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A Review on Metallic Nano-Particles: Green Synthesis and Biomedical Applications

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Abstract: In the last few years green synthesis of metallic nanoparticles has been a highly attractive research area. A variety of biocomponents e.g plant, bacteria, fungi, yeast, and plant extracts have been used for the synthesis or fabrication of nanomaterials. Among them, plant extracts have been proven highly efficient stabilizing and reducing agents with controlled shapes, sizes, structures, and other specific features. Green synthesis approach reduces the harmful effects associated with other traditional methods. Now this is commonly used in laboratory and many industries for various applications. In this review paper, we have summarized the basic process and possible mechanism of silver (Ag) and other metallic nanoparticles synthesised with plant extract as natural reactants. We have discussed here the role of many phytochemicals and other biological components, such as alkaloids, flavonoids, terpenoids, sugars, aldehydes and amides, as reducing, capping and stabilizing agents. Moreover, we have also covered potential biomedical applications of such synthesized bioinspired nanomaterials. In this paper, our main aim is to review silver nanoparticles formation with green synthesis and presenting important applications for healthcare and treatment. Lastly, we have concluded this review with a summary and challenges associated with use of metallic nano-particles in biomedical field.

Keywords: Metallic nanoparticles, green synthesis, bioinspired nanomaterials, biogenic nanoparticles, plant mediated synthesis, biomedical applications

I. Introduction

In the last decade, new synthesis methods for nanomaterials (metallic nanoparticles (MNPs), carbon nanotubes (CNTs), quantum dots (QDs), graphene, and their composites) have been an interesting area [1-10]. Many physical, chemical and biological methods have been used to obtain these nanomaterials of desired size, shape, and functions. Two different basic approaches of synthesis viz. 1. Top to down and 2. Bottom to up; have been mostly used in the existing literature. In the first approach (top to down), nanomaterials/nanoparticles are prepared through chemical etching, laser ablation, mechanical ball milling, sputtering and electro explosion of bulk material [11]. While in case of using the second approach (bottom to up) nanoparticles are grown from simpler molecules. In this approach, several methods like chemical vapour deposition, sol–gel processes, laser pyrolysis, spray pyrolysis, atomic/molecular condensation, aerosol processes and green synthesis may be employed (Fig. 1). Interestingly, the morphological features of nanoparticles (e.g., size and shape) can be modified by changing the concentration and reaction conditions (e.g., temperature and pH).Now in real world; it is desirable to improve the different properties of nanomaterials. So, these challenges associated with synthesis of nanoparticles are opening new and great opportunities in this field of research.

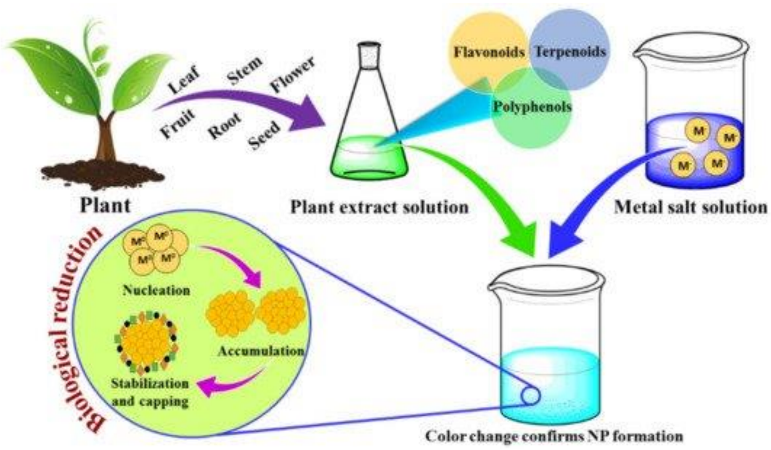

Figure1. Plant-mediated biosynthesis of metallic nanoparticles (Schematic) [58]

