engineering. This biomimetic calcium phosphate mineralized hybrid scaffold will be having a great influence on osteochondral tissue repairing and thus bone differentiation. The calcium and phosphate ions release can activate osteoblasts and osteoclasts, facilitating bone regeneration. This micro and the nanostructured biomimetic calcium phosphate mineralized organic-inorganic hybrid scaffolds, being highly biocompatible and biodegradable, can be efficiently used in bone tissue engineering.

11. Bioinspired and biomimetic carbon-based nanostructures

Versatile bioinspired and biomimetic carbon nanostructures are being fabricated with the intention of getting improvised characteristics. The bioinspired spider silk-single walled carbon nanotubes (BISS-SWCNTs) are integrating the tensile strength and extensibility of spider silk and the conductivity of carbon nanotubes. Thus, the mechanical properties of single-walled carbon nanotubes are enhanced. Upon embedding the Fe nanoparticles on the SWCNTs surface and later coating with an amorphous carbon layer, the hierarchical structure of spider silk can be fabricated [175].

Bioinspired and biocompatible carbon nanotubes have been developed with silver nanoparticle (AgNPs) loading and shielded with a biocompatible polymer. This AgNP loaded oxidized carbon nanotubes with mussel inspired polymer coating has prominent antibacterial activity with minimum cellular toxicity. Thus self-sterilizing biocompatible surfaces can control the potential bacterial infections in various biomedical devices [176]. Studies also reveal the enhanced mechanical properties of graphene and aluminum nanocomposites with a bioinspired nanolaminated structure [177].

The birth of bioinspired graphene nanocomposites has opened a plethora of opportunities in various sectors, which includes artificial muscle fabrications, flexible electronic devices, aerospace, supercapacitors, etc. This bioinspired carbon-based nanostructure is a promising candidate for the fabrication of 1-dimensional fibers, 2D films, three dimensional (3D) monoliths, and gels. The highly water-soluble graphene oxide-based biomimetic nanocomposites offer a high potential with their unique characteristic of having a large number of surface functionalities in the biomedical field. This surface functionality is providing high crosslinking capability with different polymers and mechanical properties for this bioinspired nanocomposite [178].

Biomimetic carbon quantum dots (BCDs) are highly fluorescent and can be prepared by pyrolysis of cytidine diphosphate choline and ethylenediamine. These biomimetic quantum dots have high selectivity towards vitamin B12, and their hemolysis study of RBC shows their biocompatibility. So these BCDs can be effectively used for the detection of vitamin B12 in the various biological samples [179].

The AgNP loaded oxidized carbon nanotubes with mussel inspired polymer coating exhibiting prominent antibacterial activity with minimum cellular toxicity. These self-sterilizing biocompatible surfaces can be used for the fabrication of different biomedical devices having potential antibacterial activity. This provides an effective method for health care professionals and researchers to combat device-related bacterial infections and the potential health risks. Most probably, the post-surgical bacterial infections related to the usage of different medical devices like stents, various implants, and heart valves can be minimized. Biomimetic fluorescent carbon quantum dots (BCDs) with high vitamin B12 selectivity synthesized from the pyrolysis of cytidine diphosphate choline and ethylenediamine. These biomimetic carbon quantum dots can be effectively used for the detection of vitamin B12 in various biological samples.

