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*Review Article*

# Biosynthesis and Potential Applications of Silver and Gold Nanoparticles and Their Chitosan-Based Nanocomposites in Nanomedicine

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Biosynthesized or biogenic metallic nanoparticles, particularly silver and gold nanoparticles (AgNPs and AuNPs, respectively), have been increasingly used because of their advantages, including high stability and loading capacity; moreover, these nanoparticles are synthesized using a green and cost-effective method. Previous studies have investigated reducing and/or stabilizing agents from various biological sources, including plants, microorganisms, and marine-derived products, using either a one-pot or a multistep process at different conditions. In addition, extensive studies have been performed to determine the biological or pharmacological effects of these nanoparticles, such as antimicrobial, antitumor, anti-inflammatory, and antioxidant effects. In the recent years, chitosan, a natural cationic polysaccharide, has been increasingly investigated as a reducing and/or stabilizing agent in the synthesis of biogenic metallic nanoparticles with potential applications in nanomedicine. Here, we have reviewed the mechanism of biosynthesis and potential applications of AgNPs and AuNPs and their chitosan-mediated nanocomposites in nanomedicine.

## 1. Introduction

Nanotechnology is a branch of technology associated with the synthesis, characterization, and application of materials in the nanoscale range of 1–100 nm [1]. The term "nanotechnology" was defined in 1974 by Norio Taniguchi of Tokyo University as the ability to manipulate materials at the nanometer scale [2]. Since then, nanoparticles have been used for various applications in science and technology. The application of nanotechnology in health sciences is in the field of nanomedicine [3].

The unique property of nanoparticles is that they have a considerably high surface area, which facilitates binding with different functional ligands [4, 5]. The small size of nanoparticles enables their use for various applications [6], including development of new devices or tools used in the biomedical and pharmaceutical fields [4, 7, 8].

In the recent years, compared to bulk metals or metal ions, metallic nanoparticles, including silver (Ag), gold (Au), platinum (Pt), and palladium (Pd), have been extensively studied because of their unique properties, particularly the effect of quantum size and large surface area. In addition, metallic nanoparticles are compatible with the biological system, and therefore, they have been used for drug delivery, diagnostic imaging, labelling, and as biosensors [9].

Numerous studies have been conducted, particularly to examine the synthesis and potential applications of metallic nanoparticles. Metallic nanoparticles are synthesized by various techniques, including a chemical method. The process of synthesis via a chemical method is divided into two steps: the first step involves reduction by a reducing agent followed by stabilization of the formed nanoparticles by using a suitable stabilizing agent; the first step is crucial in avoiding particle agglomeration that leads to the disappearance of the formed nanoparticles [10]. A nontoxic stabilizing agent or a capping agent should be selected during the synthesis of nanoparticles because the toxicity of

the nanoparticles depends on the properties of the capping agent rather than the nanoparticle itself [11].

Metallic nanoparticles stabilized using a biodegradable polymer such as chitosan can be used for the development of drug delivery systems because chitosan acts as an effective adjuvant owing to its efficient interaction with and permeation across the cellular membranes. Chitosan is widely used because of its low toxicity and high biocompatibility. The presence of a stabilizer such as chitosan in the synthesis of metallic nanoparticles can facilitate modification of the surface physical absorption, specific recognition, and electrostatic interaction and thus improve stability [12, 13], which is important for determining the potential use of metallic nanoparticles as therapeutic agents [14].

Chitosan is used as a stabilizer [15] and as a reducing agent [16] in the synthesis of gold nanoparticles (AuNPs). The concentration of chitosan affects the size and stability of the prepared nanoparticles [17]. The electrostatic attraction between the metal anions and protonated amine groups is because of the interaction between chitosan and the anionic tetrachloroauric ions.

Biosynthesis of metallic nanoparticles is gaining popularity because of the eco-friendly and cost-effectiveness nature of this method, whereas the chemical method is associated with biological hazards and environmental toxicity [18]. Metallic nanoparticles synthesized using biological agents, including fungi, plants, bacteria, and other microorganisms, have high stability. Many studies have investigated the applications of silver nanoparticles (AgNPs) and AgNPs in health sciences; therefore, in this article, we have reviewed the mechanism of biosynthesis and the potential applications of silver nanoparticles (AgNPs) and AuNPs and their chitosan-mediated nanocomposites.

## 2. Potential Applications of AgNPs

Unlike the bulk form of the noble metal, AgNPs of various shapes and sizes have different catalytic characteristics, including surface plasmon resonance (SPR), large effective scattering cross section of individual AgNPs, and strong toxicity to a wide range of microorganisms. Recent studies have investigated the effects of AgNPs although silver ions and salts have long been used for their inhibitory effects against microorganisms [19].

*2.1. Antimicrobial Agents.* Many industries have started exploiting silver for its use as an antibacterial agent, and silver is often added to wound dressings, topical creams, antiseptic sprays, and fabrics [20]. AgNPs also exert their antibacterial activity by acting as antibacterial complements to antibiotics. Thus, AgNPs can be used in the case of development of resistance to conventional antibiotics [21]. AgNPs exert antibacterial effects by attaching to the bacterial cell wall and subsequently penetrating it, and thus, result in a structural alteration of the cell membrane. Thus, a compromise in the permeability of the cell membrane leads to cell death. The formation of gaps known as "pits" on the cell surface causes accumulation of nanoparticles [22].

Further, AgNPs tend to interact with sulfur- and phosphorus-containing biomaterials present in the bacterial cells, such as DNA bases, and then, act on the soft bases and destroy the DNA, which leads to death of the cell [23]. Moreover, inhibition of respiratory enzymes by silver ion causes release of reactive oxygen species (ROS) by the cell, which results in cells to self-attack. In addition, nanoparticles modulate signal transduction in bacteria; nanoparticles dephosphorylate the peptide substrates on tyrosine residues, which lead to inhibition of signal transduction and thus prevention of the growth of bacteria [24].

Several studies indicate that the positive charge on the silver ion plays an important role in the antimicrobial activity exerted through electrostatic attractions between the negatively charged cell membrane and the positively charged nanoparticles [25]. AgNPs are used as coating materials for medical devices because of their unique antimicrobial properties. AgNPs protect the outer and inner surfaces of the devices and facilitate continuous release of silver ions to induce antibacterial activity [26]. In addition, the synthesized AgNPs are dispersed in various types of vehicles such as chitosan-alginate composites [27] and a chitosan nanocarrier [28] to achieve an enhanced antibacterial effect.

*2.2. Leishmanicidal Agent.* Leishmaniasis is a disease caused by parasites of the genus Leishmania, transmitted to the host by a sand fly vector [29]. Current drugs caused severe toxicity and the parasites have developed resistance to the available leishmanicidal agents [30, 31]. Strategies to overcome these problems include a combined therapy of leishmanicidal agent with AgNPs. Amphotericin B was adsorbed on the surface of AgNPs synthesized from the aqueous extract of *Isatis tinctoria* [32]. The leishmanicidal activity of these nanoparticles ($IC_{50}$ = 2.43 $\mu$g/mL) was greater than the blank AgNPs ($IC_{50}$ = 4.2 $\mu$g/mL). Similarly, *Anethum graveolens* leaf extract was used as a source of reducing agent to produce biogenic AgNPs. The AgNPs augmented antileishmanial effect of miltefosine by ~2-folds, even though AgNPs alone did not show any inhibition against leishmanial parasite [33]. Therefore, the combination of leishmanicidal agent with biogenic AgNPs could be the answer for a safer and more effective alternative to treat leishmaniasis.

The effects of light exposure on the AgNPs leishmanial activity was investigated against *L. tropica promastigotes in vitro*. The morphology and other parameters, including glucose consumption and mitochondrial dehydrogenase activities of the parasite, were altered and by exposing to visible light; the antileishmanial activity was enhanced compared to those in the dark condition [34]. Similar findings were reported when the parasites were exposed to AgNPs and UV light [35].

*2.3. Catalytic Agents.* Metal particles in the nanometer size range exhibit physical properties that are different from both the ion and the bulk material counterparts, including increased catalytic activity [36]. The catalytic activity of these nanoparticles is dependent on their particle size as well as size distribution, structure, shape, and chemical-physical

environment. Catalytic agents are important for many chemical reactions and degradation of many synthetic chemicals such as dyes like methylene blue and Congo Red and caused adverse effects to human health and environment. Currently, nanocatalyst is used to remove harmful chemicals that are widely applied in many products, including cosmetics and pharmaceuticals [37].

Photocatalytic activity of AgNPs biosynthesized from the extract of lychee (*L. chinensis*) was reported to be significantly higher when compared to commercial AgNPs; 99.24% of methylene blue degraded within 11 min. The catalytic activity was maintained even after the third time of reusing the AgNPs [38]. The high activity is attributed by the small size of AgNPs that provides large surface area for catalysis to occur on the surface of nanoparticles [38].

*2.4. Wound Healing Agents.* AgNPs are used as excellent healing wound dressings because they accelerate reepithelialization and increase the bacterial clearance from infected wounds [39]. These effects of AgNPs are because of a decrease in the activity of local matrix metalloproteinase (MMP) and an increase in the apoptosis of neutrophils within the wound [40]. In addition, AgNPs inhibit the activities of proinflammatory cytokines interferon gamma and tumor necrosis factor alpha [41]. In an animal model, topical application of chitosan-capped AgNPs accelerated the healing of a burn wound healing by decreasing the inflammatory reaction, and subsequently, decreasing the duration of the repair phase [42]. A previous report has described the applications of biosynthesized AgNPs and AuNPs in wound healing [43].