In ‘Green synthesis’ the use of unwanted harmful by-products is avoided and production takes place by using eco-friendly synthesis procedures. The use of natural resources (organic systems) is essential to achieve this goal. Green synthesis of metallic nanoparticles uses various biological materials (e.g., bacteria, fungi, algae, and plant leaves, roots, flower extracts). Use of plant extracts for green synthesis of metallic nanoparticles, is simple and easy process at large scale relative to other synthesis routes. These products are collectively known as biogenic nanoparticles. Green synthesis is eco-friendly approach as toxic chemicals are not involved in it. Here, biological components itself act as reducing, capping and stabilizing agents, therefore, reducing the overall cost of production. External conditions like high energy, temperature, pressure are also not required which leads to energy saving. So it can be used for large scale production of nanoparticles. Green synthesis is affected by various reaction conditions like solvent, temperature, pressure, and pH etc. For metallic nanoparticles, plants have been largely used due to the presence of many phytochemicals in plant extracts. In leaves aldehydes, ketones, flavones, terpenoids, carboxylic acids, phenols, and ascorbic acids are found. These phytochemicals can reduce metal salts into metal nanoparticles [12]. The basic features of nanomaterials have been utilized in biomedical applications (diagnosis, antimicrobial agents, catalysis, molecular sensing, optical imaging, and bio labelling) [13]. Physical and chemical synthesis approaches require many steps, high energy in the form of heat or radiations, toxic reactants and stabilizing agents, which may be harmful to different life forms. While, green synthesis of metallic nanoparticles is single step eco-friendly reduction method which needs relatively less energy. So this bio-reduction method is cost efficient [14-20].

Components for “green” synthesis- Bacterial species have been utilized for various biotechnological applications such as bioremediation, genetic engineering, and bioleaching [21]. Many bacteria have the ability to reduce metal ions and can be used in nanoparticles preparation [22]. Bacteria mediated synthesis of nanoparticles is suitable due to easy manipulation [23]. Metallic nanoparticles with different size shape and morphology can be produced using bacterial strains: Escherichia coli, Lactobacillus casei, Bacillus cereus, Aeromonas sp. etc.

Fungi mediated biosynthesis of metallic nanoparticles is also a very efficient process due to the presence of a variety of intracellular enzymes [24]. Many fungal species have been used to synthesize metal and metal oxide nanoparticles of silver, gold, titanium dioxide and zinc oxide. Some fungi can synthesize higher amount of nanoparticles compared to bacteria [25]. Moreover, fungi may serve better due to the presence of many enzymes, proteins and reducing agents on their cell surfaces [26]. Formation of metallic nanoparticles by fungal cells may be due to enzymatic (reductase) reduction.

Yeasts are single-celled eukaryotic micro-organisms. A total of 1500 yeast species have been identified [27]. Successful synthesis of silver and gold nanoparticles by Saccharomyces cerevisiae has been reported. Many diverse species of yeast can be employed for the preparation of metallic nanoparticles.

Plants mediated green biosynthesis techniques for nanoparticles preparation using plant extracts have now become very popular. These are simple, efficient, cost effective and feasible methods. They can be excellent alternative routes to conventional preparation methods. Plants have many biomolecules such as carbohydrates, proteins, and coenzymes to reduce metal salt into nanoparticles. Many plants like aloe vera (*Aloe barbadensis miller*), oat (*Avenasativa*), alfalfa (*Medicago sativa*), tulsi (*Osimum sanctum*), lemon (*Citrus limon*), neem (*Azadirachta indica*), coriander (*Coriandrum sativum*), mustard (*Brassica juncea*), lemon grass (*Cymbopogon flexuosus*) and many others have been used to synthesize silver and gold nanoparticles. Mostly, research has explored the ex vivo synthesis, while metallic nanoparticles can also be formed in living plants (in vivo). The in vivo synthesis of nanoparticles like zinc, nickel, cobalt, and copper was observed in mustard (*Brassica juncea*), alfalfa (*Medicago sativa*), and sunflower (*Helianthus annuus*) [28]. ZnO nanoparticles have been prepared with plant leaf extracts such as coriander (*Coriandrum sativum*) [29], crown flower (*Calotropis gigantean*) [30], copper leaf (*Acalypha indica*) [31], china rose (*Hibiscus rosa-sinensis*) [32], green tea (*Camellia sinensis*) [33], and aloevera leaf extract (*Aloe barbadensis*) [34]. Iravani reported overview of plant materials utilized for the biosynthesis of nanoparticles [35].