12. Bioinspired polymeric nanocomposites

A composite is a material composed of two or more constituents having different mechanical properties. Certain additives and fillers are added to the polymer matrix, and a polymer composite is formed. The additives or fillers in a nanocomposite must be in nanoscale. Nanoscale fillers have a high aspect ratio and great surface area per mass. In early times, the commonly used additive was glass fiber (10-30 μm). Polymeric composites may be a hybrid, both organic and inorganic components, or wholly organic, and are polymeric or copolymeric nanoparticles dispersed in the polymeric matrix having different shapes and sizes. Organic polymer composites are developed through three methods; small self-assembled molecules, pre-formed nanorods from renewable resources, and electrospun nanofibers [180]. Three-dimensional approaches are usually employed in design models [181]. When polymeric nanocomposites are hydrated and filled with nanomaterials, it becomes polymeric nanocomposite hydrogels. As it is a hydrated system, it could be used to mimic various biological systems especially the properties of tissue, inside the body by incorporating polymers. The porous interconnecting networks nanocomposite hydrogels, we could create a network that enables the exit and entry of wastes and nutrients inside the body [182]. Rather than depending on various traditional methods for constructing the polymeric nanocomposites, the strategy of bioinspired assembly seems to be more beneficial as it offers the advantage of great mechanical strength and physicochemical properties, which attributes to the high-level performance of the bioinspired polymer nanocomposites. The nacre, composed of organic and inorganic elements obtained from mollusks seems to be an excellent platform for the bioinspired nanocomposite fabrication [183]. Multiple polymer composites mimic the extracellular matrix (ECM) and are successfully used for cartilage regeneration. These tissues have physical and chemical characteristics as that of native cells. The hydrogel provides the best microenvironment for encapsulated stem cells. Inorganic elements loaded polymers are also used in tissue regeneration. The conductivity of metal nanoparticles especially gold nanoparticles, responds to electrical stimulations to mimic neuronal pathways, and thus they are suitable for tissue regeneration [184].

The polymeric nanocomposite hydrogels loaded with metal nanoparticles can be used in tissue regeneration. The polymers loaded with metal nanoparticles help to mimic the neuronal pathways upon responding to the electrical stimulations provided. This enables these bioinspired polymeric nanocomposites for the advanced possibilities in the field of regenerative medicine, including stem cell therapies and tissue engineering.

13. Bioprinting

Bioprinting utilizes the possibilities of 3D printing to study biomaterials, growth factors, etc., to mimic the natural living tissue/cell features. This technique holds up the idea of artificial tissue or cells, which will make a revolutionary change in the field of biomedicine; bioprinting allows the hierarchical arrangement of cells or tissues in a 3D environment. The idea of 3D printing chooses a whole area of application like mechanical, physical, chemical, and biological, while the bioprinting deals with an area of biological aspects. In the past few years, 3D bioprinting technology has been found to incorporate the printing of scaffolds, thereby regenerating living organs, joints, ligaments [184]. The other important field of bioprinting is in cancer therapy. 3D printing of microstructures was successfully implemented for cancer cell migration detection and to understand the physical behavior of cancer cells. Another example is the bioprinting of supporting cells and endothelial cells. 3D in vivo microchip was designed inside a hydrogel by Digital Microstructure Device-based Projection Printing (DMD-PP). This microchip mimics the honeycomb structure of our blood vessels and they can differentiate between cancerous HeLa cells and non-cancerous 10 T1/2 cells. Differences in the migration speed of both cells are well understood by this microchip [185].

Cancer bioprinting involves the production of cancer cells, tissues, and other materials with the same characteristics of cancer tissues in terms of cancer initiation and progression. By using extrusion printing a tumor model is developed with the help of gelatin bio-ink to mimic the extracellular matrix. Thus, high cell viability can be achieved. The bio-ink material can be easily prepared from the patient's own cell or tissue [186].

3D bioprinting technique can print both cells and scaffolds at the same time. This can be used to make human cell-based scaffolds that can be used to replace in vivo study conditions and animal models. 3D printed chitosan-based nanostructures have less antibiotic resistance so it can be used for the treatment of bone injuries [187]. Auricular cartilage 3D bioprinting can be used for the production of 3D auricular tissues to mimic all conditions of auricular cartilage. A printable bio-ink was created by using the combination of human chondrocyte with alginate and cellulose as living tissue. This can be used to print cartilage tissues like auricle and meniscus [188,189]. Fig. 13a shows the illustration of a 3 D printed bionic ear. Human neuroblastoma cells can be constructed with the help of a 3D bioprinting technique by using sodium alginate hydrogels. These hydrogels have low toxicity, cost, and immunogenicity, which makes them favorable for 3D bioprinting [190]. The latest four-dimensional (4D) bioprinting is capable of the construction of very complex functional structures. 4D bioprinting is not only responsible for cell generation but also responsible for the functionalization and maturation of cells with time. These 4D printed structures are capable of changes with time under various stimuli to adapt to the microenvironment [191]. Fig. 13b shows the application of 4D bioprinting in bone tissue engineering. Besides, the 3D bio-printed human neuroblastoma cells being a more complex and physiologically relevant 3D cancer model, can be used inorder to get more insight regarding tumorogenesis and tumor progression. This can further lead to the progression of different innovative strategies for effective cancer therapy.

