RSC Advances

REVIEW

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Cite this: *RSC Adv.*, 2021, **11**, 24722

Potentialities of bioinspired metal and metal oxide nanoparticles in biomedical sciences

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Received 2nd June 2021
Accepted 1st July 2021

DOI: 10.1039/d1ra04273d

rsc.li/rsc-advances

To date, various reports have shown that metallic gold bhasma at the nanoscale form was used as medicine as early as 2500 B.C. in India, China, and Egypt. Owing to their unique physicochemical, biological, and electronic properties, they have broad utilities in energy, environment, agriculture and more recently, the biomedical field. The biomedical domain has been used in drug delivery, imaging, diagnostics, therapeutics, and biosensing applications. In this review, we will discuss and highlight the increasing control over metal and metal oxide nanoparticle structures as smart nanomaterials utilized in the biomedical domain to advance the role of biosynthesized nanoparticles for improving human health through wide applications in the targeted drug delivery, controlled release drug delivery, wound dressing, tissue scaffolding, and medical implants. In addition, we have discussed concerns related to the role of these types of nanoparticles as an anti-viral agent by majorly highlighting the ways to combat the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pandemic, along with their prospects.

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1. Introduction

Nanotechnology mainly focuses on the structures of matter from a dimension of the order of less than 100 nm. Nanoparticles with ranged lengths and specific ratios exhibit unique chemistry and physics, awakening abundant properties. In

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addition, the change in the surface-to-volume ratio is one of the main reasons behind more spontaneous effects. With the decrease in the structure size, the surface-to-volume ratio increases, leading to better chemistry and physics of the conformation than the bulk matter. Nevertheless, these nano-dimensional structures possess extraordinary properties, and it is evident from the fact that nanotechnology relies on the novel properties and behavior shown by nano-range structures of the bulk confirmation of the same matter. These nanoparticles are considered unique as they exist in small size, possess high surface area, surface chemistry and charges, and are therefore known for their multi-functionalities.

Moreover, these nanoparticles are considered reliable drug carriers with a robust, targeted delivery of therapeutic molecules, as they can be easily surface modified for the better attachment of the targeted ligands. Usually, a targeted drug delivery system (DDS) mainly includes four steps: retain, target, evade, and release. It also holds its constituents either by encapsulating, linking, or allowing them to escape the defense mechanism in the body.[1–4] Metal and metal oxide nanoparticles and nanomaterials are found in different forms and dimensions (zero-dimensional nanoparticles, one-dimensional nanomaterials, two-dimensional nanomaterials, and three-dimensional nanomaterials). In addition to metal and metal oxide nanoparticles, several other forms of nanostructures, including polymers, liposomes, dendrimers, carbon, and silicon-based nanoparticles, have been successfully utilized for drug delivery and other therapeutic purposes.[5,6] Furthermore, Table 1 shows several metal-based nanomaterials that are utilized in various fields for enormous applications.

Several works have been reported on nanostructured metal and metal oxides, which are considered future materials for

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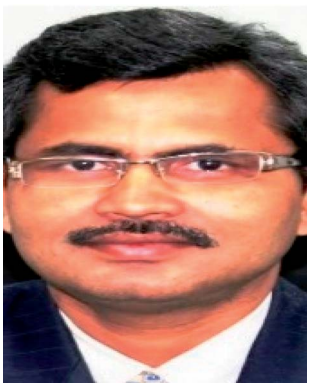

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Table 1 Represents various types of metal-based nanomaterials that are utilized in various domains

S. no.	Nanoparticle	Example	Applications
1	Metal-based nanoparticles	Manganese (Mn), iron (Fe), silver (Ag), gold (Au), platinum (Pt), selenium (Se), zinc (Zn), and others	Therapeutics, bio-imaging, electronics, magnetic resonance imaging (MRI), data storage, antimicrobial agent, and textile
2	Doped metal nanoparticle	Au–CuO, Pt–ZnO, and others	Antimicrobial, drug delivery, sensors, and others
3	Sulfide-based metal nanoparticle	FeS, CuS, and others	Bio-imaging, cancer therapy, drug delivery, diagnosis
4	Metal oxide nanoparticle	CeO_3, ZnO, CuO, and others	Antimicrobial, biomedical, electronics, optical, detection
5	Metal organic frameworks (MOFs)	Zn-MOF, Mn-MOF	Solar cells, super capacitors, fuel cells, sensors, drug delivery, super capacitors, photoelectrocatalysis, and others

nanobiosensors and exhibit potential applications in the biomedical domain.[7–9] These metallic nanoparticles can be synthesized by various biological and physicochemical approaches, and are further studied for their applications. These synthesized nanoparticles show enormous biological properties, namely antimicrobial, anti-inflammatory, anti-cancer, and anti-angiogenesis, making them good agents to be considered in the biomedical field.[10–12] Nowadays, to fight against drug-resistant bacteria, the metallic nanoparticle is combined with antibiotics that enhance the drug's antibacterial activity and are non-toxic to the other cells.[13,14] Keeping the same idea in consideration, gentamicin–silver nanoparticles were reported to exhibit excellent antibacterial effects.[15]

Many years have passed with the successful utilization of metal and metal oxide nanoparticles in the biomedical field for diagnostics and therapeutics. Among all of the metallic nanoparticles, magnesium (Mg), gold (Au), silver (Ag), aluminum (Al), palladium (Pd), cerium (Ce), copper (Cu), iron (Fe), selenium (Se), platinum (Pt), and titanium (Ti) are the most widely used ones because they exhibit remarkable and distinct properties. Many researchers have reviewed the properties, applications, and their synthesis with many other details.[16–18] In this review, the major focus is laid on the biomedical aspects of biogenic metal and metal oxide nanoparticles by covering their utilities in both diagnostics and therapeutic applications. The review also highlights metal and metal oxide nanoparticle properties, and simultaneously covers the biogenic synthesis route of metal and metal oxide nanoparticles. Furthermore, a brief overview of the utility of metal and metal oxide nanoparticles during the current pandemic [Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)] has been discussed, as these metals and metal oxide nanoparticles exhibit great anti-viral properties. In short, the review has compiled the up-to-date research works performed on the biogenic metal and metal oxide nanoparticles, giving a detailed literature overview on the topic, and this review work is and will be one of its kind.

2. Physicobiochemical properties

The metal and its oxide-based nanoparticles have an enormous list of properties that include non-toxicity, antimicrobial activity, and anti-insecticidal activity. Therefore, they exhibit vast applications in the biomedical field for the diagnosis and treatment of life-threatening diseases.[19] Various metals and metal oxides play an important role in maintaining life processes, and their slight deficiency in the body could lead to several disorders. Here, we focus on several essential biogenic metals and metal oxide nanoparticles that are mainly utilized in the biomedical domain by highlighting their importance in the human body. For instance, a minute amount of cerium can boost an organism's metabolic rate. This leads to enhanced antioxidant and antimicrobial activities, and therefore helps in combating cancer and Alzheimer's disease. Owing to their lack of stability in living systems, the use of nanoceria has often been limited.[20–23] Although traditional solid-state reactions are required with some specialized techniques for synthesizing nanoceria, some methods persist with solution-based techniques that utilize hydrothermal, solvothermal, and co-precipitation reactions, providing stability to the nanoceria.[24] Nanoceria shows antibacterial activity that acts as an effective oxidant in prophylactic protocols.[25] The unique properties of nanoceria have been utilized in ultraviolet absorbance, oxygen sensing, and automotive catalytic converters; for example, nanoceria shows brilliant sensing performance towards methyl orange and can be used in nano-therapeutics to decrease mediators of chronic inflammation.[26,27] However, there are reviews available that highlight the green synthesis of cerium oxide nanoparticles and their use in the biomedical domain by discussing their properties.[28] Similarly, highly stable, fluorescent and water-resistant cerium oxide nanoparticles have been reported that enrich the soil by increasing catalase and ascorbate peroxidase activity.[29]

Furthermore, cobalt nanoparticles (CoNPs) have found use in various dimensions as they exhibit good magnetic, optical, mechanical, chemical, and electronic properties. The reduced dimensions of cobalt provide modified, but effective profits in

the areas of industrial and biomedical applications.[30,31] Compared to other nanoparticles, CoNPs have gained great interest from researchers over time, as they are known to possess high purity and quality, and are therefore widely utilized in magnetic resonance imaging (MRI) and drug delivery. Moreover, they also eliminate the alteration in response stability or magnetization.[32] Usually, nanoparticles that show metallic nature showcase magnetic, optical, and catalytic properties, which can be used for developing sensor-based devices, as they possess special features such as small dimensions, high surface-to-volume ratio, and heat transfer. Furthermore, these metal and metal oxide nanoparticles can be utilized to develop anodes of different types that help them develop highly sensitive biosensors.[33,34] Similarly, Au NPs exhibit distinctive physical and chemical features that support exploiting various arrays of solicitations in diagnostics, therapeutics, drug delivery, bio-labeling, biological and chemical sensing, imaging, nonlinear optics, photovoltaic and catalysis.[35–38] On the other hand, physical properties and the surface plasmon resonance (SPR) band of silver nanoparticles (Ag NPs) depend on their physiology and morphological characters, including shape, size, core charge, surface ligand, and temperature. Similarly, iron nanoparticles' high reactivity with water and oxygen is their greatest drawback, but their catalytic nature helps them find various uses in industrial applications. Moreover, iron nanoparticles' magnetic properties contribute to manipulating the treatment and diagnosis of diseases and applications for fabricating electrical components, transducers, and sensors.[39,40] Furthermore, magnesium oxide nanoparticles (MgONPs) possess numerous properties. They can act as anti-biofilm agents, *i.e.*, they inhibit the growth of biofilm and remove pre-established biofilms. They also exhibit self-cleaning activity, helping in the degradation of methyl violet dye, as well as the removal of phosphorus from wastewater, which is one of the reasons for inhibiting plant growth.[41–43]

Quasi-one-dimensional nanomaterials, such as nanorods, nanotubes, and nanobelts, are widely used to produce chemo-resistive nanosensors. Moreover, a drastic change was noticed in MgO nanocrystals when a small amount of base substance was added, showing that the crystals' size increased with increasing temperature and decreased with increasing pH.[44] MgO and magnesium hydroxide nanoparticles possess excellent luminescence for photonic applications because they exhibit excellent thermal properties, biodegradability, and non-toxic nature. MgONPs also exhibit potential antibacterial activity, and are utilized in cryoinjury; therefore, they find their utility in medicine.[14,45–50] Nickel nanoparticles (NiNPs) are usually very cheap and work even in milder conditions to obtain higher yields of products with less time for reaction. Usually, nickel oxide shows a bandgap from 3.6–4.0 eV, as it is a p-type semiconductor in nature. Nickel nanoparticles have anti-inflammatory properties, and so they are exploited more in the field of biomedicine. NiO has unique characteristics, such as high surface area, fast rate of metal ion release, and good absorption ability, which decreases their cytotoxic effects.[51,52] Selenium is the most studied metal nanoparticle. It appears red, black, and metallic grey in color when it is in powder form, vitreous form and crystalline form, respectively. Furthermore, it is a semi-solid metal similar to sulfur or tellurium, and it exists in various oxidation states (2^-, 2^+, 4^+ and 6^+). Moreover, various selenoenzymes, such as glutathione peroxidase (GPx), thioredoxin reductases (TrxR), and deiodinases (DIO), have selenium as their core when they are involved in several physiological antioxidant defense systems. Depending on the dose, duration and oxidation state, selenium possesses unique pro-oxidant and antioxidant effects.[53–56] Similarly, zinc oxide nanoparticles (ZnO NPs) possess exclusive optical, electrical, catalytic, and photochemical properties utilized mostly in the industrial and biomedical fields. These properties are adjusted by doping with other compounds and adjusting their synthesis conditions.[57] These various properties of the metal and metal oxide nanoparticles also help them find their immense potentialities in energy domains. For example, they can be used to develop various energy storage devices, developing batteries[58–60] that can be further utilized in the biomedical domain.