Plant leaf extract-based mechanism of “green” synthesis for metallic nanoparticles

In nanoparticle synthesis mediated by plant leaf extract, the extract is mixed with metal precursor solutions at different reaction conditions [36]. Nature and concentration of phytochemicals, metal salt, pH, and temperature are supposed to control the nanoparticle formation. Their yield and stability is also depend on these paraameters [37]. The phytochemicals in plants have better potential to reduce metal ions as compared to fungi and bacteria [38]. Therefore, plant leaf extracts are excellent source for metallic nanoparticles synthesis. Plant leaf extract play a dual role by acting as reducing and stabilizing agents in nanoparticles synthesis [39]. The plant leaf extract composition is also an important factor in nanoparticle synthesis as different plants have varying concentration levels of phytochemicals [40, 41]. In plants, the main phytochemicals (flavonoids, terpenoids, sugars, ketones, aldehydes, carboxylic acids, and amides) are responsible for bioreduction of nanoparticles [42]. In sweet basil (Ocimumbasilicum) extracts, enol- to keto-transformation is important factor in the synthesis of biogenic silver nanoparticles [43]. Sugars (glucose and fructose) present in plant extracts can also be responsible for metallic nanoparticles synthesis with different size and shapes. Whereas, fructose-mediated gold and silver nanoparticles are monodispersive in nature [44]. FTIR analysis of green synthesized nanoparticles via plant extracts confirmed that nascent nanoparticles were associated with proteins [45]. Gruen et al. [46] observed that amino acids are proficient in binding with silver ions. Tan et al. [47] tested all of the 20 natural α-amino acids to establish potential towards the reduction of Au^0 metal ions. Plant extracts have carbohydrates and proteins biomolecules, which act as a reducing agent and promote the formation of metallic nanoparticles [48]. Proteins having amino groups ($–NH_2$) available in plant extracts can actively participate in the reduction of metal ions [49]. According to Huang et al. [50], the absorption peaks of FTIR spectra imply the stretching of (1) –C–O–C– or –C–O–, (2) –C=C– and (3) –C=O, respectively. It was confirmed that functional groups like –C–O–C–, –C–O–, –C=C–, and –C=O, are the capping ligands of the nanoparticles [51]. The main role of the capping ligands is to stabilize the nanoparticles to prevent further growth and agglomeration. Alcoholic compounds serve as main reducing agents for the reduction of silver ions to silver nanoparticles [52]. Numerous phytochemicals including alkaloids, terpenoids, phenolic acids, sugars, polyphenols, and proteins play a significant role in the bioreduction of metal salt into metallic nanoparticles. Shankar et al. [53] confirmed that the terpenoids present in geranium leaf extract actively take part in the conversion of silver ions into nanoparticles. Eugenol is a main terpenoid component of Cinnamomum zeylanicum (cinnamon) extracts, and it plays a crucial role for the bioreduction of $HAuCl_4$ and $AgNO_3$ metal salts into their respective metal nanoparticles. FTIR data showed that –OH groups originating from eugenol disappear during the formation of Au and Ag nanoparticles. After the formation of Au nanoparticles, carbonyl, alkenes, and chloride functional groups appeared [54]. The exact mechanism for metallic nanoparticle synthesis via plant extracts is still not fully known. In general, there are three phases of metallic nanoparticle synthesis from plant extracts: (1) activation phase or bioreduction of metal ions (2) growth phase or combination of small particles) via Ostwald ripening, and (3) termination phase defining the final shape of the nanoparticles [55, 56].

Biomedical Applications of Metallic Nanoparticles Formed By Green Synthesis:

In recent years, metallic NPs and their alloys have been studied and used in various fields e.g. sensor technology, optical devices, catalysis, biological labelling, drug delivery system, and treatment of some cancers. Metallic NPs are very suitable as a marker. They are used for the optical detection of biomolecules, antimicrobial, antiplatelet, drug delivery and photo thermal therapeutic applications, due to their excellent SPR properties [57]. Here are some extremely promising prospects in the field of healthcare and medicines (Fig. 2).