*2.5. Biosensors.* The plasmonic properties of AgNPs enable the detection of a large of proteins that are not detected by normal biosensors. AgNPs are used as biosensors in the detection of cancers [44]. The SPR peaks and line widths are sensitive to the size and shape of the nanoparticles, the metallic species, and the surrounding medium [45]. Thus, AgNPs are very sensitive and can be used for bioimaging. AgNPs can be used as agents for photothermal therapy for ablation of unwanted cells such as breast carcinoma cells [46]. AgNPs were also used as cation marker in glucose biosensors, and the method could determine glucose with good selectivity, accuracy, and reproducibility [47]. Additionally, AgNPs could be used in sensing DNA hybridization by which the success of a sensing assay depends on the salt concentration which should be greater than a minimum threshold [48].

*2.6. Drug Delivery.* Nanoparticles have advantages such as small particle size, high stability, and specific targeting ability through surface functionalization; thus, nanoparticles can be used as versatile drug delivery systems. The surface of AgNPs was functionalized with a targeting ligand, for example, folic acid. Then, the AgNPs were conjugated with diminazene aceturate, a drug used to treat animal trypanosomiasis [49]. In addition, AgNPs have been developed as vehicles for various drugs [50] and biomolecules, e.g., oligodeoxynucleotides [51] and interleukin-10 [52], for treating cancers and inflammatory diseases, respectively.

## 3. Potential Applications of AuNPs

AuNPs are extensively used in biomedicine because of their properties such as ease of detection, high functionality, and low toxicity [53]. Precise modification of the structure of nanoparticles at the nanoscale increases their solubility in an aqueous environment, improves compatibility with the biological system, and facilitates conjugation other biological molecules [54]. Moreover, administration of AuNPs in humans is safe because of their low cytotoxicity [55].

AuNPs have many advantages, and thus, previous studies have investigated various applications of AuNPs in nanomedicine as antimicrobial agents and in drug and gene delivery systems [56–59]. AuNPs are used for various applications because of their high stability and unique electronic, optical, and spectroscopic properties [60]. Brief descriptions about the applications of AuNPs in nanomedicine are shown in Table 1.

*3.1. Antimicrobial Agents.* AuNPs have excellent antibacterial activities. Moreover, they have bactericidal effects on various microorganisms. However, the bactericidal effects are dependent on the shape and size of the AuNPs [61]. The mechanism underlying the antibacterial effects of AuNPs is the same as that of AgNPs in that the AuNPs attach to the surface of the bacterial cell membrane and cause significant damage and disruption of the membrane, which increases the permeability of the cell surface, inhibits the respiratory function of the cell, and ultimately leads to the death of the cell [62–64]. In addition, a previous study has shown that AuNPs can be effectively used as a vehicle for antibiotics [61]. The combination of AuNPs with another antibacterial agent such as ciprofloxacin showed synergistic effects, and the antibacterial activity of the combination was higher than that of AuNPs alone [65].

*3.2. Leishmanicidal Agents.* Leishmanial parasites multiply in host macrophages. Specific drug delivery to macrophage is therefore needed in combating leishmanial parasite infections [66]. AuNPs as drug delivery systems for leishmanicidal agents have been reported previously. In a study by Das et al. [66]; quercetin-functionalized AuNPs were developed and they were effective against selected drug resistant strains. Other phytochemicals used to synthesize AuNPs as leishmanicidal agents include the aqueous extract of *Rhazya stricta decne* [67, 68] and *Maytenus royleanus* stem [31].

*3.3. Catalytic Agents.* Like AgNPs, AuNPs has been also developed as catalytic agents for various kinds of reactions, including removal of harmful chemicals. In a study by Khan et al. [37], longan fruit juice was employed to biosynthesize AuNPs. The degradation of methylene blue by the catalytic action of the AuNPs was reported to be as high as 76%, attributed by the surface-capped biomolecules that continuously

Table 1: Brief descriptions about the applications of gold nanoparticles (AuNPs) in nanomedicine.

| Application | Description |
|---|---|
| Photodynamic therapy | Near-infrared- (IR-) absorbing AuNPs produce heat when excited by light at wavelengths from 700 to 800 nm. Exposure of a tumor containing AuNPs to light at these wavelengths rapidly heats up the particles and thus destroys the tumor cells. |
| Drug-delivery agent | AuNPs have a large surface area, which enables adsorption of various molecules such as polymers, therapeutic agents, and targeting ligands on their surface. |
| Diagnostics | AuNPs are used to detect biomarkers of various diseases, including cancers and infectious agents as well as in the home pregnancy test. |

provided electrons for maintaining gold in its reduced form [37] in addition to their advantage of being small size particles. Recently, biogenic AuNPs produced from the aqueous extracts of *Alpinia nigra* leaves showed high photocatalytic activity; about 83% and 88% methyl orange and rhodamine B were degraded, respectively [69].

Advantages of using metal nanoparticles as catalysts include the following: (1) the need of low reaction temperature (below the boiling point of solvent), (2) transparency to light that allows photo catalysis, (3) easy control of their size as well as shape, and (4) the ability to be immobilized on solid supports for the reaction to occur in different phases, even for gaseous phase [70]. Taken together, metal nanoparticles are showing great potentials as a simple and cheap catalysis platform.

*3.4. Diagnostic and Imaging Agents.* Binding of the AuNPs with the analytes alters the physicochemical properties of the AuNPs, for example, conductivity, redox behavior, and SPR, and thus, forms detectable signals that enable their use as diagnostic agents. AuNPs play an important role as a probe in the microscopic examination of cancer cells because they can accumulate and exert optical scattering effect in the tumor cells. Therefore, AuNPs can be used in the diagnosis of cancer [71, 72].

AuNPs allow *in vitro* detection and act as a diagnostic agent for diseases such as cancer by readily conjugating with biomarkers such as oligonucleotides or antibodies to detect the target biomolecules [73]. For example, AuNPs are used in the bio-barcode assay, which is an ultrasensitive method used to detect nucleic acids and target proteins. The bio-barcode assay involves conjugation of AuNPs with target-specific antibodies, barcode oligonucleotides, and magnetic microparticles functionalized with monoclonal antibodies for the target molecule. Detection of the target molecule by these complexes is followed by the release of a large amount of barcode oligonucleotides, which enables quantification and identification of the target [74].

Recently, a photoelectrochemical immunosensor based on cadmium sulfide films and AuNPs deposited on indium tin oxide-coated glass slide (AuNP/CdS/ITO) was developed for the detection of anti-*Leishmania infantum* antibodies. The ability of AuNPs sensitized electrodeposited CdS to determine specific *L. infantum* antibodies with high sensitivity provided a simple alternative in diagnosing leishmaniasis [75].

AuNPs have been used as imaging agents in different techniques such as dark-field light scattering, computed tomography (CT), photothermal heterodyne imaging technique, optical coherence tomography (OCT), and Raman spectroscopy because of their electronic and optical properties [76].

*3.5. Drug Delivery.* Nanoparticles, including AuNPs, are used as gene and drug delivery agents because of their capacity of high surface loading [77] in addition to other advantages. The high surface area of AuNPs acts as a platform for therapeutic agents and facilitates dense binding of multifunctional moieties such as targeting agents and drugs [76]. AuNPs can be delivered into the cells via active or passive targeting mechanisms. The passive targeting process involves accumulation of AuNPs within the tumor via its irregular vasculature, which allows penetration of large-sized particles through the endothelium. The passive targeting process is based on the enhanced permeability and retention (EPR) effect. Active targeting depends on binding to a surface functional ligand specifically designed for the target analytes to provide selectivity and specificity [76]. AuNPs can be used for various applications, including genetic regulation, photothermal therapy, and therapeutic agents, via effective delivery and targeting strategies [78–80].

## 4. Biosynthesis of Metallic Nanoparticles

Metallic nanoparticles are typically synthesized using chemical methods. However, the costly and toxic reagents used as stabilizing and reducing agents during synthesis may limit the applications of these nanoparticles. Moreover, these toxic agents may excessively accumulate in solid, liquid, or gaseous forms in the environment [81]. Chemical and physical methods [64] of synthesis of nanoparticles involve the use of hazardous chemicals and high energy; moreover, the process of purification of nanoparticles synthesized using this method is difficult and wasteful [20]. Therefore, an alternative method that is environmentally friendly and involving biological agents is necessary for the synthesis of metallic nanoparticles.

Moreover, metallic nanoparticles synthesized using chemical methods have harmful effects when used for biomedical applications [82, 83] because of the chemical residues. Thus, development of cost-effective and environmentally friendly methods is urgently needed to synthesize metallic nanoparticles without the use of any toxic chemicals. Recently, a green method using naturally occurring reducing agents such as polysaccharides, microorganisms (bacteria and fungus), or plants extract has been used as a simple, nontoxic, and environment friendly alternative to the complex chemical methods for synthesis of metallic nanoparticles. The applications of biogenic metal nanoparticles are shown in Figure 1.