14. Other applications

14.1. Dry adhesion

Bioinspired dry adhesives produced from mushroom-shaped microstructures (micropillars) with strong pull-off strength. The shapes of microstructure from spiders, toads are not usually preferred for dry adhesives because they get fall off when in contact with the wet surface. Most of the studies show that the mushroom-shaped microstructures an excellent adhesion even in the rough surfaces due to long electrostatic attractive forces, and these adhesives have a wide application that ranges from daily routine purpose to the industrial field. Moreover, the idea of using mushroom-shaped micropillars inspired dry adhesives is economical also. The progress in the research field increases it will pave a new path in the commercial field and biomedicine [79,192–195].

Octopus is a soft-bodied aquatic creature that has several unique characters as it can camouflage according to the surroundings, and another specialty is in its eight bulbous hollow limbs, which help them to

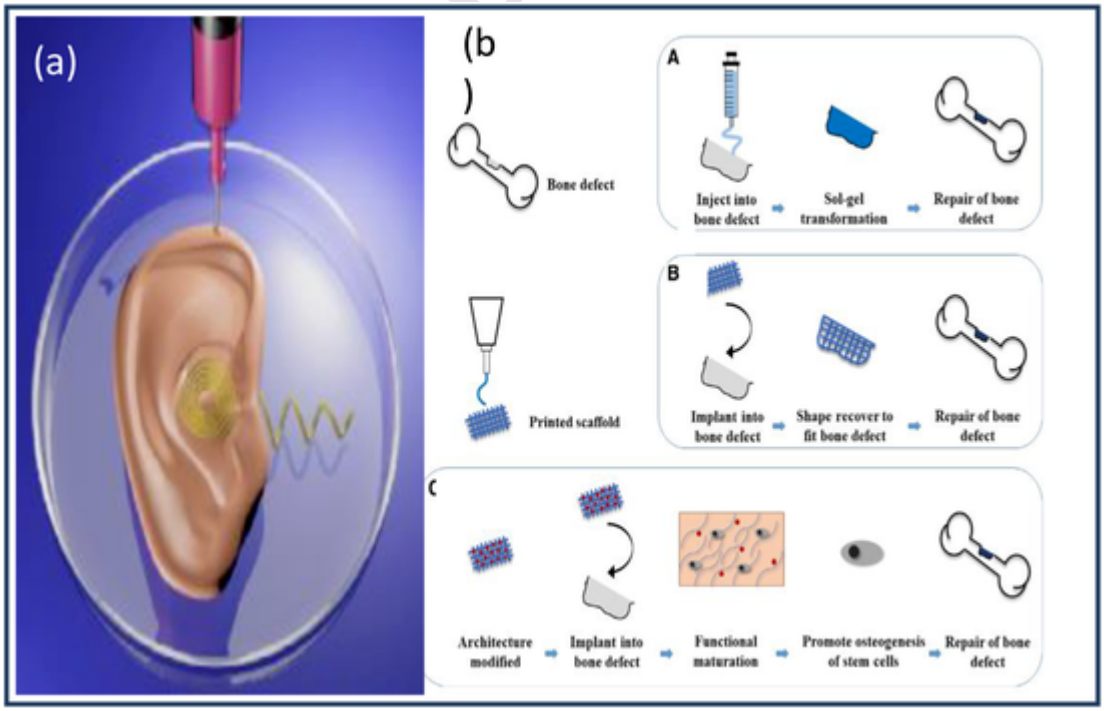

Fig. 13. (a) Illustration of a 3 D printed bionic ear. Reproduced with permission from Ref. [188]. Copyright 2013, American Chemical Society. (b) Application of 4D bioprinting in bone tissue engineering. Reproduced with permission from Ref. [191]. Copyright 2019, Elsevier.