3. Biogenic synthesis

Nanoparticle synthesis is the process of creating nanoparticles, and is considered the most important part of nanotechnology because the synthesis route of a nanoparticle highly defines its properties and applications; this can be achieved through physical, chemical or biological routes. Some metals listed in the periodic table are highly utilized in nanoparticle synthesis, and employed in the biomedical field for diagnostic and therapeutic applications. Various techniques like top-down and bottom-up are mostly utilized to synthesize metallic nanoparticles. Top-down approaches mainly break a bulk-piece into nanoscale dimensions with the use of different techniques, like mechanical milling, etching, cutting, and grinding techniques *via* laser ablation, vapor-phase synthesis and pulsed wire discharge, whereas the bottom-up approach is the chemical reduction, sonochemical reduction, microemulsion, electrochemical, hydrothermal, sol–gel, polypol process, microwave-assisted and biological methods.[11] Fig. 1 combines different approaches to synthesize metallic nanoparticles, and this review combines and presents various biogenic routes to synthesize metal and metal oxide nanoparticles. Furthermore, Fig. 2 illustrates the harmful effects of the chemical and physical synthetic routes, and highlights the benefits of the biogenic routes for the synthesis of the metal and metal oxide nanoparticle.

A study on green approaches to synthesize metal and metal oxide nanoparticles exclusively includes the utilization of fungi, bacteria, yeasts, and plant extracts, in which plant extracts have been widely used. The various kinds of phytochemicals in plant extracts, namely terpenoids, ketones, flavonoids, aldehydes, amides, and carboxylic acids, play a crucial role in formulating and increasing the bioactivity of the nanoparticles. Unlike chemically synthesized nanomaterials, green synthesized nanomaterials show various distinctive properties, like mechanical, optical, thermal, surface, electrical, chemical, physical and biological. These help them show a variety of potentialities in various domains, like health care, agriculture,

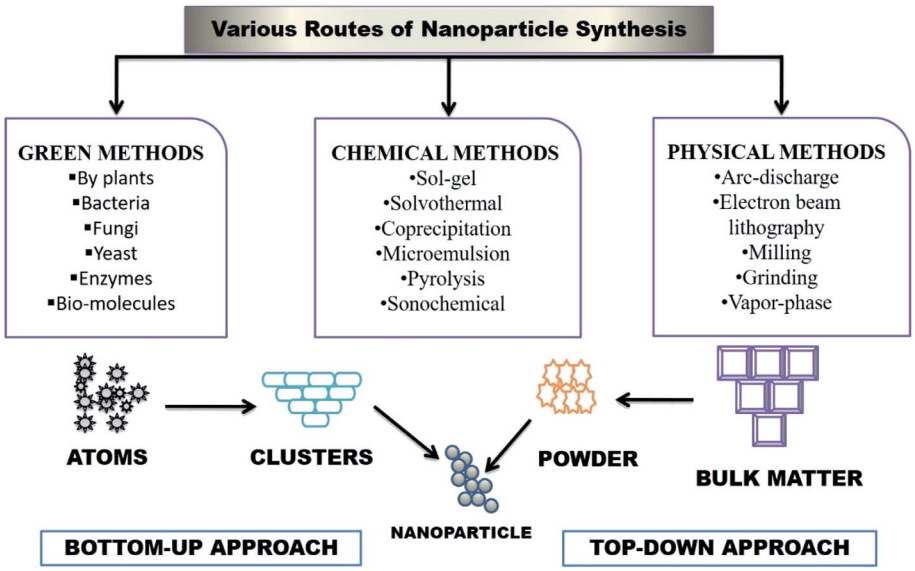

Fig. 1 An illustration of nanoparticle synthesis *via* different biological/green, chemical, and physical methods, along with top-down and bottom-up.

environment, robotics, energy, information technology, aeronautics, mass communication, heavy industry, consumer goods, and the development of various sensors, like biosensors, nanosensors, and nanobiosensors. Moreover, these green synthesized metal and metal oxide nanoparticles are used in designing different agents for various diagnostic purposes, therapeutic drug and gene delivery, the development of treatments/cures for several infectious and non-infectious diseases, and neurodegenerative and cardiovascular disorders.[61–63] Furthermore, there is a lot of data available in the literature that briefly discuss the various properties, characterization methods, biogenic route of synthesis of metal and metal oxide nanoparticles, and highlight their utilities in various domains, like agriculture, environment, cosmetics, food industries, sensors, among others.[19,64–66]

The biological approach utilizes various biological molecules as alkaloids, flavonoids, and proteins derived from plant sources to synthesize metal nanoparticles that are mostly accountable for providing stability and the development of biologically active properties.[8] Mainly using the extract of plant parts has arisen as a new, innovative, simple, environment-friendly, cheap, strong, and fast technique for synthesizing metal and metal oxide nanoparticles. This biological approach is also known as green chemistry methodology, and is more systematic and effective than using microorganisms and other physical or chemical methods. All plant parts from root to aerial, *i.e.*, root hair, root, stem, leaves, flowers, barks, fruits, peels, seeds and gels, consist of various phytochemicals that provide an efficient base for the synthesis of metal and metal oxide nanoparticles by reducing the use of toxic chemicals, and additionally provides natural stabilizing, chelating, and capping agents. In the biological synthesis route, plant-mediated approaches are considered more as it reduces the extra time of identification, preparation of culture media, and isolation of microorganisms. Various biologically synthesized metal and metal oxide nanoparticles and their biomedical applications are summarized in Table 2.

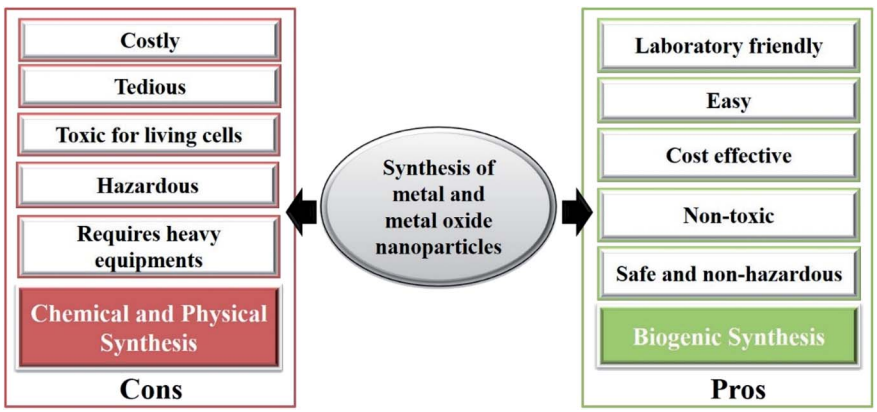

Fig. 2 A schematic illustration showing the positive aspects of green synthesis techniques over chemical and physical routes.

Table 2 Different metal and metal oxide nanoparticles covered in this review, along with their biomedical applications

S. no.	Source	Metal and metal oxide	Morphology	Applications	Ref.
1	L-Glutathione	Gold nanoclusters	Size is 2 nm, with intense red fluorescence and high photostability	Tumor targeted imaging, rapid imaging, fluorescence-imaging guided photothermal therapy of tumor	67
2	Rose Bengal and dextran	Gadolinium nanoparticles	Paramagnetic behavior with 17 nm in size and spherical	Bioimaging and tracking of cancer cells	68
3	PLGA and glycol chitosan shell	Iron oxide nanoparticles	Superparamagnetic spherically shaped of 100–750 nm	MRI contrasting agent	69
4	Black beans (*Phaseolus vulgaris*)	CuONPs	Crystalline and uneven, spherical-shaped nanoparticles	Inhibited the growth of cervical carcinoma cells by generating ROS	70
5	*Nepeta deflersiana*	AgNPs	Spherical and 33 nm in size	Inhibited the growth of cervical carcinoma cells	71
6	*Sargassum wightii*	MgONPs	Spherical with 68.06 nm in size	Cytotoxic activity against lung cancer cells Antimicrobial activity Photocatalytic activity	72
7	*Vaccinium arctostaphylos*	ZnONPs	Spherical, 70–75 nm in size	Antioxidant activity Anticancer activity Antibacterial activity	73
8	*Butea monosperma*	AgONPs	Spherical with 35 nm	Chemotherapeutic drug delivery	74
9	Citrus paradise	ZnONPs	Spherical shaped 24.5 nm	Anti-oxidant activity	75
10	*Moringa oleifera*	La_2O_3 NPs	Spherical, 308 nm	Antimicrobial, anti-oxidation activities and for drug delivery	76
11	Bacterial cellulose	TiO_2 nanocomposites	Dispersed nanoparticles of size between 20–30 nm	Wound healing and antibacterial activity	77
12	Artemisia annua	ZnONPs	Agglomerated, crystallized, spherical shaped, 20 nm in size	Antimicrobial activity for effective mineralization and cytotoxic impact on MG-63 cells	78

Additionally, plants are easily available, safe to handle, and possess various phytochemicals and different secondary metabolites, which act as an important material in synthesizing different metal and metal oxide nanoparticles by acting as reducing, capping, and stabilizing agents. Co-enzyme and co-factors act as desired, reducing the starting agent, and can also act as a precursor in the formation of the nanoparticle. On the other hand, enzymes and protein contents reduce the metal salts into their corresponding nanoparticles. It is proven that certain plants could naturally uptake and biologically reduce the metal ions into nanoparticles from soil that contain salts, minerals or ores by detoxification process and ultimately convert them into nanoparticles.[11]

The review highlights various biological approaches for synthesizing various metal and metal oxide nanoparticles, which are easy, cost-efficient, environment-friendly, and stable using various plant extracts as stabilizing, capping, and reducing agents. These biosynthesized metal and metal oxide nanoparticles have also established their profound uses in various biomedical applications to improve human health. Recently, the biological synthesis of nanoparticles using different plant extracts, fungi, and bacteria has greatly escalated as the synthesized nanoparticles from this method showed excellent polydispersity, dimensions, and stability. Nanoparticles can be utilized in therapeutics and diagnostics, optics, electronics, green energy, wastewater treatment and bioremediation. In this review, apart from the biological approaches for synthesizing metal and metal oxide nanoparticles, their potential applications in the biomedical field are also discussed. Nowadays, the biological synthesis of nanoparticles is more promoted over other physical and chemical methods due to rapid and fast synthesis, better control over size and shape, low toxicity, and cost- and eco-friendly approaches.[8,11,79]

3.1. Synthesis of nanoparticles using plant extracts

Different extracts of plant parts have been used to synthesize various nanoparticles that are mentioned in this review. The leaf extracts of chickpea have been used to synthesize AuNPs, in which the chickpea leaf extract acts as a reducing and capping agent.[80] Furthermore, by using the *Gnidia glauca* flower extract, AuNPs can be synthesized.[81] It was reported that the biosynthesis of both AuNPs and AgNPs could be achieved using the natural precursor clove (*Syzygium aromaticum*).[82] Similarly, another method to synthesize bimetallic Au core–Ag shell nanoparticles is by utilizing *Azadirachta indica* (neem) leaf broth.[83] Furthermore, the synthesis of gold nano-triangles and