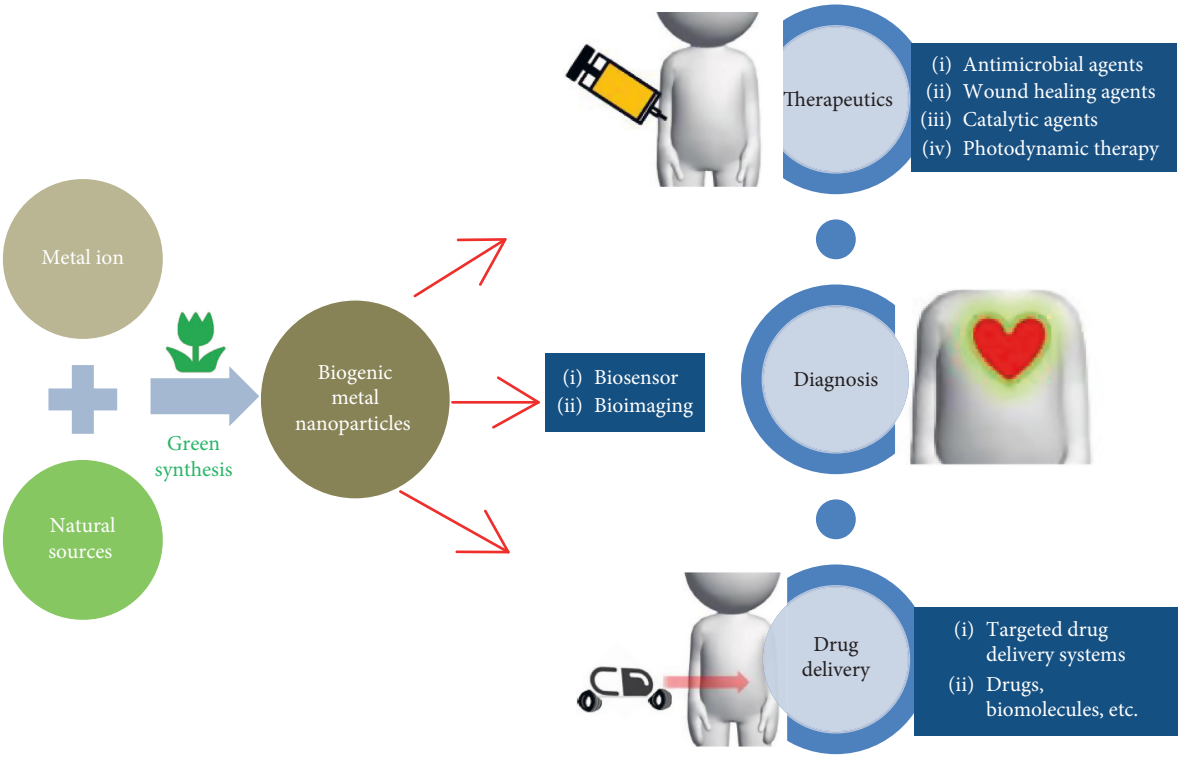


Figure 1: Potential applications of biogenic metal nanoparticles in nanomedicines.

*4.1. Advantages.* Biosynthesis of metallic nanoparticles has received much attention because of the advantages of this method. Synthesis of nanoparticles by using a biological method is environmentally friendly, and agents found on plants, bacteria, or fungi can be used as reducing agents [84, 85]. Biosynthesis of metallic nanoparticles using plant extracts, enzymes, and microorganisms has been extensively investigated in the recent years as an eco-friendly and green method (Mohanpuria et al. 2008, [87]). Plant-mediated biosynthesis of metallic nanoparticles is gaining increasing popularity, because this is a simple method that enables modification of size and shape of nanoparticles and is an economical, nontoxic, and eco-friendly method [88].

In addition, biosynthesis of nanoparticles does not require high temperature, pressure, energy, and toxic chemicals [89]. The size and shape of extracellularly synthesized nanoparticles can be controlled by modifying the pH, temperature, substrate concentration, and reaction time [90]. Moreover, the large amounts of naturally secreted proteins and secondary metabolites produced when using fungi as reducing agents rapidly produce large amounts of nanoparticles [90]. Fungi secrete large amounts of bioactive substances, and thus are appropriate agents for large-scale production and offer ease of downstream processing [91]. In addition to the eco-friendly nature, the biosynthesis method offers better control over crystal growth because of the slow rate of synthesis and stabilization and because of dilution and steric hindrance [92]. These characteristics of this method have been used to control shape and size of the nanoparticles [93].

Large quantities of metallic nanoparticles that are free from contaminants can be biosynthesized using plant extracts, and these nanoparticles have better defined morphology and size than those synthesized using chemical methods [94]. The synthesis of metallic nanoparticles using plant extracts is simpler, easier to scaleup, and inexpensive than that using microbes and whole plants [95, 96]. Moreover, plant extracts can act as stabilizing agent and reducing agents in the production of AuNPs. The source of the plant extract affects the characteristics of the nanoparticles because different extracts may contain different combinations and concentrations of organic reducing agents [97, 98]. In addition, the nature and concentration of the plant extract, pH, temperature, and the concentration of the metal salt affect the rate of production, quantity, and other properties of AuNPs. The various chemical molecules present in the plant extracts that may be used for bioreduction of metal salts are, for example, flavonoids, alkaloids, terpenoids, and polyphenols (Figure 2).

*4.2. Biosynthesis of AgNPs.* The three major biological sources for synthesizing AgNPs are bacteria, fungi, and plant extracts. Plant extracts can be used as reducing and capping agents in the synthesis of AgNPs. The components involved in the biological synthesis of nanoparticles include a solvent medium for synthesis, an environmentally friendly reducing agent, and a nontoxic stabilizing agent [24]. The plant extracts consist of various components such as enzymes, amino acids, polysaccharides, and vitamins that act as environmental friendly reducing agents. Moreover, a review by Sharma et al. [64] has shown that AgNPs can be successfully synthesized using bioorganic compounds.

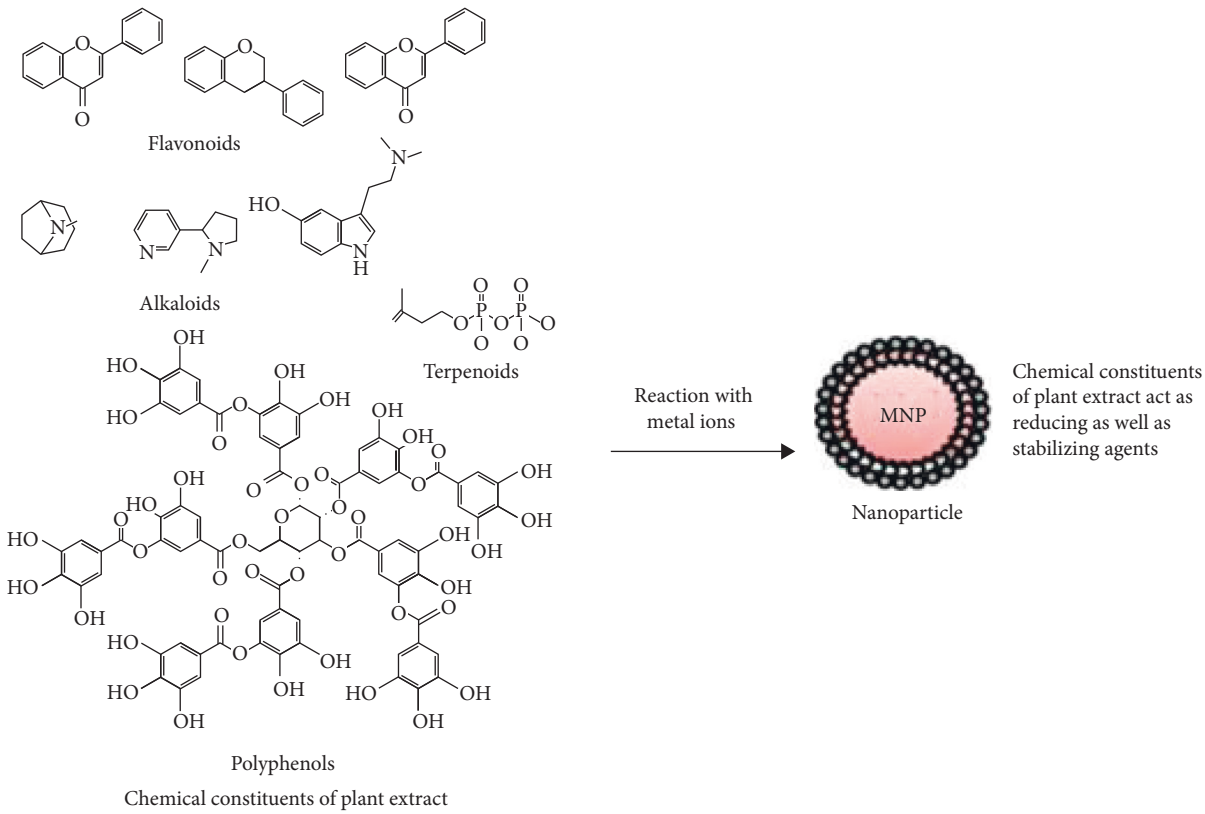


Figure 2: The chemical constituents present in plant extracts that are responsible for the reduction of metal ions (MNP: metallic nanoparticle) [99].

Biological synthesis of nanoparticles involves two mechanisms, namely, enzymatic and nonenzymatic reduction. Synthesis of nanoparticles using the enzymatic reduction method involves nicotinamide adenine dinucleotide phosphate-dependent reductase; however, the rate of reduction achieved using this method is slower than that using the method involving nonenzymatic reduction, which is usually faster, and the chemical reaction involved is identical to that of enzymatic reduction, except that microorganisms or plants are used as reducing and stabilizing agents. In addition, nonenzymatic reduction can be performed in extreme conditions such as high pH or temperature, which accelerates the synthesis [39]. Additional details on different methods of synthesizing biogenic AgNPs have been described by Firdhouse and Lalitha [100]. Recent developments in biosynthesis AgNPs and their potential therapeutic applications are listed in Table 2.

*4.3. Biosynthesis of AuNPs.* The application of AuNPs in nanomedicine is depends on their size, shape, and stability. AuNPs should ideally have a high surface area, disperse well in an aqueous medium, and have good stability at room temperature for an extended period. AuNPs tend to aggregate and form larger particles, because they have large surface area [109].

The methods of preparation of AuNPs are based on the reduction of gold (III) chloral hydrate in a chloroauric acid (HAuCl4) solution. A protecting agent is required in the synthesis of AuNPs that prevents further growth and agglomeration of particles by adsorbing onto the surface of the nanoparticles. Thus, it is important to control the size and shape of AuNPs by using proper reduction and agitation methods, selecting an appropriate type and concentration of a protecting agent, and controlling the conditions of synthesis, such as temperature, pH, stirring, and the use of external fields. Green reducing and stabilizing agents are mostly found in plants [110, 111], algae, bacteria, and fungi [112].