swim. From its hollow bulbous limbs, scientists developed temperature resistant adhesives that exhibit strong adhesion under dry, cold conditions as well as on different surfaces like skin, glass, and rough surfaces. Most of the polymer-based adhesives are thermolabile so bioinspired poly(N isopropylacrylamide) adhesives are developed inspired by the microstructures present in the limbs of octopus with high peel-off strength [79,196]. Dry adhesion is best studied in Geckos. The toes of Tokyo Geckos are highly hydrophobic in nature and have an equal affinity for both hydrophilic and hydrophobic surfaces. Researchers proved that the force of interaction between their toe and the surface is van der Waals' interaction by using a hydrophobic gallium arsenide (GaAs) semiconductor wafer. The toe was pulled down and measured the shear force on toe [197]. Later, the photoresponsive bioinspired dry adhesive tape was developed by doping photoresponsive chromophore spiropyran into polydimethyl siloxane (PDMS) films. They interconvert between neutral spiropyran and zwitterion merocyanines [198,199].

The self-cleaning and adherence properties of Gecko was mimicked to produce synthetic micropatterned carbon nanotube self-cleaning adhesives, which have a wide range of applications in robotics, especially to design wall-climbing robots and in microelectronics. These synthetic adhesive tapes have greater shear stress than Gecko [200]. The robot Mini Wheg™ was designed to walk through walls and ceilings like an insect by mimicking the insects. This mechanism can also be applied in manipulating smooth surfaces such as lenses, CDs, and DVDs [201,202]. Insect-derived adhesive tapes are less affected by contamination than pressure-sensitive adhesive tapes, and if they are contaminated, they can be washed with soap water [203].

Bioinspired mushroom-shaped micropillars have a strong pull of strength, which has excellent adhesion capacity on the rough surfaces due to electrostatic attractive forces. These are very economical and can be employed to manufacture artificial, self-cleaning, re-attachable adhesives.

14.2. Anti-reflection

Several insects possess the property of anti-reflection. Eyes of different moth, eyes of mosquitos, flies and wings of butterflies, and cicadas have the property of anti-reflection surfaces. Certain micro/nanostructures present in the eyes and wings as protuberances in the form of pillars or arrays reduce the reflection of light and helps them to detect its predators and prey in the dark. These micro/nano protuberances can be inspired to produce a surface for signal lights, solar panels, displays of phones, televisions, the lens of eyeglasses, camera, etc. [204,205]. In addition to the antireflection property, self-cleaning, hydrophobic characteristics are also expected [7,206].The corneal surface of the moth's eye contains very fine microstructured arrays becomes the main reason for the reduction of reflection [3]. Iridescence is a mechanism of differential refraction of light waves, which will become the anti-reflection properties of most of the insect wings [207]. Micro/nano protuberances inspired activity can be used to produce a surface for signal lights, solar panels, displays of phones, televisions, the lens of eyeglasses, camera, etc., and reduce reflection of light and self-cleaning.

14.3. Bioinspired fur

A bioinspired nano-fur material has been developed inspired by the *Salvinia* fern and *Notonecta glauca,* which is having air retaining and drag reduction capacities.A satisfactory air retention capacity is maintained by covering dense layers of micro and nano-sized hairs having microcavities between them. This superhydrophobic air retaining mechanism finds enormous applications in various fluid systems.