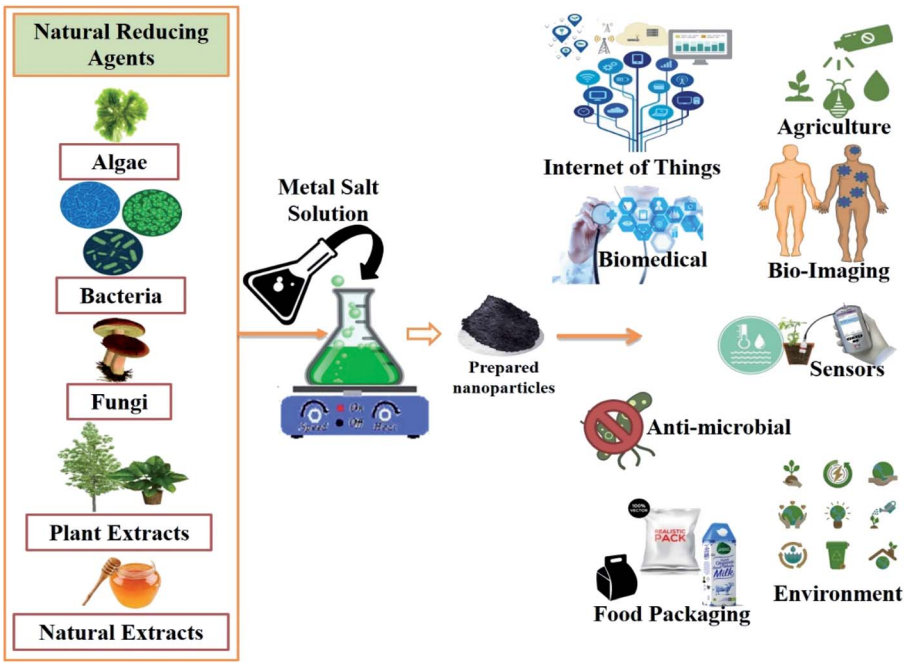

Fig. 3 An illustration of the laboratory-based method to synthesize various metal and metal oxide nanoparticles using plant extracts, algae, fungi, bacteria, and natural extracts, along with the metal salt, which results in the production of the desired metal and metal oxide nanoparticles. Various applications of these biosynthesized metal and metal oxide nanoparticles are also shown in the figure.

silver nanoparticles was completed using *Aloe vera* plant extract. It was also suggested that these gold nanotriangles could be used as various therapeutic agents.[84] In another study, AuNPs synthesis was achieved by an aqueous extract of *Mirabilis jalapa* flowers,[85] and AgNPs were synthesized *via Cardiospermum helicacabum* leaf extracts and *Pulicaria glutinosa* extract.[86,87] Moreover, *Annona squamosa* was used to synthesize the copper oxide nanoparticle, which exhibited efficient antibacterial properties when tested against plant pathogenic bacteria. Furthermore, the experiment reported that the bio-synthesized CuONPs could be utilized for sensing H_2O_2, as it showed good electro-oxidation response towards H_2O_2.[88] Crystalline and spherical-shaped selenium nanoparticles were synthesized using an aqueous *Allium sativum* extract that showed excellent pH stability, which found its potentialities in various biomedical utilities.[89] Similarly, extracts of *Asteriscus graveolens* were also used to synthesize spherical-shaped selenium nanoparticles for targeted anticancer drug delivery.[90] Furthermore, stable selenium nanoparticles were synthesized using *Aloe vera* extracts.[91,92] Moreover, a comparative study was performed between aqueous *Hordeum vulgare* (monocotyledonous) extracts and *Rumex acetosa* (dicotyledonous) plants to synthesize iron oxide nanoparticles.[93] An experiment reported the green-mediated synthesis of platinum nanoparticles using *Diopyros kaki* leaf extract.[94] Furthermore, a systematic overview of the laboratory-based synthesis of various metal nanoparticles using plant extracts, fungi, bacteria, and algae is displayed in Fig. 3. These plant-based synthetic routes are more preferred as compared to the other chemical and physical routes as they are easy, laboratory-friendly, cost-effective, and the presence of various biological compounds makes them more suitable in the therapy of various diseases, like cardiovascular disease, neurodegenerative diseases, inflammatory diseases, wound healings, development of anti-microbial films and agents, among others.

3.2. Synthesis of nanoparticles using bacteria

The synthesis of nanoparticles using various bacterial species has also attracted the attention of researchers. For instance, it has been reported that by using *Escherichia coli*, AgNPs were biosynthesized and were found to be of a size of 50 nm. This process was found to be stable and cost-effective.[95] Similarly, AgNPs were also synthesized by *Bacillus thuringiensis*, *Corynebacterium strain* SH09, *Bacillus cereus*, and extremophilic *Ureibacillus thermosphaericus*.[96–99] Furthermore, Sintubin *et al.* reported that lactic acid bacteria acted as both reducing and capping agent to synthesize AgNPs.[100] Cadmium sulfide nanocrystals were also reported to be biosynthesized using *E. coli*.[101] Selenium-respiring bacteria, namely *Sulfurospirillum barnesii*, *Selenihalanaero bactershriftii*, and *Bacillus selenitireducens*, were used to synthesize uniform and stable nanospheres.[102,103] Moreover, there are many metal and metal oxide nanoparticles that have been reported to be synthesized using different bacteria. Most of the bacteria-mediated syntheses were reported to be cost-effective, easy, and simple, and were also found to be non-toxic to the living cells, making them more suitable and efficient for use in therapeutic applications.

3.3. Synthesis of nanoparticles using fungi

The myogenic route for nanoparticle synthesis has been established for better nano factories over bacteria and plants from researchers worldwide, as they show better metal accumulation

activity. Recent research on the few most commonly synthesizing nanoparticles using various fungi has been discussed. It has been reported that monodispersed AgNPs can be biosynthesized using *Rhizopus stolonifer*, and it showed good antibacterial activity, suggesting its utility as potential antibacterial agents.[104] Similarly, in another study, it has been reported that AgNPs can be synthesized using *Phoma glomerata*. Furthermore, it was suggested that it acted as a better candidate for DDS, and exhibited antibacterial efficacy against resistant *E. coli*, *P. aeruginosa*, and *S. aureus*.[105] However, several other fungi, like *F. oxysporum*, *Fusarium solani*, *Pleurotussajorcaju*, and *Fusarium semitectum*, can also be utilized for the biosynthesis of AgNPs.[106–108] Several other studies have also reported the mycosynthesis of antimicrobial silver nanoparticles by the endophytic fungus *Aspergillus clavatus*, *A. flavus*, and *A. flavus NJP08*, respectively.[96,109,110] Another study reported the biosynthesis of protein-capped AgNPs using fungus proteins of *Coriolus versicolor*, as the fungal proteins and glucose were responsible for the reduction. Moreover, these intracellularly synthesized AgNPs could be modified to exhibit both intracellular and extracellular AgNPs under alkaline conditions, whereby the surface S–H groups of the fungus played a major role.[111] Similarly, Qian *et al.* reported the synthesis of AgNPs from an endophytic fungi *Epicoccum nigrum* isolated from the cambium of *Phellodendron amurense*.[112] In another study, AgNPs were synthesized using the fungus *F. oxysporum* and reported to have antifungal activity against pathogenic yeasts.[113] Various fungi have been reported to synthesize platinum nanoparticles using the fungi *Neurospora crassa* and *F. oxysporum*.[114,115] Although fungi exhibit sensitivity towards selenium, as selenium nanoparticles show antifungal activity, certain fungi like *Trichoderma viride*, *Chaetomium globosum*, *Aspergillus niger*, and *Pleurotus ostreatus* can synthesize stable selenium nanoparticles.[116] It was observed that these fungi-synthesized selenium nanoparticles exhibited enhanced biomedical activities. Similarly, *Humicola* sp. were used to synthesize cerium oxide nanoparticles.[117]

Various fungi are being utilized to synthesize gold nanoparticles, such as *Penicillium* sp., *Geranium* leaves and its endophytic fungus, edible mushroom *Pleurotus florida*, and the glucan content of mushroom.[83,118–121] The enzyme-mediated biosynthesis of CdS nanoparticles was reported using the fungus *F. oxysporum* and *S. cerevisae*.[122,123] CdTe quantum dots were synthesized using *F. oxysporum*, and also exhibited excellent antibacterial activity.[124,125] Moreover, it was reported that the biosynthesis of cadmium crystal particles was achieved using the white-rot fungus *C. versicolor*.[126] Several other metal and metal oxide nanoparticles were also synthesized *via* different fungi, like the nanosized magnetite from *Mucor javanicus*, *F. oxysporum*, and *Verticellum* sp.[127,128] Similarly, *A. alternate* was used to synthesize selenium nanoparticles.[116] *F. oxysporum* was used to synthesize strontium carbonate crystals,[129] and this fungus was also used to synthesize titanium and silica nanoparticles.[130] Jha *et al.* reported another approach to synthesize TiO_2 nanoparticles by using *S. cerevisiae*, which exhibited efficient antibacterial activity against Gram-positive bacteria, making them a potential antibacterial agent for use in various biomedical purposes.[131] Apart from these, various other biological routes, like using nutrient media (*e.g.*, honey, egg, starch) and natural polymers (*e.g.*, starch, pectin), are also utilized to synthesize various metal and metal oxide nanoparticles.

Fig. 4 Schematic representation of the biomedical utility of bio-inspired metal and metal oxide nanoparticles.

4. Applications

Effective attachment of the biological constituents in green synthesized materials enhances the therapeutic and diagnostic potential of metals and metal oxide nanoparticles. Fig. 4 shows the wide range of applications of biogenic metal and metal oxides nanoparticles in diagnostics and therapeutics. The following sections shall elaborate on the vast areas of biomedical sciences, where biogenic metal and metal oxide nanoparticles are of great concern.

4.1. Diagnostics

There is an urgent need for accurate and precise analysis systems to understand mechanisms at the cellular and molecular levels, enabling the visualization and observation of cellular components, and therefore understanding their functions and alterations properly. Sensing various analytes and their metabolites shall be efficient using biogenic metal and metal oxide nanoparticles, which have characteristic SPR (surface plasmon resonance) with extreme sensitivity in the surrounding medium with brilliant sensing ability.

4.1.1. Bio-imaging. There are various types of nanoparticles, such as solid lipid nanoparticles, nanotubes, metallic nanoparticles, quantum dots, dendrimers, polymeric nanoparticles, and liposomes, used for biomedical imaging purposes. The diverse properties of nanoparticles, such as surface chemistry, magnetic, absorption, and emission properties, make them potential probes for detecting diseases.[132] For example, red fluorescent Au nanoclusters were synthesized using L-glutathione, and were studied to detect cancer and non-cancer cells by combining them with porphyrin derivatives [tetrasodium pyrophosphate (TSPP)] for both *in vivo* and *in vitro* imaging purposes, as represented in Fig. 5. Moreover, these synthesized nanoclusters were so small in size that they could be easily excreted from the body, which eases the bio-imaging process by creating no toxic effects on the living cells. Therefore, researchers can explore this method to design new bio-

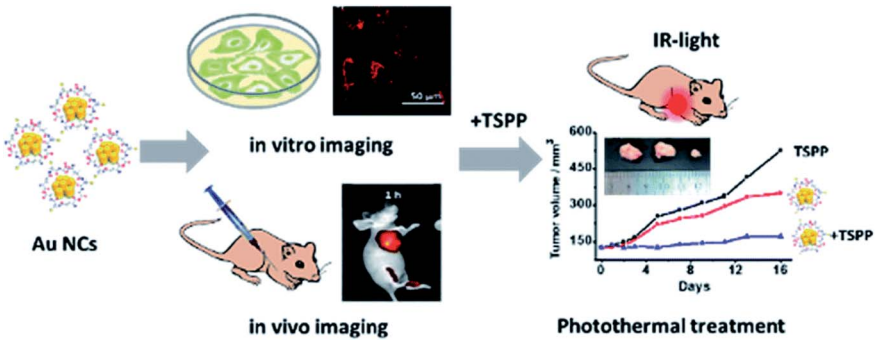

Fig. 5 A schematic representation of Au nanoclusters combined with porphyrin derivative (TSPP) utilized for fluorescence-based bioimaging and photothermal treatment to detect cancer (reproduced with permission from Y. Zhang, J. Li, H. Jiang, C. Zhao and X. Wang, *RSC Adv.*, 2016, **6**, 63331–63337 (ref. 67)).