Steric and electrostatic repulsions of surface charge are present on the nanoparticles [113]. The biodistribution of AuNPs in the body is strongly dependent on their size and surface charge. Findings from a previous study indicate size-dependent accumulation of AuNPs in various organs, and the extent of accumulation in various organs depends on the charge of the AuNPs, which is mediated by dynamic protein binding and exchange [114]. The three types of AuNPs are positively charged AuNPs, neutral AuNPs, and negatively charged AuNPs. AuNPs with different surface charges show dose-dependent toxicity and can disrupt the cell morphology. Unlike the neutral AuNPs, the positively and negatively charged AuNPs induce mitochondrial stress [115].

Among the various routes of biosynthesis of AuNPs, the method involving the reduction of gold ions Au (III) to Au (0) using plant extracts in solution phase has gained considerable attention in the recent years. Plant extracts are renewable, are made using environmentally friendly aqueous medium, are nontoxic in nature, have less toxic byproducts, and require mild reaction conditions [116].

Table 2: Sources and potential applications of recently biosynthesized AgNPs in nanomedicine.

| No. | Source of extract | Application | Reference |
|---|---|---|---|
| Plant | | | |
| 1. | *Euphorbia milii* leaf | Wound healing agent | [101] |
| 2. | *Cestrum nocturnum* | Antibacterial agent and an antioxidant | [102] |
| 3. | *Sida cordifolia* | Antibacterial agent against selected fish and human pathogens | [103] |
| 4. | *Ligustrum ovalifolium* fruits | Anticancer agent (tested on human ovarian carcinoma cell lines) | [104] |
| 5. | *Saccharum officinarum* stem | Antibacterial agent | [105] |
| 6. | *Cuscuta reflexa* | Antibacterial agent for wound dressing made from fungal chitosan | [106] |
| 7. | *Coptis chinensis* rhizome | Antibacterial agent (AgNPs were coated with chitosan to enhance their antibacterial activity) | [32] |
| Marine | | | |
| 1. | Fucoidan isolated from *Spatoglossum asperum* | Antibacterial agent | [107] |
| 2. | Fucoidan isolated from brown seaweeds | Antibacterial and anticancer agent | [108] |

Therefore, synthesis of AuNPs using plant extracts is more popular than synthesis using other biosynthetic methods, because the plant extract can also act as a stabilizer in the synthesis of AuNPs [117]. Many plants have been successfully used for rapid and efficient extracellular synthesis of AuNPs.

In a plant extract-mediated bioreduction of AuNPs, the aqueous plant extract is added to gold chloride, also known as chloroauric acid ($HAuCl_4$), solution at normal room temperature and pressure [117]. The reaction is typically completed within a few minutes. The change in color from a pale greenish to a purplish red color indicates the formation of gold nanoparticles. A previous report has described the biosynthesis of AuNPs using plants and microbes and the antimicrobial activity of these nanoparticles [118]. In addition, other applications of biogenic AuNPs are described in a review by Menon et al. [119].

In addition to various plants and microbes, marine sources have been used as reducing agents for the green synthesis of AuNPs. Carrageenan oligosaccharide derived from marine red algae was used as a reducing and capping agent to obtain AuNPs that exhibited antitumor activity against HCT-116 and MDA-MB-231 cells [120]. Moreover, an extract obtained from upcycling sea wastes by jellyfish (*Nemopilema nomurai*) was used successfully as a reducing agent to obtain AuNPs that showed antitumor and anti-inflammatory activities [121]. In addition, a recent study showed a green method of synthesizing AuNPs by upcycling cartilage waste extract from yellow-nose skate (*Dipturus chilensis*) [122]. Various biological or natural sources for synthesizing AuNPs are shown in Figure 3.

*4.4. Chitosan as a Reducing and/or Stabilizing Agent.* Chitosan is an extensively investigated biomolecule for the synthesis of metallic nanoparticles. Previous studies have shown that chitosan can be used as a protecting or a stabilizing agent [16, 42]. Moreover, chitosan has been used as a reducing agent in the synthesis of metallic nanoparticles.

Chitosan (a (1⟶4) 2-amino-2-deoxy-b-D-glucan) is a naturally abundant biopolymer obtained by alkaline deacetylation of chitin [123]. Chitosan is a positively charged polysaccharide that consists of glucosamine and *N*-acetylglucosamine residues. Chitosan is less toxic, nonimmunogenic, biocompatible, and easily degradable by enzymes [124]. The concentration and molecular weight of chitosan affect the stability, morphology, and the size of the synthesized nanoparticles [18, 125].

Recently, chitosan was used to produce silver-based bionanocomposites. The extract obtained from the stem of *Saccharum officinarum* was used as a reducing agent to form AgNPs and chitosan-Ag bionanocomposites. The antibacterial activity of silver-based chitosan bionanocomposites was the highest against *Pseudomonas aeruginosa* (ATCC 9027) followed by that against *Bacillus subtilis* (MTCC 3053), *Klebsiella planticola* (MTCC 2277), *Streptococcus faecalis* (ATCC 8043), and *Escherichia coli* (ATCC 8739). The difference between the antibacterial activities of AgNPs and nanocomposites has not been compared in a previous study [105]. Chitosan was used to coat AgNPs biosynthesized using seaweed polysaccharide fucoidan. The chitosan-coated AgNPs had biocidal and anticancer effects. A previous study showed that *E. coli* was more sensitive than *S. aureus* to treatment with the same concentration of chitosan-coated AgNPs, whereas the anticancer activity was associated with the alteration in the morphology and loss of cell adherence [108].

Several studies have investigated and showed the capability of chitosan as a stabilizing and reducing agent in the synthesis of AuNPs. Huang and Yang [125] used the naturally occurring polysaccharide chitosan as a reducing and stabilizing agent to obtain cationic chitosan-stabilized AuNPs. The AuNPs did not show the obvious signs of aggregation after being stored for more than two months, which indicated a high stability of the AuNPs. In addition, their results showed that chitosan itself could reduce the gold salt to zero-valent AuNPs without the addition of any other reducing agents. Interestingly, the addition of tripolyphosphate into chitosan solution before the reduction of gold salt influences the size distribution and shape of particles, and thus in addition to spherical particles, polygonal particles are obtained [125]. In addition, chitosan is used to reduce and stabilize AuNPs using a two-step technique at low temperatures that involves an initial reaction at room temperature (6 h) followed by a second reaction at 35°C (1 h) [126]. Moreover, chitosan-stabilized AuNPs developed to analyze uric acid levels were prepared at high temperatures, which involved stirring and heating the mixture of HAuCl4 and chitosan at 85°C [127].

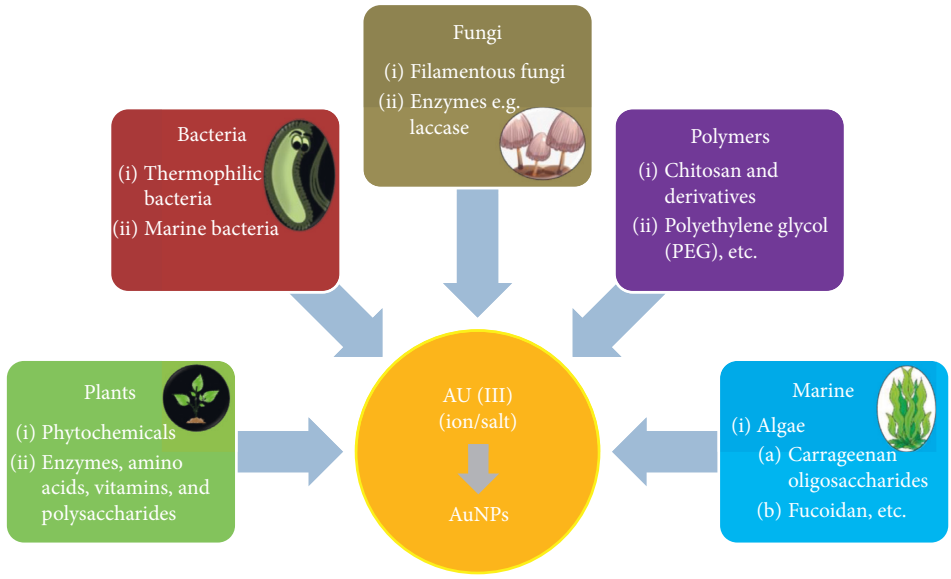


Figure 3: Various biological/natural sources for the synthesis of AuNPs.

The electrostatic forces between tetrachloroaurate ions ($AuCl_4^-$) in the solution and the amino groups in chitosan play an important role in the stabilization and formation of AuNPs [125]. Moreover, the charge transfer from polar groups present in chitosan, for example, hydroxyl or amino groups, can reduce the gold ions to neutral atoms [128]. Thus, chitosan not only acts as a good reducing agent for green synthesis, but also acts as a stabilizing agent in the formation of AuNPs.

*4.5. Characterization of Metallic Nanoparticles.* Characterization is necessary in controlling the outcome of the study and to control the properties of the product. Moreover, characterization of metallic nanoparticles is necessary to evaluate the result of surface modification, particularly in the case of nanoparticles functionalized with biomolecules. Different instruments and techniques have been used to evaluate the physical characteristics of the nanoparticles. Characterization of nanoparticles involves determination of different parameters such as particle crystallinity, morphology, size, and surface area.

*4.5.1. AgNPs.* The first indication of formation of nanoparticles is color change. A change in color from yellow to brown indicates the formation of AgNPs. Further, UV-spectrometry is used to confirm the formation of nanoparticles on the basis of their SPR. UV-spectrometry is one of the easy techniques to verify the formation of metallic nanoparticles provided the metal has SPR. Silver nitrate solution used to form AgNPs shows a maximum absorbance of around 436 nm [129].

The morphology and particle size of AgNPs is determined using transmission and scanning electron microscopy (TEM and SEM) and atomic force microscopy (AFM). Further, dynamic light scattering and X-ray diffraction is used for the analysis of particle size distribution and crystallinity, respectively [45].