14.4. Fmoc-modified amino acids and short peptide

Fluorenylmethyloxycarbonyl chloride is used to introduce the fluorenylmethyloxycarbonyl protecting group as the Fmoc-carbamate to protect naturally occurring amine groups in protein synthesis as well as other peptides. This functionalization results in excellent self-assembling properties. Fmoc has high aromatic and hydrophobic features. Single amino acids, dipeptides, tripeptides, tetrapeptides, and pentapeptides are modified with Fmoc and possess a wide variety of applications. Traditional peptides have complicated molecular structures and sophisticated extraction and synthetic procedures; thus, they are replaced with Fmoc modified peptides. Fmoc modified peptides exhibit broad-spectrum anti-inflammatory effects by preventing neutrophil entry into inflammatory lesions and by inhibiting T cell activation. Single amino acid modified Fmoc can be used as a therapeutic agent for inflammatory diseases. Fmoc-WFF was found to be an alternative for the mammalian ribonucleotide reductase inhibitor. Their antibacterial activity was also studied; a cationic Fmoc-FF derivative can be prepared by conjugating pyridinium moiety to the C-terminal of Fmoc-FF, which possesses effective antibacterial activity against Gram-positive and Gram-negative bacteria. The antibacterial activity can be modified more sensibly by changing the amino acid residue [208].

14.5. Micro swimmers

These are helical microdevices that are inspired by different plants and different unicellular organisms. The plants contain vessel element-spiral vessels mainly contained the water-conducting tissue called xylem in flowering plants from which the concept of helical microswimmers generated. These are made by simply coating the plant's helical fibers with a magnetic element. The advantage of using plants is that from a single plant, one could produce millions of helical swimmers [209].

14.6. Bioinspired pressure sensors

Mimosa/shame plants are creeping flowering plants. The specialty of this versatile plant is they are very sensitive. i.e., they rapidly close up their leaves in one touch and return to their original position after a few minutes. Mimosa plant contains an array of pinnules above and below a portion of the leaves which is responsible for the total sensitivity to external stimuli. This is the main defense mechanism behind the function of these plants. Inspired by this plant, a pressure sensor is developed with high sensitivity [210,211]. Another system is hydrogel actuators inspired by the motion of the mimosa leaves, which functions in different aqueous and non-aqueous environments [212].

14.7. Miscellaneous

Other major examples include *Escherichia coli* and sperm cells which are great swimmers. *E. coli* consists of peritrichous flagella, which is responsible for its motility, while sperm cells are monotrichous. In the case of sperm cells, its tail is the reason for its motion. Helical swimmers in the case of sperm cells it are called helical spermbots are employed to catch and deliver immotile sperm cells. The effect of helical sperm bots can be effectively increased with the help of a magnetic field. Another application of spermbots is cancer treatment by delivering doxorubicin in cancer cells [213,214]. Widespread butterfly species *Vanessa cardui*, painted lady, was used as a model for developing simultaneous diffractive and hydrophobic surfaces. The natural structures of butterflies were replicated with the help of the technique of soft lithography or nanoimprinting. Dental wax is used for the purpose since common polymers such as polydimethylsiloxane and other resins are unsuitable for immediate use with sensitive natural specimens. Dental wax is compati-

ble with the fragility of butterfly wings. This is applied in optofluidics [215].

Lotus leaf-like superhydrophobic polystyrene film with porous microspheres was prepared by the electrohydrodynamic method. Superhydrophilic nanowire array has a surface with great bio-adhesion properties. They can selectively capture circulating tumor cell and inhibits the adhesion of normal blood cells. Thus, they are used for cancer diagnosis. During cancer metastasis, the cancer cells may detach from the solid tumor and circulate through the bloodstream. These cells can be captured by rose petal inspired poly dimethyl siloxane (PDMS) surface-immobilized with epithelial cell adhesion molecule antibodies (anti-EpCAM). Rose petals have microcavities and micro papillae and are the best templates for this purpose [216]. Biomimetic micro/nanostructure surfaces can be made functional surfaces for microfluidic and tissue engineering applications. Surface modification is made by an ultrafast super pulsed laser, Femto-second laser. Direct irradiation of materials by this fast laser leads to modifications on the surfaces, which mimic natural surfaces [86].