imaging metal-based nanomaterials.[67] Similarly, dextran-coated gadolinium oxide nanoparticles (Gd_2O_3 NPs) were synthesized using Bengal Rose extract, which exhibited excellent paramagnetic behavior, facilitating their utilization for bio-imaging and tracking purposes.[68] In another experiment, biodegradable nanoparticles, *i.e.*, hydrophobic poly(lactic-*co*-glycolic acid) [PLGA] core and a positively charged glycol chitosan shell, were used to fabricate the core–shell structure of a superparamagnetic iron oxide nanoparticle that was then utilized as an MRI contrasting agent.[69] Similarly, PEGylated bismuth (PEG-Bi) nanoparticles were synthesized using methoxy[poly(ethylene glycol)]trimethoxy-silane (PEG-silane) and bismuth oxide (Bi_2O_3). The synthesized PEG-Bi nanoparticle showed excellent performance in X-ray computed tomography imaging and photothermal cancer therapy *in vivo*.[133] Furthermore, in an experiment, the nanostructured bismuth oxide was utilized as a radiosensitizer and gadolinium nanoparticles as a contrasting agent for detecting glucose.[134]

4.1.2. Biosensing. An analytical device used for analyzing different biological samples by converting their chemical response to an electrical signal is known as a biosensor. A biosensor comprises three components: a bio-element, the transducer, and an electronic unit. The bio-element constitutes bioreceptors, like enzymes, nucleic acids, amino acids, antibodies, and tissues. These bio-elements react with the biological sample and generate chemical signals, which are detected and converted into electrical signals by the transducers. The transducer efficiently detects the signals and converts them into electric signals, which are then further modified, processed, and displayed by the electronic unit. The different metal and metal oxide nanoparticles, like silver, copper, zinc, iron, cerium, manganese, titanium, zirconium, platinum, cobalt, gold, nickel, tungsten, and vanadium, have efficiently played a key role in the biosensing of chemical and biochemical analyses. For example, iron oxide nanoparticles were utilized to modify electrodes to detect glucose, H_2O_2, various heavy metals (like Pb, Zn and Cd); urea, nitrites and nitrates; dopamine and bisphenol-A. Furthermore, manganese oxide nanomaterials, namely MnO, MnO_2, and Mn_3O_4, are the most researched and are found to be beneficial for bioelectrode materials in biosensing. However, the most extensively used metal oxide nanostructures considered for electrochemical sensing are copper(II) oxide (CuO) and copper(I) oxide (Cu_2O). It was reported that cobalt oxide-doped copper oxide nanofibers were used as a sensing platform for the label-free detection of fructose.[135] Similarly, it was also reported that CuO–Cu nanocomposites on graphene could be used for the detection of fructose,[136] as the determination of fructose can be used for the early detection of various lifestyle diseases, like diabetes and digestive disorders. Furthermore, another sensor to detect glucose and fructose in blood serum was reported using the CuO/multi-walled carbon nanotube nanocomposite-modified glassy carbon electrode.[137] A nanosensor was reported to detect glucose in drugs and human serum, which used immobilized glucose oxidase on an iron ferrite magnetic particle/chitosan composite-modified gold-coated glass electrode.[138] Furthermore, it was reported that cholesterol oxidase, when co-immobilized with α-Fe_2O_3, showed a micro-pine-shaped hierarchical structures-based cholesterol biosensor.[139] A hybrid material of chitosan (CS), fishbone-shaped Fe_2O_3 (f-Fe_2O_3), and electrochemically reduced graphene oxide (ErGO) was fabricated to act as a better sensing matrix for the electrochemical detection of gallic acid, which was further used to detect the effect of the antioxidant activity of the wine. The results suggested that CS-fFe_2O_3-ERGO/GCE can be efficiently used to develop electrochemical sensors.[140]

It was proposed that the use of arc-discharging graphite rods containing copper wires to synthesize single-wall carbon nanotubes (SWCNTs) with nanocomposites of CuO would have good stability and linear glucose detection with higher sensitivity, quick response time and lower detection limit. Comparatively, the combination offered better performance in sensing, conductivity, and a higher response towards human serum samples.[141] Another fabricated non-enzymatic electrochemical sensor for the simultaneous detection of glucose and fructose in hydrolyzed sucrose samples was proposed, which can also measure glucose in blood serum samples.[137] Another study showed that the combined effect of copper nanoparticles and graphene sheets produced Cu-graphene sheets allowed for high selectivity, accuracy, and fast and stable amperometric sensing

to detect glucose.[142] The Cu-graphene sheets shall be an optimistic factor for the development of a non-enzymatic glucose sensor. Another study reported that the CuO_2-like nano spindle combined with straight multi-walled carbon nanotubes-modified electrode sensed glucose with higher sensitivity and lower limit of detection.[143] The metal oxide nanoparticle is considered a potential candidate for developing a new transducer capable of being utilized as an electrochemical biosensing platform.[144] An electrochemical biosensor is an integral unit of biological elements, like an antibody, enzyme, proteins, and nucleic acid, with a transducer capable of efficiently sensing the element and transfer signal. Many studies have been conducted, which describe the potentialities of optical, electronic, and electrochemical properties of metal-oxide nanoparticles in suspended media and their surface activities at the nano-bioelectrode for biosensing uses. The electron transfer rate highly relies on the type of reaction occurring between the biomolecules and metal-oxide nanoparticles, leading to an increased biosensing response signal.[145] Moreover, these metal oxide nanoparticles can easily immobilize the targeted biomolecule on their surface, and are therefore considered more in electrochemical sensing. Fig. 6 (ref. 146) schematically describes the procedure of electrochemical biosensing by immobilizing the enzyme on the surface of a metal oxide nanofiber. Furthermore, the non-enzymatic biosensor with $Cu(OH)_2$ dendritic structure fabricated from the boron-doped nanocrystalline diamond based on a Cu electrode for glucose detection reported better reproducibility, long-term stability, selectivity, and no interference from other oxidable species.[147] The circular cobalt oxide nanorods were also found to be very efficient for easy non-enzymatic detection of glucose by amperometric method.[148] Moreover, it was proved that the Ni nanoparticles-loaded TiO_2 nanotube arrays (Ni-NPs/TiO_2NTs) were first prepared by the anodization of the Ti foil, tracked by the electrodeposition method for better detection of glucose with a higher sensitivity, in addition to great analytical performance and simpler preparation method. This simple and effective method was helpful for the early detection of diabetes.[149] Nano nickel oxide (NiO)-modified sensors with non-enzymatic sensing activity were also proposed for the assay of glucose with better electrochemical properties and electrocatalytic performance for glucose oxidation.[150] Nowadays, many point-of-care devices have been developed, which eases the detection of various biomolecules (like glucose, fructose, and others), and can be used to develop effective therapeutic approaches for the treatment of various lifestyle diseases. Moreover, the onset of the internet of things (IoT) and wearable sensors have opened gates for researchers to develop and modify the traditional synthetic routes for the effective detection of biomolecules.

The minute amount of glucose was detected by an electrochemical biosensor made up of a ZnO nano tetrapod that utilized the multi-terminal ZnO nanostructure as a material adsorption.[151] It was proposed that the electrodeposition of the chitosan gold nanocomposite (CGNC) and nickel hydroxide ($Ni(OH)_2$) on a bare gold electrode with immobilized glucose oxidase and fabricated with electron transport for glucose-sensing would provide higher selectivity, sensitivity, and stability for better practical and clinical applications.[152] Furthermore, it was ascertained that nanoflake ZnO, when immobilized with glucose oxidase, performed as a better potentiometric glucose biosensor.[153] Similarly, it was mentioned that a novel enzymatic amperometric biosensor was formed when ZnO nanoparticles were electrodeposited on the glassy carbon electrode surface with multi-walled carbon nanotubes to immobilize the second layer of glucose oxidase

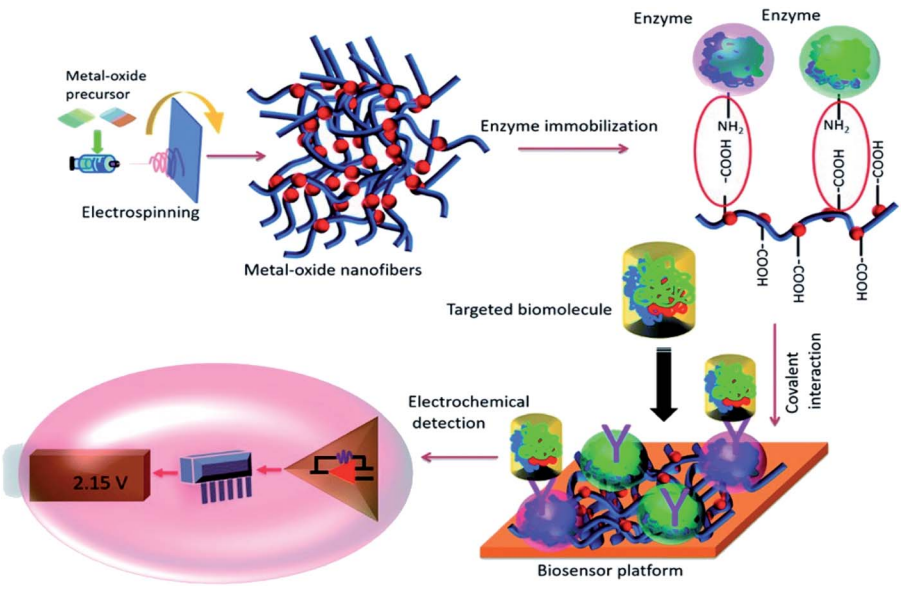

Fig. 6 A schematic representation of the complete procedure of electrochemical biosensing utilizes the surface of the metal oxide nanofiber to immobilize the enzyme. This interaction between the enzyme and metal oxide nanofiber generates signals that are electrochemically detected and amplified (reproduced with permission from K. Mondal and A. Sharma, *RSC Adv.*, 2016, **6**, 94595–94616 (ref. 146)).

with good stability and reproducibility.[154] The nickel nanowire array and Pt-coated nickel nanowire array (Pt/NiNAE) can efficiently detect the glutamate electrochemically by enzyme-free sensing, and exhibit better electrocatalytic activity towards glutamate as compared to the pure Ni electrodes. This particular sensing promises a cost-efficient, enzyme-less, sensitive, accurate, selective, and stable sensor platform.[155] Furthermore, the hemoglobin immobilized glassy carbon electrode was developed using the nanocomposites of Ag nanoparticles that were self-supported on the silver vanadium oxide ($Ag_2V_4O_{11}$) nanobelts, and fabricated a critical sensitive biosensor for the detection of H_2O_2.[156] Similarly, a modified glassy carbon electrode was developed using the reduced graphene oxide/Fe_2O_3 nanocomposite. This electrode was then used to prepare a very simple, novel, sensitive, and non-enzymatic electrochemical sensor to detect hydrogen peroxide that could efficiently display better sensing performance for the detection of H_2O_2 amperometric reduction.[157] Furthermore, Wang *et al.* proved that hematite nanoparticles (α-Fe_2O_3) could be utilized for fabricating a non-enzymatic sensor that was applied in the catalytic reduction of H_2O_2, and thus results in the highly sensitive and selective reduction of H_2O_2. In another experiment, Wang *et al.* disclosed that Prussian blue-based (PB) nanocubes-nitrobenzene-reduced graphene oxide (rGO) nanocomposites (PB-nanocubes-nitrobenzene-rGO) detected H_2O_2 very promisingly.[43]