*4.5.2. AuNPs.* Several factors play important roles in determining the morphology, size distribution, and stability of synthesized AuNPs, such as the concentration of the precursor ($Au^{3+}$) ion, selection of an appropriate solvent for the extraction of phytochemicals, reaction temperature, and nature of the stabilizing agent [130]. AuNPs are characterized using different techniques such as UV-Vis spectroscopy, Fourier-transform infrared (FTIR) spectroscopy, TEM, and by using a zetasizer system.

Formation of AuNPs can be determined by UV-Vis spectroscopy by measuring the absorbance band in the visible region of localized surface plasmon resonance (LSPR) of AuNPs. A strong absorbance band is observed in the range of 500 to 600 nm. The AuNPs exhibit a distinct optical feature in that the collective oscillation of electrons in the conduction band of AuNPs is in resonance with a specific wavelength of the incident light. The particle size of AuNPs is strongly related to the SPs, and therefore, SPs can be used to study the size of the AuNPs. For example, AuNPs of 40 nm produced using a chemical method show a SP peak at 520 nm. AuNPs synthesized using microorganisms and a chemical method show absorbance peaks within the range of 500 to 600 nm as shown in Figure 4 [131].

FTIR data are used to identify the functional groups while TEM is used to determine the particle size and structural morphology of AuNPs. TEM, which uses a magnified micrograph to measure particle size, is used to identify the mean diameter and size distribution of the AuNPs [132]. In addition, particle size affects the appearance of the AuNPs in that an increase in particle size results in a change in the color of AuNPs from pink to blue, and this may be attributed to the changes in SPs of AuNPs.

*4.6. Drawbacks.* Green synthesis has some limitations. Nanoparticles synthesized using this method may be contaminated by pathogenic bacteria during the purification process, and thus these nanoparticles should be carefully used

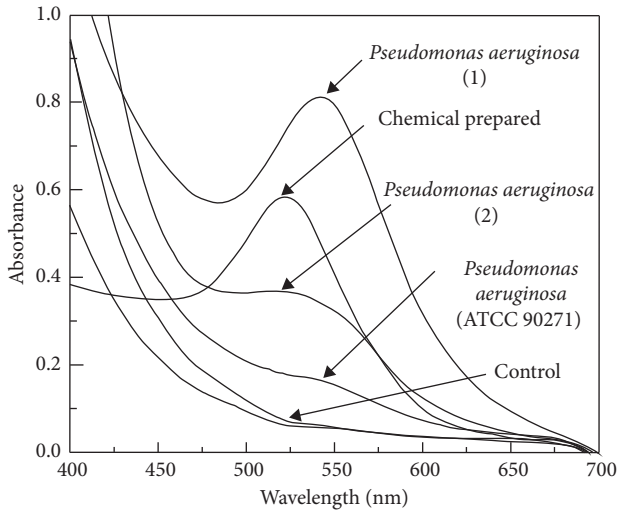


Figure 4: The absorption spectra of the gold nanoparticles (AuNPs) synthesized using different methods [131].

for medical applications [39]. In addition, several studies have shown that metallic nanoparticles, including biogenic ones can cause toxicity, including nephrotoxicity and neurotoxicity. AgNPs synthesized using a chemical method and biogenic AgNPs showed similar toxicity *in vitro* and *in vivo* [133]. Furthermore, similar to the chemically synthesized AgNPs, biogenic AgNPs cause neurotoxicity owing to their capability of binding to the free acetylcholine enzyme (AChE) and the enzyme-substrate (AChE-acetylcholine) complex [134].

## 5. Closing Remarks

Development of biogenic metallic nanoparticles, particularly AgNPs and AuNPs, has received increasing attention because of their potential applications in many fields, including nanomedicine. Green development of these nanoparticles is important to avoid the adverse effects on the human body and environment that are commonly associated with chemically synthesized metallic nanoparticles. Although biogenic metallic nanoparticles are considered to be safer than chemically synthesized nanoparticles; several studies have shown similar toxicities of both types of nanoparticles. Further studies should be performed to investigate the potential toxicity, including chronic toxicity, of biogenic nanoparticles to minimize the risks to human health.

## Disclosure

The authors alone are responsible for the content and writing of this article.

## Conflicts of Interest

The authors report no conflicts of interest.

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## References

[1] S. K. Sahoo and V. Labhasetwar, "Nanotech approaches to drug delivery and imaging," *Drug Discovery Today*, vol. 8, no. 24, pp. 1112–1120, 2003.

[2] N. Taniguchi, "On the basic concept of nanotechnology," in *Proceedings of the International Conference on Production Engineering, Part II*, pp. 18–23, Japan Society of Precision Engineering, Tokyo, Japan, 1974.

[3] G. H. Hawthorne, M. P. Bernuci, M. Bortolanza, A. C. Issy, and E. Del-Bel, "Clinical developments in antimicrobial nanomedicine: toward novel solutions in nanostructures for antimicrobial therapy," *Micro and Nano Technologies*, pp. 653–668, 2017.

[4] A. Azam, F. Ahmed, N. Arshi, M. Chaman, and A. Naqvi, "One step synthesis and characterization of gold nanoparticles and their antibacterial activities against *E. coli* (ATCC 25922 strain)," *International Journal of Theoretical and Applied Sciences*, vol. 1, no. 2, pp. 1–4, 2009.

[5] X. Li, S. M. Robinson, A. Gupta et al., "Functional gold nanoparticles as potent antimicrobial agents against multi-drug-resistant bacteria," *ACS Nano*, vol. 8, no. 10, pp. 10682–10686, 2014.

[6] Y. Sun and C. An, "Shaped gold and silver nanoparticles," *Frontiers of Materials Science*, vol. 5, no. 1, pp. 1–24, 2011.

[7] L. Dykman and N. Khlebtsov, "Gold nanoparticles in biomedical applications: recent advances and perspectives," *Chemical Society Reviews*, vol. 41, no. 6, pp. 2256–2282, 2012.

[8] Y. Zhou, Y. Kong, S. Kundu, J. D. Cirillo, and H. Liang, "Antibacterial activities of gold and silver nanoparticles against *Escherichia coli* and bacillus Calmette-Guérin," *Journal of Nanobiotechnology*, vol. 10, no. 1, p. 19, 2012.

[9] M. Noruzi, D. Zare, and D. Davoodi, "A rapid biosynthesis route for the preparation of gold nanoparticles by aqueous extract of cypress leaves at room temperature," *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, vol. 94, pp. 84–88, 2012.

[10] P. Zhao, N. Li, and D. Astruc, "State of the art in gold nanoparticle synthesis," *Coordination Chemistry Reviews*, vol. 257, no. 3-4, pp. 638–665, 2013.

[11] A. M. Derfus, W. C. Chan, and S. N. Bhatia, "Probing the cytotoxicity of semiconductor quantum dots," *Nano Letters*, vol. 4, no. 1, pp. 11–18, 2004.

[12] M. K. Corbierre, N. S. Cameron, and R. B. Lennox, "Polymer-stabilized gold nanoparticles with high grafting densities," *Langmuir*, vol. 20, no. 7, pp. 2867–2873, 2004.

[13] R. K. DeLong, C. M. Reynolds, Y. Malcolm, A. Schaeffer, T. Severs, and A. Wanekaya, "Functionalized gold nanoparticles for the binding, stabilization, and delivery of therapeutic DNA, RNA, and other biological macromolecules," *Nanotechnology, Science and Application*, vol. 3, no. 1, pp. 53–63, 2010.

[14] A. Chompoosor, G. Han, and V. M. Rotello, "Charge dependence of ligand release and monolayer stability of gold nanoparticles by biogenic thiols," *Bioconjugate Chemistry*, vol. 19, no. 7, pp. 1342–1345, 2008.

[15] Y. Yonezawa, I. Kawabata, and T. Sato, "Photochemical Formation of Colloidal Gold Particles in Chitosan Films," *Berichte der Bunsengesellschaft für Physikalische Chemie*, vol. 100, no. 1, pp. 39–45, 1996.

[16] K. Esumi, N. Takei, and T. Yoshimura, "Antioxidant-potentiality of gold–chitosan nanocomposites," *Colloids and Surfaces B: Biointerfaces*, vol. 32, no. 2, pp. 117–123, 2003.

[17] N. Ishizuki, K. Torigoe, K. Esumi, and K. Meguro, "Characterization of precious metal particles prepared using chitosan as a protective agent," *Colloids and Surfaces*, vol. 55, pp. 15–21, 1991.

[18] D. Wei and W. Qian, "Facile synthesis of Ag and Au nanoparticles utilizing chitosan as a mediator agent," *Colloids and Surfaces B: Biointerfaces*, vol. 62, no. 1, pp. 136–142, 2008.

[19] J. S. Kim, E. Kuk, K. N. Yu et al., "Antimicrobial effects of silver nanoparticles," *Nanomedicine: Nanotechnology, Biology and Medicine*, vol. 3, no. 1, pp. 95–101, 2007.

[20] S. Ahmed, M. Ahmad, B. L. Swami, and S. Ikram, "A review on plants extract mediated synthesis of silver nanoparticles for antimicrobial applications: a green expertise," *Journal of Advance Reseach*, vol. 7, no. 1, pp. 17–28, 2016.

[21] N. Beyth, Y. Houri-Haddad, A. Domb, W. Khan, and R. Hazan, "Alternative antimicrobial approach: nano-antimicrobial materials," *Evidence-Based Complementary and Alternative Medicine*, vol. 2015, Article ID 246012, 16 pages, 2015.

[22] I. Sondi and B. Salopek-Sondi, "Silver nanoparticles as antimicrobial agent: a case study on *E. coli* as a model for gram-negative bacteria," *Journal of Colloid and Interface Science*, vol. 275, no. 1, pp. 177–82, 2004.

[23] R. Singh, M. S. Smitha, and S. Singh, "The role of nanotechnology in combating multi-drug resistant bacteria," *Journal of Nanoscience and Nanotechnology*, vol. 14, no. 7, pp. 4745–4756, 2014.