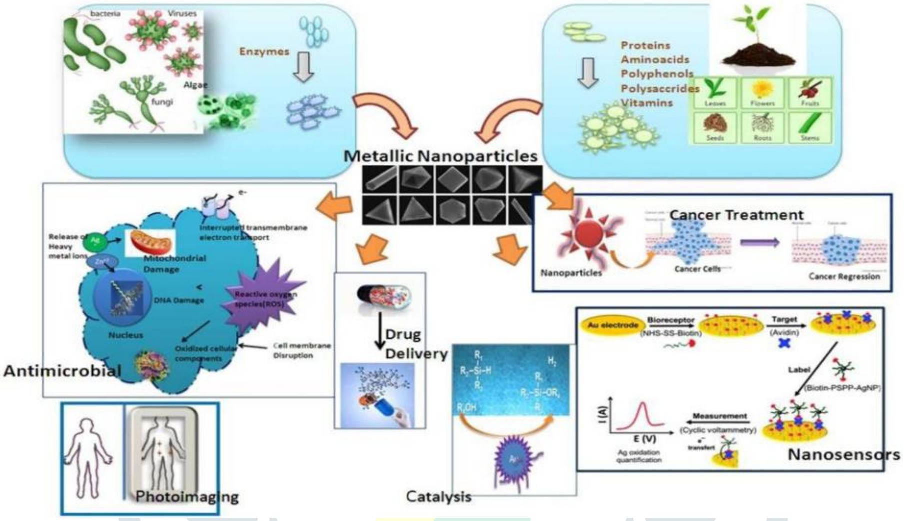

Figure 2. Biomedical applications of metallic nanoparticles formed by green synthesis. [59]

1. Antimicrobial applications- The metallic nanoparticles effectively prevent growth of several microbial species [60]. The antimicrobial effectiveness of metallic nanoparticles depends upon: (a) material used for nanoparticles synthesis and (b) particle size. Over the time, microbial resistance to antimicrobial drugs has raised considerable threat to public health. Antimicrobial drug resistant bacteria contain methicillin-resistant, sulfonamide-resistant, penicillin-resistant, and vancomycin-resistant properties [61]. Antibiotics face many current challenges such as multidrug-resistant mutants and biofilms. The effectiveness of antibiotic is likely to decrease due to the drug resistance capabilities of microbes. Biofilms also provide multidrug resistance against heavy doses of antibiotics. Drug resistance mainly occurs in infectious diseases such as lung infection and gingivitis [62]. The best approach for avoiding multidrug-resistance and biofilm formation is utilization of nanoparticles. Various nanoparticles act by multiple mechanisms to fight microbes [e.g., metal-containing nanoparticles, NO-releasing nanoparticles, and chitosan-containing nanoparticles]. Due to multiple mechanisms, microbes must have multiple gene mutations in their cell to overcome nanoparticles. However, multiple gene mutations in the same cell are unlikely [63]. Silver nanoparticles are efficient antimicrobial, antifungal, antiviral, and anti-inflammatory agents [64]. The antimicrobial ability of silver nanoparticles can be due to (1) membrane denaturation [65], (2) fragmentation of bacterial cell membrane. [66, 67], and (3) disruption in metabolic processes; leading to cell death [68]. Triangular nanoparticles are more reactive because of high atom-density on their surfaces [69]. Au nanoparticles are highly useful and effective antibacterial agents because of their non-toxic nature and photo-thermal activity [70-72]. Antimicrobial action of gold nanoparticles is not linked with the production of reactive oxygen species [73]. Azam et al. [74] reported the antimicrobial potential of zinc oxide, copper oxide, and iron oxide nanoparticles toward gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*) and gram-positive bacteria (*Staphylococcus Aureus* and *Bacillus subtilis*). The most intense antibacterial activity was reported for the ZnO nanoparticles. In contrast, Fe_2O_3 nanoparticles exhibited the weakest antibacterial effects. The size of nanoparticles have important role in the antibacterial activity [74]. The anticipated mechanism of antimicrobial action of ZnO nanoparticles is: (1) ROS generation, (2) release of zinc ion on the surface, (3) membrane dysfunction, and (4) entry into the cell. Antimicrobial potential of ZnO nanoparticles depends upon concentration and surface area [75]. Mahapatra et al. [76] determined the antimicrobial action of copper oxide nanoparticles for several bacterial species such as *Klebsiella pneumoniae*, *P. aeruginosa*, *Shigella*, *Salmonella paratyphi* s. They found that CuO nanoparticles exhibited antibacterial activity against these bacteria. It was assumed that nanoparticles should enter bacterial cell membrane to damage enzymes of bacteria, which leads to cell death. Nanoparticles formed by green synthesis show higher antimicrobial activity than chemically synthesized nanoparticles because the plants [such as *Ocimum sanctum* (tulsi) and *Azadirachta indica* (neem)] used for synthesis of nanoparticles, already have medicinal properties [77, 78]. Green synthesized silver nanoparticles showed larger zone of inhibition against various bacterial strains compared to commercial silver nanoparticles [79]. Recently some studies have shown that metal nanoparticles can be effective antiviral agents against HIV-1, hepatitis B virus, respiratory syncytial virus, herpes simplex virus, monkeypox virus, influenza virus and Tacaribe virus [80].