When novel graphene sheets were wrapped with CuO_2 nanocubes, they exhibited good electrochemical stability, proving to be a good option for enzyme-free glucose and hydrogen peroxide sensors with good stability and sensitivity, selectivity, and faster amperometric response.[158] It was observed that when photosynthesized silver nanoparticles were combined with fluorine-doped tin oxide in a conducting mode and were slightly modified with the help of zinc oxide nanorods, it worked well as an amperometric sensor for the detection of hydrogen peroxide.[159] Furthermore, the synthesized γ-Fe_2O_3 nanoparticles by the one-pot method under hydrothermal conditions formed *meso*-tetrakis(4-carboxyphenyl)-porphyrin-functionalized γ-Fe_2O_3 nanoparticles, which were assumed to be a cheap, simple, convenient, selective, sensitive, accurate, and easy to handle colorimetric assay that could also catalyze the decomposition of H_2O_2 into H_2O and O_2.[160] Another study by Low *et al.* demonstrated the strong interfacial bonding effect when bio-mineralized hydroxyl functionalized multi-walled carbon nanotubes were added onto calcium phosphate cement, which could be beneficial for fabricating electrodes for biosensing application with higher sensitivity and selectivity towards analytes of interest.[161] To detect ricin, a silica-coated magnetic nanoparticle-based silver enhancement immunoassay was developed.[162] Similarly, Tyagi *et al.* proposed a method to detect urea, in which a thin film NiO nanoparticle was deposited onto an indium tin oxide (ITO)-coated glass substrate that showed higher affinity and catalytic activity with redox behavior due to the great properties of NiO-NPs.[163] Furthermore, by immobilizing uric acid, a potentiometric uric acid biosensor was developed, in which uricase was immobilized upon zinc oxide (ZnO) nanowires.[164] It was observed that by conjugating biomolecules with colloidal nanoparticles of gold, the obtained signals from biosensors could be modified.[165] The role of the ITO thin film modification methods and the immobilization of bio-recognition elements were studied. They demonstrated the utility of ITO for fabricating electrochemical metal and metal oxide nanomaterial-based ITO biosensors that were highly sensitive, conductive, and selective towards the analyte of interest.[166] Owing to the distinguished properties of the metal and metal oxide nanoparticles, they have found profound use in both imaging and diagnostic applications. These metal and metal oxide nanoparticles are now considered as promising materials that can efficiently revolutionize the biomedical practices and researches.

4.2. Therapeutics

Nanostructures of biogenic metal and metal oxides can elicit tremendous therapeutic applications, such as anticancer, antidiabetic, anti-inflammatory, and antioxidant, which will be discussed in this section. Furthermore, the green synthesized nanoparticles have more demand due to their characteristics, such as bioavailability, cost-effectiveness, and environment-friendly nature.

4.2.1. Anti-cancer activity. Cancer is marked as one of the leading causes of death worldwide, and results in 8.2 million deaths per year. Furthermore, it has been estimated that the number of deaths due to cancer will increase each year, and it will reach about 13.2 million deaths per year by 2030. To date, nearly more than 200 different types of cancer are recognized, which exhibit six biological characteristics: replicative immortality, angiogenesis, invasion and metastasis, resistance to apoptosis, proliferative signaling, and evasion of growth.[167] With the introduction of bionanotechnology, novel and innovative techniques have been developed to diagnose and treat different types of cancer. Furthermore, the fusion of nanotechnology with immunology has developed nano-immune-chemotherapy, which efficiently works in cancer treatment. Furthermore, cancer treatment effects are being restricted due to several factors, such as lack of bioavailability, drug resistance, and the non-specific toxic nature of chemotherapy. Thus, there is now a crucial demand for alternative strategies to combat cancer. Thus, various biogenic metal oxide nanoparticles have shown amazing results for cancer therapy by inducing cytotoxicity in cancerous cells, while not affecting the normal cells. Some biogenic metal and metal oxide nanoparticles that are widely used to treat cancer include black bean-synthesized copper oxide nanoparticles (CuONPs) and *Nepeta deflersiana*-synthesized AgNPs, which exhibit efficient anticancer activity when studied on HeLa cells by increasing the intracellular reactive oxygen species (ROS) in a concentration-dependent manner.[70,71]

Moreover, MgONPs are known to exhibit biomedical properties as they show biocompatible nature, and are also highly stable under harsh conditions. They are mostly used for the relief of heartburns, inhibiting tumor-generating activities and others. Therefore, an experiment was performed that used aqueous extracts of brown seaweed *Sargassum wightii* to

synthesize MgONPs, which exhibited good cytotoxic activity against lung cancer cell line A549 by increasing ROS generation, leading to apoptosis of the cancer cells. *Sargassum wightii* is a marine algae that is readily available. It is rich in polysaccharides, polyphenols, carotenoids, proteins, amino acids, vitamins, and minerals, which help them act as capping and reducing agents for the fabrication of metal and metal oxide nanoparticles. The synthesized MgONPs exhibited high zeta potential that enhanced their stability, and helped them show antimicrobial activity against both human pathogenic bacterial and fungal strains in a concentration-dependent manner. In addition, the synthesized MgONPs efficiently degraded the organic dye methylene blue under UV radiation and sunlight by showing photocatalytic activity.[72]

Furthermore, titanium oxide nanoparticles (TiO_2) were synthesized using the bulb extract of *Ledebouria revolute*, which exhibited excellent anticancer activity against A549 cells. *Ledebouria revolute* was chosen as it is one of the medicinal plants, which is widely known to exhibit anticancer activity and antimicrobial properties, and also inhibits the larvicidal activity of *Aedes aegypti*.[168] An advanced and cost-effective cancer therapy was developed using selenium nanoparticles. These selenium nanoparticles were synthesized using carboxylic acid, which efficiently generated cell apoptosis in the cancer cells.[169] A comparative study was conducted to explore the anticancer potentiality of surface-modified selenium nanoparticles by different amino acids, mainly valine, lysine, and aspartic acid. This study showed that the aspartic acid and valine-decorated selenium nanoparticles exhibited less anticancer activity than the lysine-decorated selenium nanoparticles, suggesting that the lysine-decorated selenium nanoparticles can be used as a potential chemotherapeutic agent for combating cancer.[170] Similarly, selenium nanoparticles exhibited good antitumor activity, and were functionalized by hyaluronic acid (HA-SeNPs). The HA-SeNPs efficiently controlled the immune-regulating properties and decreased the tumor mass.[171–174] Moreover, a study reported that magnesium oxide nanoparticles combined with human serum albumin exhibited better plasma distribution and mediate apoptosis by ROS induced in the cell lines of cancer.[175] Furthermore, a similar study on magnesium oxide (MgO) nanostructures showed excellent photocatalytic, antibacterial, and anticancer performance.[176] Similarly, other metal and metal oxide nanoparticles (like gold, palladium, and zinc) synthesized *via* biogenic routes were utilized for obtaining better results in radiation oncology.[177–179]

4.2.2. Anti-diabetic activity. The production of insufficient insulin in the body does not allow the cells to reciprocate towards insulin, resulting in sugar accumulation in the blood, leading to a metabolic disorder known as diabetes. Therefore, diabetes can be both insulin-dependent and insulin-independent. Many enzymes interfere with this disease, upon which two of them are the key regulators: α-glucosidase and α-amylase. Here, we discuss some of the bio-synthesized nanoparticles of metal oxides that aid in treating diabetes by suppressing the secretion level of the enzymes. Ag NPs were biologically synthesized from *Lonicera japonica*, as the plant is known to consist of various medicinal properties, like antiviral, anti-inflammatory and anti-diabetic activities. The synthesized nanoparticle exhibited effective antidiabetic activity against carbohydrate digestive enzymes for diabetes, namely, α-amylase and α-glucosidase.[180] Similarly, green synthesized silver nanoparticles utilizing the leaf extracts of *Pouteria sapota* inhibited the action on α-amylase, and the non-enzymatic glycosylation of hemoglobin confirmed the anti-diabetic activity.[181]

Similarly, selenium nanoparticles are also known to cure diabetes, as they act as an anti-hypoglycemic agent by reducing oxidative damage and preventing hypoglycemic activity.[182] Moreover, chitosan-stabilized selenium nanoparticles (Cs-SeNPs) exhibited anti-diabetic effects when observed in a rat model.[183] It has also been observed that when selenium was combined with the cerium oxide nanoparticle, ROS levels were decreased with increasing insulin secretion, hence regulating the secretion of insulin and decreasing the oxidative stress.[184–186] Similarly, ZnO NPs were synthesized through the microwave-assisted method with the help of *Vaccinium arctostaphylos* L. fruits extract that exhibited efficient anti-diabetic activities. They reduced the fasting blood glucose (FBS) levels and showed good control over the levels of some lipids in the treated diabetic rats. Moreover, the experiment reported that the green synthesized ZnO NPs exhibited better anti-diabetic properties than conventional synthesized ZnO NPs.[73] Furthermore, there are many research studies that have been performed on the role of biogenic metal and metal oxide nanoparticles and their composites for anti-diabetic applications. However, there are very few commercialized products based on it, so there is a very urgent need for researchers working in this area to focus on developing commercial products based on biogenic metal and metal oxide nanoparticles and their composites for diabetes treatment. However, there are various plants that are known to possess anti-diabetic properties. Therefore, they can be considered for the preparation of the metal oxide nanoparticles to study their effective roles in combating diabetes.

4.2.3. Anti-inflammatory activity. Inflammation is the type of defense machinery shown by our body that responds to external stimuli, such as certain pathogens, allergens, irritants, and damaged cells. At times, this mechanism also lasts long after its beneficial activity, showing a prolonged effect. Metal-based nanoparticles exhibit excellent penetrating capacity in epithelial cells and inflammatory cells, which results in developing an effective and stable treatment for many diseases like cardiovascular diseases and gastric ulcers. Moreover, they exhibit better selectivity of target sites, such as inflammatory cells or tissues.[187] There are many green synthesized metal and metal oxide nanoparticles that are known to exhibit anti-inflammation activity. The review discusses the anti-inflammation activity of various metal oxide nanostructures. Peptide-based Au NPs hybrid libraries have been used to inhibit Toll-like receptor (TLR) signaling, which was considered helpful in many acute and chronic human inflammatory diseases.[188] The European cranberry bush is astringent and is consumed directly, and their fruit juice is the best-known product. It is a traditional drink in the Central Anatolia region (Turkey). The berries consist of high amounts of pectins, ascorbic acids, and

flavanoids, which help them exhibit various medicinal properties. Moreover, they exhibit high antioxidant activity. Therefore, silver nanoparticles were synthesized from the European cranberry bush fruit (*Viburnum opulus*) extract that showed the effective release of IL-1α triggered by the irradiation of keratinocytes, and compared with the control and treated cells approving anti-inflammation activity.[189] Enhanced anti-inflammatory activity was reported using AgNPs synthesized from the unripe fruit aqueous extract of *Piper nigrum*.[190]

Moreover, it has been observed that the cerium oxide nanoparticle exhibits free radical scavenging activity, which makes them a suitable anti-inflammatory agent.[191] Similarly, polysaccharide-modified selenium nanoparticles, along with inhibitory proteins like the Ik-B subunit, efficiently inhibited the phosphorylation of the JNK1/2, p38MAPK1 and NF-kB pathway (nuclear factor kappa B), which helped them show anti-inflammation activity.[192] Moreover, gum-arabic stabilized selenium nanoparticles (GA-SeNPs) exhibited excellent anti-inflammatory activities, and thus prevented various inflammatory diseases.[193] Many other properties of green synthesized selenium nanoparticles, like better anti-oxidant properties, also help them to exhibit anti-inflammation activity, making them suitable for treating cardiovascular diseases, wound treatment, and others. Other metals, like titanium oxide and zinc oxide nanoparticles, have also been reported to exhibit anti-inflammation properties in various mechanisms. For instance, the biofabricated zinc oxide nanoparticle shows anti-inflammatory activity by hindering the denaturation of albumin, inhibiting proteinase, and also possessing wound healing properties. Therefore, this suggests that green synthesized ZnONPs can be effectively used to treat wounds and can be used as a nano-ointment.[194] Titanium oxide nanoparticles mostly exhibit anti-inflammation activity by decreasing platelets or increasing the thrombin-anti-thrombin levels. This is achieved by creating oxidative stress in the macrophages and increasing the TAT levels by suppressing the PAR pathways (Protease-Activated Receptors), respectively, which are responsible for generating inflammation in the body.[195] Furthermore, many other metal and metal oxide nanoparticles synthesized *via* the biogenic way play an important role in the biomedical application and exhibit great anti-inflammatory activity. Thus, the researchers working toward this must focus more on finding the mode of mechanism of the biogenic metal and metal oxide nanoparticles for their great anti-inflammatory activity.