[24] S. Prabhu and E. K. Poulose, "Silver nanoparticles: mechanism of antimicrobial action, synthesis, medical applications, and toxicity effects," *International Nano Letters*, vol. 2, no. 1, p. 32, 2012.

[25] R. Al-Bahrani, J. Raman, H. Lakshmanan, A. Hassan, and V. Sabaratnam, "Green synthesis of silver nanoparticles using tree oyster mushroom *Pleurotus Ostreatus* and its inhibitory activity against pathogenic bacteria," *Materials Letters*, vol. 186, pp. 21–25, 2017.

[26] M. Wilcox, P. Kite, and B. Dobbins, "Antimicrobial intravascular catheters - which surface to coat?," *Journal of Hospital Infection*, vol. 38, no. 4, pp. 322–324, 1998.

[27] J. Venkatesan, D. J. Y. Lee, S. Kang et al., "Antimicrobial and anticancer activities of porous chitosan-alginate biosynthesized silver nanoparticles," *International Journal of Biological Macromolecules*, vol. 98, pp. 515–525, 2017.

[28] S. Sharm, "Enhanced antibacterial efficacy of silver nanoparticles immobilized in a chitosan nanocarrier," *International Journal of Biological Macromolecules*, vol. 104, pp. 1740–1745, 2017.

[29] L. I. McCall, W. W. Zhang, S. Ranasinghe, and G. Matlashewski, "Leishmanization revisited: immunization with a naturally attenuated cutaneous *leishmania donovani* isolate from Sri Lanka protects against visceral leishmaniasis," *Vaccine*, vol. 31, no. 10, pp. 1420–1425, 2013.

[30] S. Natera, C. Machuca, M. Padrón-Nieves, A. Romero, and E. Díaz, "Leishmania spp.: proficiency of drug-resistant parasites," *International Journal of Antimicrobial Agents*, vol. 29, no. 6, pp. 637–642, 2007.

[31] A. Ahmad, F. S. M. Imran, A. U. Khan, K. Tahir, Z. U. H. Khan, and Q. Yuan, "Phytosynthesis and anti-leishmanial activity of gold nanoparticles by *Maytenus royleanus*," *Journal of Food Biochemistry*, vol. 40, no. 4, pp. 420–427, 2016.

[32] A. Ahmad, Y. Wei, F. Syed et al., "*Isatis tinctoria* mediated synthesis of amphotericin B-bound silver nanoparticles with enhanced photoinduced antileishmanial activity: a novel green approach," *Journal of Photochemical and Photobiology B*, vol. 161, pp. 17–24, 2016.

[33] S. K. Kalangi, A. Dayakar, D. Gangappa, R. Sathyavathi, D. S. Maurya, and D. N. Rao, "Biocompatible silver nanoparticles reduced from *Anethum graveolens* leaf extract augments the antileishmanial efficacy of miltefosine," *Experimental Parasitology*, vol. 170, pp. 184–192, 2016.

[34] A. M. Allahverdiyev, R. C. Koc, S. C. Ates, M. Bagirova, S. Elcicek, and O. N. Oztel, "*Leishmania tropica*: the effect of darkness and light on biological activities *in vitro*," *Experimental Parasitology*, vol. 28, no. 4, pp. 318–323, 2011.

[35] A. M. Allahverdiyev, E. S. Abamor, M. Bagirova et al., "Antileishmanial effect of silver nanoparticles and their enhanced antiparasitic activity under ultraviolet light," *International Journal of Nanomedicine*, vol. 6, pp. 2705–2714, 2011.

[36] J. R. Morones, J. L. Elechiguerra, A. Camacho et al., "The bactericidal effect of silver nanoparticles," *Nanotechnology*, vol. 16, no. 10, pp. 2346–2353, 2005.

[37] A. U. Khan, Q. Yuana, Y. Weia et al., "Photocatalytic and antibacterial response of biosynthesized gold nanoparticles," *Journal of Photochemical and Photobiology B: Biology*, vol. 162, pp. 172–177, 2016.

[38] A. ,U. Khan, Q. Yuana, Y. Weia et al., "Ultra-efficient photocatalytic deprivation of methylene blue and biological activities of biogenic silver nanoparticles," *Journal of Photochemical and Photobiology B: Biology*, vol. 159, pp. 46–58, 2016.

[39] L. Ge, Q. Li, M. Wang, J. Ouyang, X. Li, and M. M. Q. Xing, "Nanosilver particles in medical applications: synthesis, performance, and toxicity," *International Journal of Nanomedicine*, vol. 9, no. 1, pp. 2399–2407, 2014.

[40] R. S. Kirsner, H. Orsted, and J. B. Wright, "The role of silver in wound healing part 3 matrix metalloproteinases in normal and impaired wound healing: a potential role of nanocrystalline silver," *Wounds*, vol. 13, no. 3, 2001.

[41] S.-H. Shin, M.-K. Ye, H.-S. Kim, and H.-S. Kang, "The effects of nano-silver on the proliferation and cytokine expression by peripheral blood mononuclear cells," *International Immunopharmacology*, vol. 7, no. 13, pp. 1813–1818, 2007.

[42] A. Oryan, E. Alemzadeh, J. Tashkhourian, and S. F. N. Ana, "Topical delivery of chitosan-capped silver nanoparticles speeds up healing in burn wounds: a preclinical study," *Carbohydrate Polymers*, vol. 200, pp. 82–92, 2018.

[43] M. Ovais, I. Ahmad, A. T. Khalil et al., "Wound healing applications of biogenic colloidal silver and gold nanoparticles: recent trends and future prospects," *Applied Microbiology and Biotechnology*, vol. 102, no. 10, pp. 4305–4318, 2018.

[44] W. Zhou, Y. Ma, H. Yang, Y. Ding, and X. Luo, "A label-free biosensor based on silver nanoparticles array for clinical detection of serum P53 in head and neck squamous cell carcinoma," *International Journal of Nanomedicine*, vol. 6, pp. 381–386, 2011.

[45] K. M. M. Abou El-Nour, A. A. Eftaiha, A. Al-Warthan, and R. A. A. Ammar, "Synthesis and applications of silver nanoparticles," *Arabian Journal of Chemistry*, vol. 3, no. 3, pp. 135–140, 2010.

[46] C. Loo, A. Lowery, N. Halas, J. West, and R. Drezek, "Immunotargeted nanoshells for integrated cancer imaging and therapy," *Nano Letters*, vol. 5, no. 4, pp. 709–711, 2005.

[47] W. Ngeontae, W. Janrungroatsakul, P. Maneewattanapinyo, S. Ekgasit, W. Aeungmaitrepirom, and T. Tuntulani, "Novel

potentiometric approach in glucose biosensor using silver nanoparticles as redox marker," *Sensors and Actuators B: Chemical*, vol. 137, no. 1, pp. 320–326, 2009.

[48] N. Farkhari, S. Abbasian, A. Moshaii, and M. Nikkhah, "Mechanism of adsorption of single and double stranded DNA on gold and silver nanoparticles: investigating some important parameters in bio-sensing applications," *Colloids and Surfaces B: Biointerfaces*, vol. 148, pp. 657–664, 2016.

[49] O. S. Adeyemi and F. A. Sulaiman, "Evaluation of metal nanoparticles for drug delivery systems," *Journal of Biomedical Research*, vol. 29, no. 2, pp. 145–149, 2015.

[50] F. Benyettou, R. Rezgui, F. Ravaux et al., "Synthesis of silver nanoparticles for the dual delivery of doxorubicin and alendronate to cancer cells," *Journal of Material Chemistry B*, vol. 3, no. 36, pp. 7237–7245, 2015.

[51] P. K. Brown, A. T. Qureshi, A. N. Moll, D. J. Hayes, and W. T. Monroe, "Silver nanoscale antisense drug delivery system for photoactivated gene silencing," *ACS Nano*, vol. 7, no. 4, pp. 2948–2959, 2013.

[52] D. R. Baganizi, E. Nyairo, S. A. Duncan, S. R. Singh, and V. A. Dennis, "Interleukin-10 conjugation to carboxylated PVP-coated silver nanoparticles for improved stability and therapeutic efficacy," *Nanomaterials*, vol. 7, no. 7, p. 165, 2017.

[53] P. M. Tiwari, K. Vig, V. A. Dennis, and S. R. Singh, "Functionalized gold nanoparticles and their biomedical applications," *Nanomaterials*, vol. 1, no. 1, pp. 31–63, 2011.

[54] R. T. Tom, V. Suryanarayanan, P. G. Reddy, S. Baskaran, and T. Pradeep, "Ciprofloxacin-protected gold nanoparticles," *Langmuir*, vol. 20, no. 5, pp. 1909–1914, 2004.

[55] E. E. Connor, J. Mwamuka, A. Gole, C. J. Murphy, and M. D. Wyatt, "Gold nanoparticles are taken up by human cells but do not cause acute cytotoxicity," *Small*, vol. 1, no. 3, pp. 325–327, 2005.

[56] K. Cho, X. U. Wang, S. Niem, and D. M. Shin, "Therapeutic nanoparticles for drug delivery in cancer," *Clinical Cancer Research*, vol. 14, no. 5, pp. 1310–1316, 2008.

[57] A. Kumar, X. Zhang, and X. J. Liang, "Gold nanoparticles: emerging paradigm for targeted drug delivery system," *Biotechnology Advances*, vol. 31, no. 5, pp. 593–606, 2013.

[58] A. J. Mieszawska, W. J. Mulder, Z. A. Fayad, and D. P. Cormode, "Multifunctional gold nanoparticles for diagnosis and therapy of disease," *Molecular Pharmaceutics*, vol. 10, no. 3, pp. 831–847, 2013.

[59] L. Zhang, F. X. Gu, J. M. Chan, A. Z. Wang, R. S. Langer, and O. C. Farokhzad, "Nanoparticles in medicine: therapeutic applications and developments," *Clinical Pharmacology and Therapeutics*, vol. 83, no. 5, pp. 761–769, 2007.