An effective separation technique has been introduced by combining the bioinspired surface modification technology with that of multi-walled carbon nanotubes (MWCNT) and membrane imprinting technology. Bioinspired porous enoxacin imprinted nanocomposite membranes (EINCMs) fabricated from the MWCNT based nanocomposites is efficient in selective purification and separation of enoxacin also exhibit an antifouling activity [217]. Peptide inspired micro and nanostructures are developed and have applications in electronics. The amphiphilic properties of phenylalanine were mimicked, and L,*L*-diphenylalanine based micro and nanostructures (FF-MNS) were designed. They are used as dielectric material in pentacene based field-effect transistors. The chemical and physical stability of phenylalanine makes them more suitable for electronic applications. FF-MNS are also used in enzyme-analyte sensing, and the functionalized FF-MNS have applications in protein detection [218]. Bio-inspired chitosan encapsulated gold nanoparticles are prepared by reducing in-situ tetrachloro auric acid. This bio-inspired gel can be used for cell immobilization, the electrochemical study of cells, and monitoring cell adhesion, proliferation, and apoptosis of cells on electrodes. A biomimetic graphene aerogel with highly ordered architecture mimicking the architectural feature of the plant *Thaliadealbata* stem, and this strategy can be adopted for elevating the mechanical properties of porous structures also strength and flexibility. The graphene oxide sheets are molded into 3D lamellar layers by the bidirectional freezing method and can potentiate its electrical conductivity [219].

Marine organisms like siliceous sponges and diatoms can be used for the production of biohybrid materials. Functional silica-based biomaterials are prepared by biomimetic and bioinspired silicification. A thin silica layer is capable of coating living cells, viruses and thereby it can provide a protective shell around them. So this bioinspired silica is a biocompatible material and can be used for the treatment of bone-related disorders and also for the production of implantable devices [220]. Contact lenses are used for the delivery of drugs to the tear fluid. Bioinspired strategies can avoid the problems associated with contact lenses. The most important bioinspired strategy to make an artificial binding site for the drug in the contact lenses is by mimicking the human binding site for that particular drug. It can also prepare by mimicking the properties of eye mucin. All these biomimetic approaches can be used for preparing contact lenses with the required amount of drug release profiles [221].

Polymeric micelles of a copolymer with biomimetic phosphorylcholine can have a suitable size and physiological stability. These micelles are get rapidly internalized into the cell due to its biomimetic phosphorylcholine property. These polymeric micelles can prolong the blood circulation and also facilitate accumulation in the target site. This biomimetic copolymer can be used for the preparation of polymeric micelle which is biodegradable and reduces toxicity and side effects associated with the loaded drug. So this delivery system can be used for anticancer agents to eliminate its side effects (Fig. 14) [222]. Cocklebur is covered with spines and it can be carried from the parent plant to a longer distance by any animal because of their unique structure. This structure inspired aptamer DNA assembly can be used for the targeted delivery of drugs. The DNA nanocockleburs have a high affinity towards the target cells which could eliminate the cytotoxicity associated with non-targeted sites. These nanocarriers exhibit greater cell uptake and it can be used for the targeted delivery of anticancer agents [223].

Nanoplatelets are the nanoparticles surrounded by platelet membranes. Phyto chemotherapy has limited anti-metastasis efficacy due to poor targeting capacity. An anticancer agent and a photothermal agent can be encapsulated into the biomimetic nanoplatelets. These nanoplatelets have a high affinity towards the tumor cells and clear the circulating tumor cells in the blood and lymphatic circulations. These have greater cellular uptake and increased cytotoxicity to tumor cells than normal nanoparticles. So, this bioinspired nanoplatelet can be used as a good strategy for the treatment of cancer [224]. A dual functional polyurethane film can be made to mimic the inner surface of the blood vessels by surface texturing and the NO release was achieved by the use of NO donor. This biomimetic surface can increase the coagulation time and also reduces the adhesion and activation of platelets and adhesion of bacteria in the plasma. It also offers good biocompatibility [225]. A multi-functional metal surface with switchable wettability is prepared by the inspiration from the natural reed leaf and lotus leaf structures. Reed leaf has anisotropic wettability while the lotus leaf has isotropic wettability. This biomimetic metal with switchable wettability is prepared by using copper metal and it shows pH-responsive wettability [226].