4.2.4. Antioxidant activity. Oxidative stress is generated inside the cell when an imbalance between the reactive oxygen species and excess nitrogen production occurs. Therefore, nanoparticles play an immense role in the biomedical domain, as they exhibit commendable antioxidant properties by hunting and killing free radicals. One of the highly researched nanoparticles is the cerium oxide nanoparticles, as they exist in two oxidation states. It was observed that when brain tissues of rats were exposed to cerium oxide nanoparticles, they increased the thiol content and started the caspase-3 activity, which proved that cerium oxide nanoparticles exhibited incredible antioxidant property.[196] Similarly, cerium oxide nanoparticles were coated with levan polysaccharide. They exhibited mutual antioxidant activity when observed against H_2O_2 in the NIH3T3 cells as levan. Its derivatives are known to exhibit antioxidant, anti-tumor, and anti-inflammatory activities, which when combined with cerium oxide nanoparticles, provides them water solubility and stability. These properties of the green synthesized cerium oxide nanoparticle help them be used for various therapeutic applications.[197]

Due to their small size and large surface-to-volume ratio, nanoparticles can act as synthetic antioxidants in the body that are suitable for several therapeutic applications. Here are a few examples showing nanoparticles as potential antioxidants in the body that would treat diseases caused by reactive oxygen species (ROS), disturbing the normal redox balance. Various experiments that have synthesized zinc oxide nanoparticles from different plant extracts, like Citrus paradise and *Cassia fistula*, have demonstrated excellent antioxidant activity of zinc oxide nanoparticles by 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging.[75,198] Therefore, it can be concluded that the citric acid-containing plants act as a better anti-oxidizing agent. Research can thus be conducted to synthesize various metal and metal oxide nanoparticles using citric acid plants that can be utilized as anti-oxidizing agents. Similar findings were reported in a comparative study of zinc oxide nanoparticles with zinc sulphate ($ZnSO_4$), where zinc oxide nanoparticles were synthesized from the *Lavandula vera* leaf extract. This experiment showed that the green synthesized zinc oxide nanoparticle exhibited better antioxidant activities than zinc sulphate by increased DPPH radical scavenging activity.[199] The antioxidant activity is required to prevent the damage caused by the free radicals. Like other metal and metal oxide nanoparticles, the green-synthesized copper oxide nanoparticles from the flower extract of *Matricaria chamomilla*, an aqueous root extract of *Desmodium gangeticum* and *Tinospora cordifolia*, have been reported to exhibit excellent antioxidant activity.[11,200–202] Similarly, zinc oxide nanoparticles synthesized from the leaf extract of *Mangifera indica* and pulp of *Vitis rotundifolia* (hybrid grapes) exhibited good antioxidant activity due to the high concentration of phenolic groups in both plants, and their major plant parts showed anti-oxidant activity.[203–205] The leaf extract of *Moringa oleifera* was used to synthesize lanthanum oxide nanoparticles (La_2O_3 NPs), which exhibited excellent antioxidant activity. *Moringa oleifera* is known to exhibit antioxidant activity and is also considered a medicinal plant. However, the synthesized La_2O_3 NPs from *M. oleifera* exhibited even better anti-oxidation activity, as they easily transported the free electrons to the free radicals of N_2 present in DPPH.[76,206]

4.2.5. Anti-bacterial activity. Numerous antibiotics are being discovered for the treatment of microbial infection. However, the problem is with increasing antibiotic resistance and toxicity, due to which the reliability is limited. On the other hand, nanostructures of metal and metal oxides confer more potentiality to treat antibacterial infections than antibiotics. For example, the nanoceria-doped composite nanofibers show toxicity against Gram-positive and Gram-negative bacterial strains, and can be used in antibacterial treatment.[27,207] Furthermore, Singh *et al.* reported various biosynthesis methods for cerium oxide nanoparticles and their effects on the

living tissues, properties, and potentialities in diagnostic and therapeutic fields, highlighting their prospects and future outlook.[28]

Furthermore, the fruit extract of *Emblica officinalis* was utilized to synthesize MgONPs. When the cotton fabric was treated with MgONPs, it showed strong antibacterial activity and could be used in medicine.[48] Another method was reported using a bacterial strain to synthesize MgONPs that exhibited good antibacterial, anti-arthritic, and anticancer activity.[208] Silver nanoparticles were synthesized from the culture supernatant of the endophytic fungus (*Raphanus sativus*), which proved to have a better antibacterial effect on Gram-negative and Gram-positive bacteria pathogens.[79] The silver nanoparticles were synthesized using *Aloe vera*, *Portulaca oleracea*, *Solanum nigrum*, and *Cynodon dactylon*, and were used as bactericidal agents against human pathogens.[209] To increase the antibacterial efficiency towards Gram-negative bacteria, selenium nanoparticles were stabilized with the help of the spider silk protein eADF4(k16), which provided the selenium nanoparticles with a positive charge on their surface.[210] The aqueous leaf extract of *Canthium dicoccum* was used to synthesize zinc oxide nanoparticles, which exhibited enhanced antibacterial activity against *Bacillus subtilis* and least towards *Staphylococcus aureus*.[211] Platinum nanoparticles exhibited antibacterial properties against various bacteria, namely *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhi*, and *Artemia salina* nauplii.[212] Recently, it has been reported that to enhance the biological properties of the metal and metal oxide nanoparticles, they should be combined, capped, stabilized or doped with other elements like polysaccharides and metals. Hence, it was reported that when iron was doped with copper oxide nanoparticles, they exhibited enhanced antibacterial properties by inhibiting both bacterial colonies and biofilm formation.[213] Similarly, chitosan-based copper nanoparticles exhibited efficient antibacterial activity against *Vibrio parahaemolyticus*.[214] Furthermore, biogenic metal and metal oxide nanoparticles exhibited antibacterial efficiency by various methods like damaging the plasma membrane (which leads to the bursting of the bacterial cells), the generation of excess ROS in the bacterial cell (which will lead to the increase in oxidative stress inside the cell), or the slow release of the drug (which will target the organelle), as described in Fig. 7.

4.2.6. Anticoagulant activity. Coagulation is when the blood turns from a liquid to a gel-like substance to form clots that stop bleeding at the injury site. Unfortunately, at times, this mechanism of protection can turn into a harmful event that causes harm to the body. Several diseases like allergies, injuries, and cardiovascular diseases require anticoagulation processes, as it turns the coagulation to malfunctioned state. In addition, increasing cardiovascular and cerebrovascular complications arise due to the formation of unusual clots in the blood vessels, leading to a phenomenon known as thrombosis.[215] A cell-free extract of *Bacillus safensis* LAU 13 was used to synthesize biogenic silver nanoparticles that acted as an efficient blood coagulant and thrombolytic agent.[216] Furthermore, the silver and gold nanoparticles synthesized from the biomass of the bacterium *Brevibacterium casei* demonstrated efficient anticoagulant activity.[217]

An experiment was performed to study the time and concentration-dependent coagulation activity in the presence of cobalt oxide nanoparticles (Co_3O_4NPs) biologically synthesized from red algae that demonstrated great anti-coagulation activity. However, the experiment did not clearly explain the mechanism of the coagulation process, which needs to be determined by the researchers working in this area of research.[218] Similarly, face-centered and crystalline nickel oxide nanoparticles were synthesized from the leaf extracts of *Euphorbia heterophylla* (Linn.), which also showed efficient anticoagulant activity.[219] *Cola nitida* (Sterculiaceae) extracts were also used to synthesize titanium oxide nanoparticles (TiO_2 NPs) that exhibited excellent anti-coagulant activity *in vitro* when observed on human blood. In addition, it was observed that these bioinspired titanium oxide nanoparticles maintained

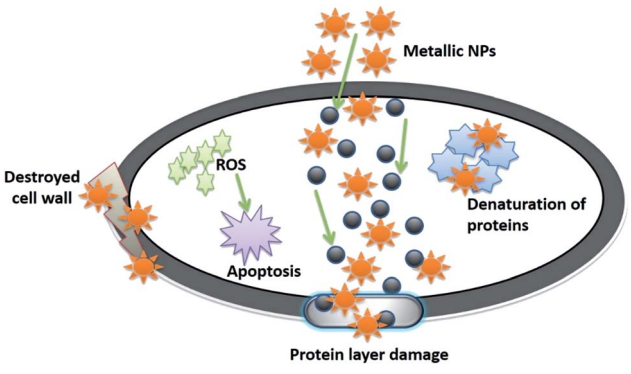

Fig. 7 Illustration of the mode of mechanism followed by metal and metal oxides to exhibit antibacterial activity against bacteria, like denaturing the protein, generating ROS, increasing oxidative stress inside the cell, and damaging the cell wall.

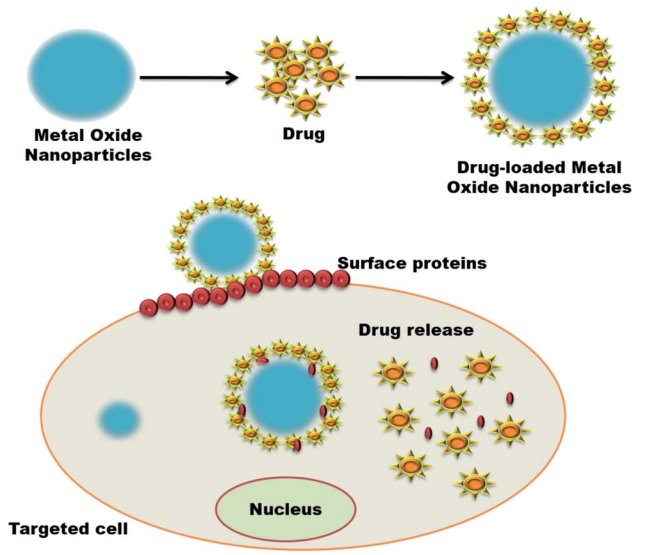

Fig. 8 Systematic mode of the mechanism of metal oxide nanoparticles loaded with drugs for delivering at the target cell by denaturing the cell's surface proteins.

the morphology of red blood cells.[220] Apart from the plants showing anti-coagulation activities, several other organisms (like Hirudinea) exhibit excellent anti-coagulation properties, and therefore can be utilized to synthesize various metal and metal oxide nanoparticles to exhibit anti-coagulation activity.