[60] P. N. Njoki, I. I. S. Lim, D. Mott et al., "Size correlation of optical and spectroscopic properties for gold nanoparticles," *Journal of Physical Chemistry C*, vol. 111, no. 40, pp. 14664–14669, 2007.

[61] A. N. Grace and K. Pandian, "Antibacterial efficacy of aminoglycosidic antibiotics protected gold nanoparticles—a brief study," *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, vol. 297, no. 1-3, pp. 63–70, 2007.

[62] W.-R. Li, X.-B. Xie, Q.-S. Shi, H.-Y. Zeng, O.-Y. You-Sheng, and Y.-B. Chen, "Antibacterial activity and mechanism of silver nanoparticles on *Escherichia coli*," *Applied Microbiology and Biotechnology*, vol. 85, no. 4, pp. 1115–1122, 2010.

[63] M. Rai, A. Yadav, and A. Gade, "Silver nanoparticles as a new generation of antimicrobials," *Biotechnology Advances*, vol. 27, no. 1, pp. 76–83, 2009.

[64] V. K. Sharma, R. A. Yngard, and Y. Lin, "Silver nanoparticles: green synthesis and their antimicrobial activities," *Advances in Colloid And Interface Science*, vol. 145, no. 1-2, pp. 83–96, 2009.

[65] M. Zawrah, S. A. El-Moez, and D. Center, "Antimicrobial activities of gold nanoparticles against major foodborne pathogens," *Life Science Journal*, vol. 8, no. 4, pp. 37–44, 2011.

[66] S. Das, P. Roy, S. Mondal, T. Bera, and A. Mukherjee, "One pot synthesis of gold nanoparticles and application in chemotherapy of wild and resistant type visceral leishmaniasis," *Colloids and Surfaces B: Biointerfaces*, vol. 107, pp. 27–34, 2013.

[67] A. Ahmad, Y. Wei, S. Ullah et al., "Synthesis of phytochemicals-stabilized gold nanoparticles and their biological activities against bacteria and Leishmania," *Microbial Pathogenesis*, vol. 110, pp. 304–312, 2017.

[68] A. Ahmad, Y. Wei, F. Syed et al., "The effects of bacteria-nanoparticles interface on the antibacterial activity of green synthesized silver nanoparticles," *Microbial Pathogenesis*, vol. 102, pp. 133–142, 2017.

[69] D. Baruah, M. Goswami, R. N. S. Yadav, A. Yadav, and A. M. Da, "Biogenic synthesis of gold nanoparticles and their application in photocatalytic degradation of toxic dyes," *Journal of Photochemistry and Photobiology B: Biology*, vol. 186, pp. 51–58, 2018.

[70] H. K. Kumar, N. Venkatesh, H. Bhowmik, and A. Kuila, "Metallic nanoparticles: a review," *Biomedical Journal of Scientific and Technical Research*, vol. 4, no. 2, pp. 1–11, 2018.

[71] W. Cai and X. Chen, "Nanoplatforms for targeted molecular imaging in living subjects," *Small*, vol. 3, no. 11, pp. 1840–1854, 2007.

[72] A. Tomar and G. Garg, "Short review on application of gold nanoparticles," *Global Journal of Pharmacology*, vol. 7, no. 1, pp. 34–38, 2013.

[73] Q. Huo, J. Colon, A. Cordero et al., "A facile nanoparticle immunoassay for cancer biomarker discovery," *Journal of Nanobiotechnology*, vol. 9, no. 1, pp. 1–20, 2011.

[74] J.-M. Nam, K.-J. Jang, and J. T. Groves, "Detection of proteins using a colorimetric bio-barcode assay," *Nature Protocols*, vol. 2, no. 6, pp. 1438–1444, 2007.

[75] S. Y. Neto, D. E. P. Souto, H. M. de Andrade, R. . deC. S. Luz, and F. S. Damos, "Visible LED light driven photoelectroanalytical detection of antibodies of visceral leishmaniasis based on electrodeposited CdS film sensitized with Au nanoparticles," *Sensors and Actuators B: Chemical*, vol. 256, pp. 682–690, 2018.

[76] Y.-C. Yeh, B. Creran, and V. M. Rotello, "Gold nanoparticles: preparation, properties, and applications in bionanotechnology," *Nanoscale*, vol. 4, no. 6, pp. 1871–1880, 2012.

[77] G. F. Paciotti, L. Myer, D. Weinreich et al., "Colloidal gold: a novel nanoparticle vector for tumor directed drug delivery," *Drug Delivery*, vol. 11, no. 3, pp. 169–183, 2004.

[78] S. D. Brown, P. Nativo, J.-A. Smith et al., "Gold nanoparticles for the improved anticancer drug delivery of the active component of oxaliplatin," *Journal of the American Chemical Society*, vol. 132, no. 13, pp. 4678–4684, 2010.

[79] K. M. Mcmahon, R. K. Mutharasan, S. Tripathy et al., "Biomimetic high density lipoprotein nanoparticles for nucleic acid delivery," *Nano letters*, vol. 11, no. 3, pp. 1208–1214, 2011.

[80] B. Van De Broek, N. Devoogdt, A. D'hollander et al., "Specific cell targeting with nanobody conjugated branched

gold nanoparticles for photothermal therapy," *ACS Nano*, vol. 5, no. 6, pp. 4319–4328, 2011.

[81] S. P. Dubey, M. Lahtinen, and M. Sillanpää, "Green synthesis and characterizations of silver and gold nanoparticles using leaf extract of R*osa rugosa*," *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, vol. 364, no. 1–3, pp. 34–41, 2010.

[82] M. Noruzi, D. Zare, K. Khoshnevisan, and D. Davoodi, "Rapid green synthesis of gold nanoparticles using *Rosa hybrida* petal extract at room temperature," *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, vol. 79, no. 5, pp. 1461–1465, 2011.

[83] S. S. Shankar, A. Rai, A. Ahmad, and M. Sastry, "Rapid synthesis of Au, Ag, and bimetallic Au core–Ag shell nanoparticles using Neem (*Azadirachta indica*) leaf broth," *Journal of Colloid And Interface Science*, vol. 275, no. 2, pp. 496–502, 2004.

[84] D. Bhattacharya and R. K. Gupta, "Nanotechnology and potential of microorganisms," *Critical Reviews in Biotechnology*, vol. 25, no. 4, pp. 199–204, 2005.

[85] M. Sastry, A. Ahmad, M. I. Khan, and R. Kumar, "Microbial nanoparticle production," *Nanotechnology*, pp. 126–135, 2005.

[86] P. Mohanpuria, N. K. Rana, and S. K Yadav, "Biosynthesis of nanoparticles: technological concepts and future applications," *Journal of Nanoparticle Research*, vol. 10, no. 3, pp. 507–517, 2008.

[87] M. Singh, R. Kalaivani, S. Manikandan, N. Sangeetha, and A. Kumaraguru, "Facile green synthesis of variable metallic gold nanoparticle using *Padina gymnospora*, a brown marine macroalga," *Applied Nanoscience*, vol. 3, no. 2, pp. 145–151, 2013.

[88] K. P. Kumar, W. Paul, and C. P. Sharma, "Green synthesis of gold nanoparticles with Z*ingiber officinale* extract: characterization and blood compatibility," *Process Biochemistry*, vol. 46, no. 10, pp. 2007–2013, 2011.

[89] S. Ahmed, Saifullah, M. Ahmad, B. L. Swami, and S. Ikram, "Green synthesis of silver nanoparticles using *Azadirachta indica* aqueous leaf extract," *Journal of Radiation Research and Applied Sciences*, vol. 9, no. 1, pp. 1–7, 2016.

[90] M. D. Balakumaran, R. Ramachandran, P. Balashanmugam, D. J. Mukeshkumar, and P. T. Kalaichelvan, "Mycosynthesis of silver and gold nanoparticles: optimization, characterization and antimicrobial activity against human pathogens," *Microbiology Research*, vol. 182, pp. 8–20, 2016.

[91] G. Li, D. He, Y. Qian et al., "Fungus-mediated green synthesis of silver nanoparticles using *Aspergillus terreus*," *International Journal of Molecular Sciences*, vol. 13, no. 1, pp. 466–476, 2011.

[92] S. Poulose, T. Panda, P. P. Nair, and T. Theodore, "Biosynthesis of silver nanoparticles," *Journal of Nanoscience and Nanotechnology*, vol. 14, no. 2, pp. 2038–2049, 2014.

[93] M. Ramya and M. S. Subapriya, "Green synthesis of silver nanoparticles," *International Journal of Pharma Medicine and Biological Sciences*, vol. 1, no. 1, pp. 54–61, 2012.

[94] J. E. Hutchison, *Greener Nanoscience: A Proactive Approach to Advancing Applications and Reducing Implications of Nanotechnology*, ACS Publications, Washington, DC, USA, 2008.

[95] G. S. Dhillon, S. K. Brar, S. Kaur, and M. Verma, "Green approach for nanoparticle biosynthesis by fungi: current trends and applications," *Critical Reviews in Biotechnology*, vol. 32, no. 1, pp. 49–73, 2012.

[96] X. Li, H. Xu, Z.-S. Chen, and G. Chen, "Biosynthesis of nanoparticles by microorganisms and their applications," *Journal of Nanomaterials*, vol. 2011, Article ID 270974, 16 pages, 2011.

[97] V. Kumar and S. K. Yadav, "Plant-mediated synthesis of silver and gold nanoparticles and their applications," *Journal of Chemical Technology and Biotechnology*, vol. 84, no. 2, pp. 151–157, 2009.

[98] K. Mukunthan and S. Balaji, "Cashew apple juice (*Anacardium occidentale L.*) speeds up the synthesis of silver nanoparticles," *International Journal of Green Nanotechnology*, vol. 4, no. 2, pp. 71–79, 2012.