15. Perspectives

The bioinspired and biomimetic systems are emerging areas of research for the development of novel technologies in biomedicine. These systems play a vital role in the field of biomedicine. They can be a cost-effective and environment-friendly technique as compared to other available techniques. They can be used as a treatment strategy for many disease conditions. In cancer therapy, it can eliminate the side effects by targeting affected cells only. By the combination of biological and synthetic systems, a novel drug or gene carrier system can be developed. Bioinspired and biomimetic macro or nanoparticle-based drug delivery are well studied. They exhibit application in drug and gene delivery, theranostics and they have a great influence on the various biological systems due to their better biocompatibility and lesser toxicity. These systems have a high potential to solve many problems associated with drug and gene delivery. Biomimetic synthesis of nano- or micromaterials is the most promising field.

The complex biological systems can be simplified by using biomimetic systems. A thorough understanding of biological systems will help in the development of efficient techniques and processes in biomedicine.Inspired by the superhydrophobic and anisotropic frictional properties of snake scale surfaces, researchers recently developed a bionic superhydrophobic stainless steel surface. The superhydrophobicity of the snake scale can mimic to design of antimicrobial surfaces for various applications [227]. Bioinspired nanoformulations can be used for the treatment of many lifestyle diseases like cancer and diabetes; with high efficiency and minimize unwanted side effects by mimicking the interaction of cells with living entities. These can also be used for the development of highly efficient nanomedicine. Although there are many achievements in this field, it is in its initial stage of development. There are many challenges ahead. Currently, only a few properties of biological materials and systems have been used in this field in the last few years, and many biological properties need to be used in this field. Mimicking the biological systems and functions will produce a greater impact on treatment strategies, but it is very difficult to achieve. Even