4.2.7. Drug delivery. The small size and large surface area of the nanoparticles help them exhibit advanced colloidal stability and bioavailability. These features help them cross the blood–brain barrier, pulmonary system and become absorbed through the endothelial cells. Specifically, metal and metal oxide nanoparticles possess some benefits like high stability, easy synthesis processes, easy fabrication to the desired size, shape and porosity, less swelling variations, advanced incorporation into hydrophobic and hydrophilic systems, and easy functionalization by various molecules due to the negative charge of the surface, which make them a promising tool for biomedical applications. Moreover, the metal and metal oxide nanoparticles react with *in vivo* systems differently depending on their size, shape, purity, stability, and surface properties. Therefore, it makes it necessary to characterize their morphology.[221] Tumor targeting, photothermal therapy, imaging, and drug delivery can be achieved using fluorescent quantum dots, carbon nanotubes, metal and metal-oxide nanoparticles, and ceramic nanoparticles.[222] The researchers have currently started focusing on the targeted DDS, which is now considered an important biomedical application as it targets to deliver various kinds of drugs to the specific sites of the body, and therefore avoids damage to nearby healthy cells. A brief overview of the targeted DDS using metal oxide nanoparticles loaded with the drug has been described in Fig. 8. Furthermore, the mode of mechanism for targeted DDS of the metal or metal oxide nanoparticles is that the desired drug is encapsulated or conjugated with the metallic nanoparticles. The metallic nanoparticle exhibits magnetic properties that help guide them through the external magnetic field to the specific site. After reaching the specific site, the drug is then released either through enzyme activity, or change in temperature or pH.[223] The therapeutic metallic nanoparticles of iron oxide, silver, gold, and gadolinium nanoparticles were used for glioblastoma treatment.[224] Similarly, the bismuth nanoparticle was used to induce autophagy and endocytic mechanisms in human kidney cells.[225] The DDS using silver nanoparticle was synthesized from a plant extract of *Butea monosperma* loaded with doxorubicin. It showed great anti-cancer potentialities with targeted on-site drug delivery, and this is now an FDA-approved chemotherapeutic drug.[74] The silver nanoparticles synthesized from *Delftia* sp. strain KCM-006 culture supernatant using antifungal drug miconazole effectually inhibited ergosterol biosynthesis and biofilm fungus formation, and can be used to develop anti-fungal medicines.[226] The metal and metal oxide nanoparticles have eased the delivery of these drugs to the targeted cells, easing cancer treatment and eliminating the risk of generating side effects of chemotherapeutic drugs. Furthermore, the green synthesis approaches have made the development of metal and metal oxide nanoparticles easily cost-effective, and have filled the gap between the biomedical domain and nanotechnology.

A study conducted to treat childhood neuroblastoma with dextran-coated cerium oxide nanoparticles loaded with curcumin was utilized. It was observed that these dextran-coated cerium oxide nanoparticle-loaded curcumin efficiently induced cellular toxicity in the neuroblastoma cells and did not affect the normal cells.[227] Moreover, cerium oxide nanoparticles exhibit redox properties that help them be considered an efficient drug-delivery agent.[228] Similarly, selenium nanoparticles are also considered a suitable agent to deliver drugs as they have efficiently delivered various inorganic cancer therapeutic drugs, like propylene oxide-modified ruthenium complexes and ethylene oxide copolymer.[229] Furthermore, transferrin-conjugated selenium nanoparticles efficiently delivered doxorubicin-cisplatin into the mammalian breast cancer cell line (MCF-7), leading to apoptosis in cancer cells.[230] It has been observed that cancer cells show a more acidic nature at high-temperature than normal tissues and blood. Thus, it is important to consider pH while developing a cancer-related DDS. For the same, ZnO–quercetin nanocomposite was developed to deliver quercetin in the cancer cells at two different pH values, 5.5 and 7.4, because pH plays a crucial role during the delivery of the quercetin in cancer cells. The results of this experiment showed that the quercetin was found to be stable at pH 7.4 as compared to pH 5.5. This is because at pH 7.4, the hard ligands (–OH groups) present in quercetin survived in the ionized form (O^-) and acted as an active ligand during the chelate formation. In contrast, at pH 5.5, these hard ligands existed in an unionized form, which led to the instability of the quercetin. Furthermore, it was noted that the controlled and slow release of quercetin at pH 7.4 could maintain the ZnO–quercetin nanocomposite in the bloodstream for a certain time without causing any side effects.[231]

4.2.8. Neuroregenerative therapy. The maintenance of neuronal activity plays a major role in neurodegenerative diseases, leading to new restorative and neuroprotective treatments in Parkinson's disease.[232,233] Furthermore, the biologically synthesized nanoparticles of several metal and metal oxides impart tremendous applications for treating various neurodegenerative diseases. Biosynthesized spherical silver nanoparticles were also studied with differentiated human neuroblastoma cells. The result of this study indicated extraordinary neurodegenerative activity.[234] Moreover, it has been observed that treatment with selenium can efficiently reduce the risk of generating neurodegenerative diseases when observed in different animal models.[235–237] Furthermore, both elemental and modified selenium nanoparticles efficiently exhibit antioxidant activity on neurons and the brain, as they are present as a cofactor in glutathione peroxidase (GPx), which helps reduce H_2O_2 and prevents oxidative damage.[28] Furthermore, it was observed that patients affected with diseases such as Huntington's disease and Alzheimer's disease exhibited selenium deficiency in their body, resulting in the loss of neuron cells and brain dysfunction.[238,239] Therefore, early detection of selenium in the body can help develop therapeutic approaches to treat various neurodegenerative diseases.

The major cause of the generation of neurodegenerative diseases, such as Parkinson's, Huntington, and Ischemic

Strokes, is due to a rise in oxidative stress and production of free radicals.[173] The distinctive pharmacological and biological properties of cerium have helped them treat various diseases for more than a century.[240] It has been observed that cerium oxide nanoparticles are considered as an excellent antioxidant agent because they exhibit excellent neutron shielding effects by restricting free radical generation and affect the signal transduction pathways, which can be used as a therapeutic agent to treat neurodegenerative diseases.[241–244] Another common cause of death globally is ischemic stroke or cerebral stroke, in which lack of blood flow is caused due to the formation of hemorrhage or clots in the brain. It was observed that cerium oxide nanoparticles, when enfolded with phospholipid-polyethylene glycol, helped in protecting from ischemic stroke.[245] However, not much data is available on the green synthesized metal and metal oxide nanoparticles, which can treat neurodegenerative diseases. Thus, there is plenty of room for researchers working on therapeutic aspects to develop bioinspired metal and metal oxide nanoparticles to treat neurodegenerative diseases efficiently.

4.2.9. Cardiovascular diseases. Vascular ailments, structural abnormalities, and blood clots are known as cardiovascular diseases, for example, coronary heart diseases, atherosclerosis, angina pectoris, and myocardial infarction. It was reported that acute myocardial infarction could be diagnosed using the biomarker myoglobin quantified by electrochemical nanobiosensors, which direct electron transfer between Fe(III)-heme and electrode modified by gold nanoparticles/didodecyldimethylammonium bromide (DDAB/Au)-antibody (anti-myoglobin).[246]

Furthermore, the AuNPs can inhibit vascular endothelial growth factor-stimulated angiogenesis *in vivo* and *in vitro*.[247] The Ag NPs synthesized using *Bacillus licheniformis* efficiently inhibit IL-1β molecules and vascular endothelial growth factor (VEGF) in porcine retinal endothelial cells and reduce vascular permeability, thus showing better anti-angiogenic properties.[248] Furthermore, the AgNPs synthesized from plant extract *Salvia officinalis* reduce hemoglobin content in chick chorioallantoic membrane blood, proving to have good antiangiogenic properties.[249] The decreased VEGF-mediated cell proliferation, tube formation and migration are inhibited by the P13K/Akt signaling pathway utilizing Ag NPs synthesized in bovine retinal endothelial cells.[95] Furthermore, many biogenic metals and metal oxide nanoparticles can be used to treat cardiovascular diseases due to their extraordinary properties. Thus, researchers working on cardiovascular disease treatment aspects can validate the utility of bioinspired metal and metal oxide nanoparticles to treat this deadly disease. They must also work on determining the mode of mechanism data of these nanoparticles for curing this disease.

4.2.10. Bone-related and dental therapeutics. The application of natural and synthetic polymer nanocomposites in bone tissue regeneration has been reported using nano zirconia and silver. It has been reported that CeO_2-incorporated mesoporous calcium-silicate (CeO_2-MCS) stimulates the proliferation and alkaline phosphatase activity of osteoblast cells. Therefore, CeO_2-MCS materials with drug delivery would be appropriate for bone regeneration.[250] Osteoporosis has gained much attention from researchers as it has become a major medical concern. Until now, no effective treatment has been reported. Osteoporosis is a musculoskeletal ailment marked by decreased bone mass or low bone mineral density (BMD) in the body, and majorly affects women over the age of 60 or women experiencing menopause. There is now an urgent requirement to develop effective and permanent medical treatments for osteoporosis. Therefore, ZnO NPs for the treatment of osteoporosis have been considered as they find their immense potentialities in the biomedical domain. *Artemisia annua* was selected as it is known for its traditional medicinal activities like anti-hyperlipidemic, anti-plasmodial, anti-convulsant, anti-inflammatory, anti-microbial, and anti-cholesterolemic activities. Furthermore, its biochemical analysis shows that it consists of 123 phytoconstituents in various parts (leaves, stem, and roots), such as terpenoids, flavonoids, caffeoylquinic acids, coumarins, acetylenes and sterols. These synthesized ZnO NPs were found to be stable and effectively exhibited stimulatory effects on the differentiation in MG-63 cells in terms of the viability of the cell, alkaline phosphatase (ALP) expression activity, collagenogenesis, and mineralization, which indicates that *A. annua*-synthesized ZnO-NPs could induce osteoblast differentiation in MG-63 cells.[78] However, there is scant scientific research related to the utility of biogenic metal and metal oxide nanoparticles for solving bone-related complications. Hence, researchers working in this field should explore more potentialities of these biogenic nanoparticles for bone-related disease.

Nowadays, the dental sector utilizes nanoparticles to a vast scale as it is biologically reliable when it comes to nanoparticles obtained *via* green synthesis. When a dental implant is substituted by biocompatible hydroxyapatite and titanium embedded into the alveolar bone and artificial tooth instead of using ceramic materials, it promises safety. New implants created using alumina/zirconia nanocomposites exhibited better efficacy than ceramic materials.[251] Furthermore, it was observed that zirconia oxide nanoparticles showed good antibiofilm activity against bacteria like *Enterococcus faecalis*, and simultaneously acted as polishing agents in dental practices.[252] Many other metal and metal oxides synthesized *via* the biogenic route can also solve dental problems, but they need to be researched further. A few of the potential metal and metal oxide nanoparticles that can be used in dental complications are silver, copper, cerium, zinc, magnesium, and vanadium, owing to their extraordinary antimicrobial properties. However, before utilization, the researchers or scientists working on this aspect have to explore their cytotoxicity and mode of mechanism data.

4.2.11. Wound healing activity. Hydrogel Ag NPs synthesized from the *Arnebia nobilis* root extract act as a beneficial wound healing agent, eco-friendly, and lack side effects.[253] Similarly, glucuronoxylan-mediated Ag NPs synthesized from the seeds of *Mimosa pudica* exhibited vast potential in antibacterial activity against a range of Gram-positive and Gram-negative bacteria, and demonstrated remarkable wound healing properties in rabbits.[254] Recent studies have shown that the *in vivo* use of microporous Ag/ZnO NPs, when loaded with

chitosan, greatly accelerates the wound healing process at the starting state when observed in mice.[255] Bacterial cellulose (BC-temporary skin substitute)-loaded TiO_2 nanocomposites showed excellent wound healing progress when observed in the mice model. This BC-TiO_2 nanocomposite treatment efficiently promoted the healing process *via* fibroblast migration and increasing growth of the epithelial cells in the blood supply, and it also formed new blood vessels.[77] Apart from the above-mentioned biogenic metal and metal oxide nanoparticles, there are many others that can also be very efficient for wound healing activity, but they need to be explored before utility.