[99] K. M. Kumar, B. K. Mandal, M. Sinha, and V. Krishnakumar, "*Terminalia chebula* mediated green and rapid synthesis of gold nanoparticles," *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, vol. 86, pp. 490–494, 2012.

[100] M. J. Firdhouse and P. Lalitha, "Biosynthesis of silver nanoparticles and its applications," *Journal of Nanotechnology*, vol. 2015, Article ID 829526, 18 pages, 2015.

[101] C.-P. Gong, S.-C. Li, and R.-Y. Wang, "Development of biosynthesized silver nanoparticles based formulation for treating wounds during nursing care in hospitals," *Journal of Photochemistry and Photobiology B: Biology*, vol. 183, pp. 137–141, 2018.

[102] A. K. Keshari, R. Srivastava, P. Singh, V. B. Yadav, and G. Nath, "Antioxidant and antibacterial activity of silver nanoparticles synthesized by *Cestrum nocturnum*," *Journal of Ayurveda and Integrative Medicine*, 2018, In press.

[103] P. P. N. V. Kumar, U. Shameem, R. L. Kalyani, S. V. N. Pammi, and Y. S. Gil, "Ultra Small, mono dispersed green synthesized silver nanoparticles using aqueous extract of *Sida cordifolia* plant and investigation of antibacterial activity," *Microbial Pathogenesis*, vol. 124, pp. 63–69, 2018.

[104] B. Moldovan, V. Sincari, M. Perde-Schrepler, and L. David, "Biosynthesis of silver nanoparticles using *Ligustrum ovalifolium* fruits and their cytotoxic effects," *Nanomaterials*, vol. 8, no. 8, 627 pages, 2018.

[105] K. Paulkumar, G. Gnanajobitha, M. Vanaja, M. Pavunraj, and G. Annadurai, "Green synthesis of silver nanoparticle and silver based chitosan bionanocomposite using stem extract of *Saccharum officinarum* and assessment of its antibacterial activity," *Advances in Natural Sciences, Nanoscience and Nanotechnology*, vol. 8, no. 3, pp. 1–9, 2017.

[106] A. Sathiyaseelan, A. Shajahan, P. T. Kalaichelvan, and V. Kaviyarasan, "Fungal chitosan based nanocomposites sponges-An alternative medicine for wound dressing," *International Journal of Biological Macromolecules*, vol. 104, pp. 1905–1915, 2017.

[107] A. Ravichandran, P. Subramanian, V. Manoharan et al., "Phyto-mediated synthesis of silver nanoparticles using fucoidan isolated from *Spatoglossum asperum* and assessment of antibacterial activities," *Journal of Photochemistry and Photobiology B: Biology*, vol. 185, pp. 117–125, 2018.

[108] J. Venkatesan, S. K. Singh, S. Anil, S. K. Kim, and M. S. Shim, "Preparation, characterization and biological applications of biosynthesized silver nanoparticles with chitosan-fucoidan coating," *Molecules*, vol. 23, no. 6, p. 1429, 2018.

[109] C. Janiak, "Ionic liquids for the synthesis and stabilization of metal nanoparticles," *Zeitschrift für Naturforschung B*, vol. 68, no. 10, pp. 1059–1089, 2013.

[110] A. K. Mittal, Y. Chisti, and U. C. Banerjee, "Synthesis of metallic nanoparticles using plant extracts," *Biotechnology Advances*, vol. 31, no. 2, pp. 346–356, 2013.

[111] P. S. Vankar and D. Bajpai, "Preparation of gold nanoparticles from *Mirabilis jalapa* flowers," *Indian Journal of Biochemical and Biophysics*, vol. 47, no. 3, pp. 157–160, 2010.

[112] S. K. Das and E. Marsili, "A green chemical approach for the synthesis of gold nanoparticles: characterization and mechanistic aspect," *Review in Environmental Science and Bio/Technology*, vol. 9, no. 3, pp. 199–204, 2010.

[113] J. Jiang, G. Oberdörster, and P. Biswas, "Characterization of size, surface charge, and agglomeration state of nanoparticle dispersions for toxicological studies," *Journal of Nanoparticle Research*, vol. 11, no. 1, pp. 77–89, 2009.

[114] S. Hirn, M. Semmler-Behnke, C. Schleh et al., "Particle size-dependent and surface charge-dependent biodistribution of gold nanoparticles after intravenous administration," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 77, no. 3, pp. 407–416, 2011.

[115] N. M. Schaeublin, L. K. Braydich-Stolle, A. M. Schrand et al., "Surface charge of gold nanoparticles mediates mechanism of toxicity," *Nanoscale*, vol. 3, no. 2, p. 410, 2011.

[116] V. Ramesh, S. A. John, and M. Koperuncholan, "Impact of cement industries dust on selective green plants: a case study in Ariyalur industrial zone," *International Journal of Pharmaceutical, Chemical and Biological Sciences*, vol. 4, pp. 152–158, 2014.

[117] M. Koperuncholan, "Bioreduction of chloroauric acid (haucl4) for the synthesis of gold nanoparticles (gnps): a special empathies of pharmacological activity," *International Journal of Phytopharmacy*, vol. 5, no. 4, pp. 72–80, 2015.

[118] M. Nadeem, B. H. Abbasi, M. Younas, W. Ahmad, and T. Khan, "A review of the green syntheses and anti-microbial applications of gold nanoparticles," *Green Chemistry Letters and Reviews*, vol. 10, no. 4, pp. 216–227, 2017.

[119] S. Menon, S. Rajeshkumar, and S. Venkat Kumar, "A review on biogenic synthesis of gold nanoparticles, characterization, and its applications," *Resource-Efficient Technologies*, vol. 3, no. 4, pp. 516–527, 2017.

[120] X. Chen, X. Zhao, Y. Gao, J. Yin, M. Bai, and F. Wang, "Green synthesis of gold nanoparticles using carrageenan oligosaccharide and their *in vitro* antitumor activity," *Marine Drugs*, vol. 16, no. 8, p. 277, 2018.

[121] E. Y. Ahn, S. J. Hwang, M. J. Choi, S. Cho, H. J. Lee, and Y. Park, "Upcycling of jellyfish (*Nemopilema nomurai*) sea wastes as highly valuable reducing agents for green synthesis of gold nanoparticles and their antitumor and anti-inflammatory activity," *Artificial Cells Nanomedicine Biotechnology*, vol. 26, pp. 1–10, 2018.

[122] E. Y. Ahn, Y. J. Lee, S. Y. Choi, A. R. Im, Y. S. Kim, and Y. Park, "Highly stable gold nanoparticles green-synthesized by upcycling cartilage waste extract from yellow-nose skate (*Dipturus chilensis*) and evaluation of its cytotoxicity, haemocompatibility and antioxidant activity," *Artificial Cells Nanomedicine Biotechnology*, vol. 29, pp. 1–12, 2018.

[123] H. Katas, Z. Hussain, and T. C. Ling, "Chitosan nanoparticles as a percutaneous drug delivery system for hydrocortisone," *Journal of Nanomaterials*, vol. 2012, Article ID 134607, 7 pages, 2012.

[124] M. R. Kumar, R. A. Muzzarelli, C. Muzzarelli, H. Sashiwa, and A. Domb, "Chitosan chemistry and pharmaceutical perspectives," *Chemical Reviews*, vol. 104, no. 12, pp. 6017–6084, 2004.

[125] H. Huang and X. Yang, "Synthesis of chitosan-stabilized gold nanoparticles in the absence/presence of tripolyphosphate," *Biomacromolecules*, vol. 5, no. 6, pp. 2340–2346, 2004.

[126] Y. Wu, F. Zuo, Y. Lin, Y. Zou, Z. Zheng, and X. Ding, "Green and facile synthesis of gold nanoparticles stabilized by chitosan," *Journal of Macromolecular Science, Part A*, vol. 51, no. 5, pp. 441–446, 2014.

[127] T. L. Le, Q. K. Dinh, T. H. Tran, H. P. Nguyen, T. L. H. Hoang, and Q. H. Nguyen, "Synthesis of water soluble chitosan stabilized gold nanoparticles and determination of uric acid," *Advances in Natural Sciences: Nanoscience and Nanotechnology*, vol. 5, no. 2, article 025014, 2014.

[128] M. Potara, D. Maniu, and S. Astilean, "The synthesis of biocompatible and SERS-active gold nanoparticles using chitosan," *Nanotechnology*, vol. 20, no. 31, article 315602, 2009.

[129] R. Nithya and R. Ragunathan, "Synthesis of silver nanoparticle using *Pleurotus sajor caju*, and its antimicrobial study," *Digest Journal of Nanomaterials and Biostructures*, vol. 4, no. 4, pp. 623–629, 2009.

[130] K. An, S. Alayoglu, T. Ewers, and G. A. Somorjai, "Colloid chemistry of nanocatalysts: a molecular view," *Journal of Colloid and Interface Science*, vol. 373, no. 1, pp. 1–13, 2012.

[131] M. Husseiny, M. A. El-Aziz, Y. Badr, and M. Mahmoud, "Biosynthesis of gold nanoparticles using *Pseudomonas aeruginosa*," *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, vol. 67, no. 3, pp. 1003–1006, 2007.

[132] Y. Badr and M. Mahmoud, "Size-dependent surface-enhanced Raman scattering of sodium benzoate on silver nanoparticles," *Journal of Molecular Structure*, vol. 749, no. 1-3, pp. 187–192, 2005.

[133] S. B. Vasanth and G. A. Kurian, "Toxicity evaluation of silver nanoparticles synthesized by chemical and green route in different experimental models," *Artificial Cells Nanomedicine and Biotechnology*, vol. 45, no. 8, pp. 1721–1727, 2017.

[134] A. Khatoon, F. Khan, N. Ahmad et al., "Silver nanoparticles from leaf extract of Mentha piperita: eco-friendly synthesis and effect on acetylcholinesterase activity," *Life Sciences*, vol. 209, pp. 430–434, 2018.