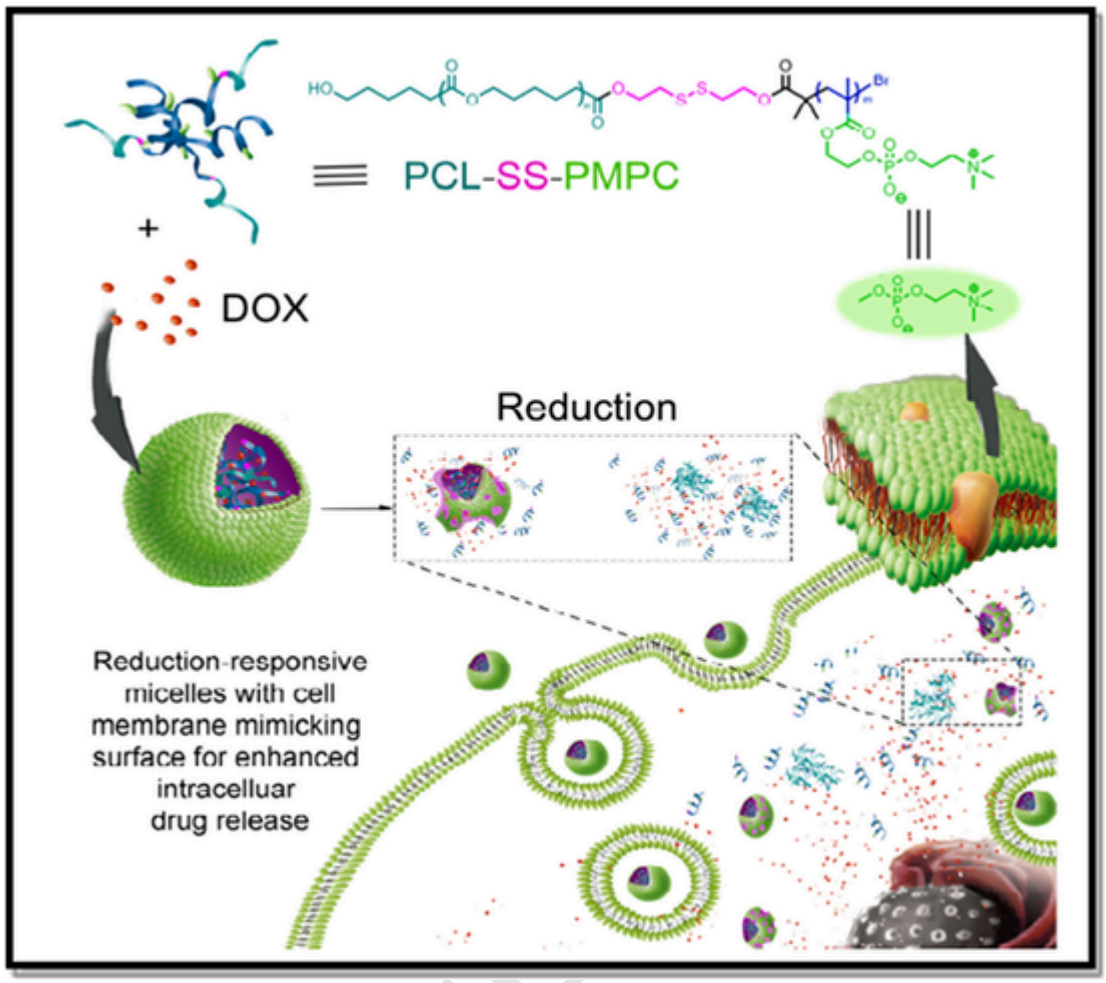

Fig. 14. Schematic illustration of self-assembly, internalization, and drug delivery of phosphatidylcholine based polymeric micelles for anticancer therapy. Reproduced with permission from Ref. [222]. Copyright 2018, Elsevier.

though these achievements are exciting, many of the studies are still in very early stages and have to face numerous challenges. Most of the reported systems have one or more disadvantages like biosafety hazards, immune response, host recognition, etc. Therefore a well planned and elaborated in vivo studies are needed to make these dream achievements into a reality.

Most of the cell inspired system does not exhibit the self-cloning capacity of the natural cell. So, it can only be used for temporary treatment and not suitable for the sustained delivery of drugs. It is very difficult to copy many natural processes. Most of the biomimetic drug delivery systems are studied in vitro. Rapid progress in this research field could necessitate the in vivo evaluation too. A better understanding of release kinetics from this biomimetic carrier will expand its clinical applications. Many studies based on biomimetic and bioinspired are presently underway. The application of artificial intelligence in the generation of bioinspired and biomimetic systems could be another area of focus in the coming years. By developing deeper knowledge and overcoming associated challenges, this can be a promising field for the future.

16. Conclusions

Bioinspired and biomimetic technology provides a plethora of opportunities in the field of biomedicine. An appropriate application of the bioinspired and biomimetic principles and strategies into different engineered systems is required for the successful fabrication and implementation of nano- and microstructures. This nature-inspired technology serving as a bridge between nature and science is having tremendous opportunities in drug and gene delivery, tissue engineering, biomedical equipment, nanosized scaffolds and hydrogel systems, carbon-based nanostructures, polymeric nanocomposites, and several others. Bioinspired and biomimetic approaches express boundless applications in cancer therapy since they can mimic the biological configuration of the human body. They exhibited various advantages over other nanomaterials like better biocompatibility, biodegradability, targeting efficiency, low toxicity, and less immunogenicity. Bioinspired and biomimetic systems can improve therapeutic efficacy by integrating the advantages of biomimetic nanocomposites with conventional or new therapeutic ideas. As the research based on bioinspired and biomimetic technology is in the developing stages, we still need to face more hurdles to make this research helpful for cancer patients. The most innovative emerging idea includes the biomimetic therapeutic device/instrument generation.The usual polymers can be replaced with naturally occurring metal nanoparticles. The bioinspired and biomimetic nano- and microstructures with their ability to imitate a biologic system are exhibiting upgraded, super modified characteristics and several other features. The bacteria, virus, fungal, sponge, mammalian cell, and several other biological systems inspired micro- and nanostructures are regarded as the most researched and interesting field in today's scenario.

Declaration of Competing Interest

There are no conflicts to declare.

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