5. Anti-viral activity of various metal and metal oxide nanoparticles

Viral infections are considered one of the major root causes of mortality worldwide, which have led to significant losses in social, economic, and human lives over the years.[256] Until now, the occurrence of sudden viral outbreaks has not been tracked, and can be settled down to the limited detection techniques and the rapid adaptive nature of viruses consisting of pretty big genomes.[257] Therefore, it has become necessary to develop rapid, sensitive and specific diagnostic tools to detect viral strains and control their mass spreading.[258] Many literature-based reviews have also started highlighting various impacts of SARS-CoV-2, and many types of research are dedicated to developing vaccines and sensors to combat this pandemic quickly.[259] The spread of viruses generally takes place either through direct contact or *via* aqueous environment. However, with the sudden outbreak of the novel coronavirus (CoV), the researchers have now started focusing on finding new ways and methods for the early detection of viruses and their related treatments. SARS-CoV-2 also belongs to the RNA virus family. It is known to cause several diseases in mammals and birds, and is spread through direct contact with patient.[260] The current strain of coronavirus is known as COVID-19 or SARS-CoV-2. It is closely related to Severe Acute Respiratory Syndrome (SARS), which appeared in 2002 and 2003, infecting ~8000 people. COVID-19 affects differently than other COVID strains and is now considered a pandemic, affecting millions of patients worldwide in just a year.[261]

Currently, nanotechnology is dominating various domains in the science and technology fields, and has also found its profound use during the outbreak of the SARS-CoV-2 pandemic. Nanotheranostics is considered an innovative fusion of diagnostic and therapeutic functions combined in a unit multifunctional nanoplatform.[262,263] Similarly, nanoparticles are also considered promising theranostic tools used in drug delivery, diagnostics, and the development of vaccines. Moreover, they have been approached to visualize and track the mechanism and treatment of various diseases, particularly viral infection.[264] In order to develop a propitious and precise "theranostics based nano-platform", three major factors should be precisely selected, including the correct therapeutic agent, the nanoparticles that will act as carriers, and the imaging agent.[265] Therefore, several biogenic metals and metal oxide nanoparticles exhibit anti-viral activity and virus diagnosis potentiality.[266–268] The modifications of the nanoparticles enhance their biological, chemical, surface, physical, and optical properties, making them more suitable for various domains. Moreover, it was observed that when lanthanide nanoparticles were doped with polystyrene, it efficiently detected anti-SARS-CoV-2 Immunoglobulin G (IgG) from human serum, therefore making a rapid sensitive and accurate nano-based diagnosis of SARS-CoV-2.[269] Many companies like MIT-spinout startup and World Nano Foundation (WNF) are designing an antibody-based COVID-19 kit consisting of gold nanoparticle-based strips that can rapidly detect Immunoglobulin M (IgM) and IgG. The main idea behind this kit is to detect SARS-CoV-2 directly from blood or urine samples by the color change, as these strips will be covered with antibodies conjugated with gold nanoparticles that will interact with the viral antigens (SARS-CoV-2) present in the sample. The interaction between the antigen and antibody will lead to the change in color being visible within 5 minutes, as represented in Fig. 9.[258,270,271] These gold nanoparticle-based strips are commercially used in the lateral flow assay with a clinical sensitivity of 57 and 81%, 100% specificity, and 69 and 86% accuracy for IgG and IgM, respectively.[271] Although the major limitation possessed by this test is that it does not specify a particular strain of virus; rather, it only detects the presence of infection. In order to subdue this limitation, researchers from MIT have designed a screening device that can easily distinguish between the two similar gene sequences so that SARS-CoV-2 can be accurately detected.[272] The biogenic copper nanoparticle exhibits good anti-oxidation properties, making them a potential antiviral agent against SARS-CoV-2.[273,274] The iron oxide nanoparticles exhibited efficient antiviral activity, and were examined on both SARS-CoV-2 and Hepatitis-C virus (HCV) *via* molecular docking studies. The results showed that the iron oxide nanoparticle efficiently interacted with the spike protein receptor-binding domain (S1-RBD) of SARS-CoV-2 and glycoproteins: E1 and E2 of HCV. The stable complex was formed (Fe_3O_4 with S1-RBD of SARS-CoV-19), whereas Fe_2O_3 formed a stable complex with glycoprotein E1 and E2 of HCV. These visible conformational modifications in the structural protein can finally lead to the death of the virus. Therefore, iron oxide nanoparticles can find their profound use in combating SARS-CoV-2, as they could be used to produce antimicrobial fabrics like lab coats, masks, gloves, bedsheets, pillow covers, and oversheets. These antimicrobial fabrics can safely be used in hospitals to control the spread of viral and nosocomial infections in hospitals.[275] Zinc-oxide nanoparticles (ZnO NPs) have previously been studied for their potential antimicrobial role. Another study showed their potential role in antiviral activity against SARS-CoV-2 by inducing oxidative stress in the cellular membranes of SARS-CoV-2, and these ZnO NPs were utilized as a potential disinfectant spray. ZnO NPs can produce cytotoxicity. Therefore, modifying them with polyethylene glycol can enhance their antiviral activity, and at the same time, decrease their cytotoxicity towards normal cells. It has also been suggested that ZnO NP can greatly enhance the immune response against the virus, which can lead to potential

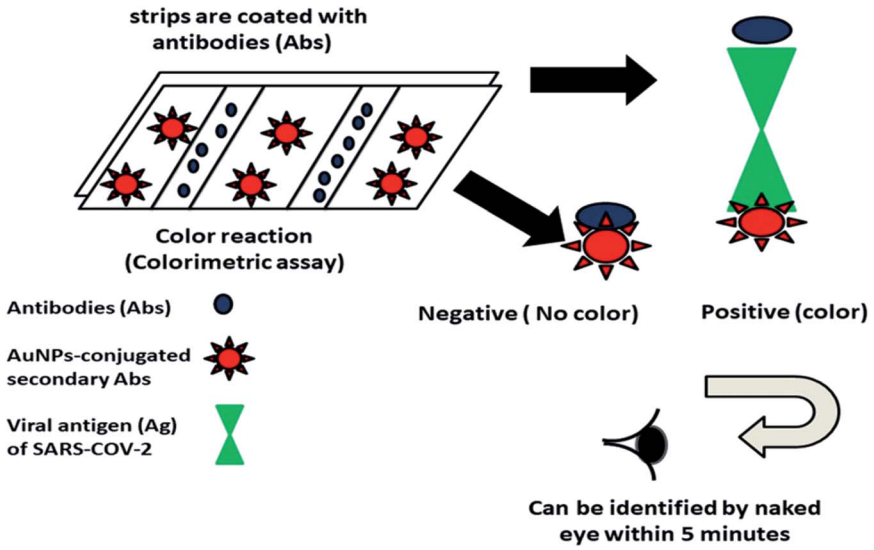

Fig. 9 Schematic illustration showing the colorimetric detection of SARS on the AuNP-based strips. Strips are coated with antibodies (Abs) that hold the capacity to actively bind with viral antigens (Ag) present on SARS-COV-2 and can subsequently form a conjugate with AuNPs-conjugated secondary Abs. This conjugation will finally result in a color change, indicating the positivity of the tested sample (reproduced with permission from G. Ibrahim Fouad, *Bull. Natl. Res. Cent.*, 2021, **45**, 36 [CC BY 4.0] (ref. 258)).

therapeutic properties that will help fight against SARS-CoV-2.[261] Furthermore, there are many other potential biogenic metal and metal oxide nanoparticles, like selenium, cerium, magnesium, vanadium, lanthanum, copper, iron, and metal–metal nanocomposites that demonstrate unique antimicrobial potential. However, their utility towards combating SARS-CoV-2 must be validated by material scientists working towards fulfilling biomedical applications, as it is the need of the hour for working to achieve this objective due to the devastating conditions caused by the SARS-CoV-2 pandemic.

6. Conclusion and prospects

Today, many types of nanoparticles are researched, like dendrimers, metallic nanoparticles, and liposomes, and this review attempts to explore the various biomedical applications explicated by the biogenic metal and metal oxide nanoparticles. Furthermore, the biogenic nanoparticles have evolved with time. Even today, they are advancing at a faster pace in various important aspects of clinical fields, such as diagnosing and treating cancer and neurodegenerative diseases, antibacterial and antioxidant activities, and biomolecular detection of analytes. Furthermore, modifying these biogenic metal and metal oxide nanoparticles will contribute a lot towards the eternal scope of research due to their magnificent combination of chemical and mechanical properties. A better understanding of the properties and modulations in their morphology shall pave the way to explore the nanoparticles' potential to cross the hurdles of many biomedical fields, like cytotoxicity and bioavailability.

The synthesis approach of nanoparticles plays a crucial role in defining their properties and utilities in different domains. Therefore, nanoparticle synthesis plays a vital role in the development of nanotechnology. Furthermore, biogenic/bioinspired synthesis has captured much attention nowadays, as they are eco-friendly, cost-effective, and easy to use. This synthesis method utilizes natural products (*e.g.*, plant extracts, microbes), which help eliminate the excessive use of chemicals and open new avenues for the utility of metallic nanoparticles. Moreover, the biological approaches to synthesize nanoparticles mainly consist of plants, algae, yeasts, fungi, and bacteria, but the plants are preferred over the other biological routes, as they are easy to find and no culture media maintenance are required. In the plant-based synthesis of nanoparticles, various phytochemicals of plants act as stabilizing, caping, and reducing agents, which replace chemical-based stabilizers and reducers. Furthermore, the biologically synthesized nanostructures are considered more for research, as they confer very little or lack any chances of toxicity. Due to this property, these bioinspired nanoparticles play a vital part in the diagnostics and therapeutics of certain life-threatening disorders. These bioinspired metal and metal oxide nanoparticle properties have helped them gain much attention during the current pandemic, as they are not only used in detecting the coronavirus, but are also being used to produce disinfectant sprays and the formation of antimicrobial films. Furthermore, the bioinspired metal and metal oxides have found their profound use in producing safety equipment, kits and suits.

This review is one of a kind, as it mainly focuses on the biologically derived metallic nanoparticles and their utilities in both diagnostic and therapeutic applications. It will also help in gaining knowledge about different kinds of biogenic metal and metal oxide nanoparticles. The current pandemic calls for advancement in public health research, biotechnology, nanotechnology, and environmental technology. Thus, the review enhances the knowledge in biomedical fields and the use of

nanotechnology in developing and enhancing this field. It will also shed light on the various uses of bioinspired metal and metal oxide nanoparticles during pandemic times by discussing their biomedical utility. Hence, this review will, in detail, provide an up-to-date literature review of biogenic metal and metal oxide nanoparticles for biomedical (diagnostics and therapeutics) applications, along with their properties, biosynthesis and role during the SARS-CoV-2 pandemic.

Funding

This review did not receive any specific grant from any funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

K. R. B. S. contributed to the conceptualization, data curation, investigation, resources, validation, visualization, and writing an original draft. V. N. contributed to the data curation, visualization, and writing an original draft. A. K. S. and J. S. contributed to the supervision and reviewing, & editing the manuscript draft. R. P. S. contributed to the conceptualization, validation, project administration, supervision, and reviewing & editing the manuscript draft.

Conflicts of interest

The authors declare no conflict of interest for this work.

Acknowledgements

K. R. B. S. and A. K. S. are thankful to Principal, Govt. V. Y. T. PG. Autonomous College, Durg, Chhattisgarh, India, for providing apt support throughout this manuscript draft's writing process. J. S. expresses gratitude for the DST-INSPIRE faculty Fellowship, BHU (IoE grant), and UGC, New Delhi, for financial support. Finally, R. P. S. and V. N. are thankful to Hon'ble Vice-chancellor, Indira Gandhi National Tribal University, Amarkantak, M. P., India, for providing financial assistance to work smoothly and diligently.

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