2. **Nanomedicines-** Nanotechnology-based drugs have also been developed in the last few years. The unique properties of NPs, viz., small size, ability to travel through fine blood capillaries, vessels, junctions, and barriers, have made them good choice for medicinal use [81]. They have great advantages like improved bioavailability of drugs, good solubility, improved pharmacological activities, toxicity safeguard, and prevention from degradation and increased stability of drugs inside the body [82]. Nanomedicines have shown higher capacity to bind with biomolecules, reduction of inflammation and oxidative stress in tissues. Nanomaterials based drugs and medicines have applications at molecular level to cure diseases. It provides a platform for the discovery of therapeutic nanomaterials or nanomedicines. The growth in nanomedicines has introduced numerous possibilities in medical sciences, specifically in the drug delivery systems. Their structural properties make them excellent for target specific quick penetration in the cell or diseased sites [83]. Depending on therapeutic need, various types of NPs have been developed e.g. liposomal, polymeric protein, metal based, and iron oxide NPs.

3. **Nanomaterials for control of multi-drug resistant pathogens-** Application of nanomaterials to control microbial proliferation has garnered much interest from scientists worldwide [84, 85]. The increase in resistance of microorganisms to antimicrobial agents or antibiotics, has led to health-related complications. It is revealed that by combining the nanotechnology, and the inherent antimicrobial activity of certain metals, innovative applications for metal NPs can be identified [86]. It is reported that metal and their metal oxide nanoparticles have toxicity towards numerous microorganisms [87, 88]. These Nano particles may be used successfully to stop the growth of various bacterial species. The surge in development of multi-drug resistant pathogens is presenting itself as a grave problem to public health, and thus, several studies have been conducted to improve the antimicrobial treatments [89]. Approximately 70% of bacterial infections have developed resistance to one or more of the first- and second-line drugs used to treat the infection [90]. The extensive use of poor quality of over-the-counter medicines in several countries has caused a steep rise in antimicrobial resistance [91]. Now development and the synthesis of effective novel antimicrobial agents are highly required. NPs based antibacterial agents can solve this challenge. They have the ability to establish an effective nanostructure, which may be used to deliver the antibacterial agents, targeting efficiently the bacterial growth. In addition, nanoparticles leaves the pathogens with little device to develop resistance. Most of the available metal oxide NPs have zero toxicity for mammalian cells at low concentrations [92]. Metals like gold (Au), silver (Ag), titanium (Ti), copper (Cu), and zinc (Zn) are known to have their own properties and shows differential activity against microorganisms. This information has been utilized across various cultures for many centuries [93]. Metal nanoparticles of [gold (Au), silver (Ag), silicon (Si), titanium (TiO_2), zinc (ZnO), copper (CuO), calcium (CaO), and magnesium (MgO)] have the potential to inhibit several microbial species, like *Escherichia coli, Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa*, etc. [94-103].

It is well known that nanoparticles show different characteristics when compared to the same material in bulk because the surface to volume ratio of the NPs increases with a decrease in the particle size [104]. Certainly, in dimensions of nanoscale, the molecular surface noticeably increases, which in turn can lead in improvement of some of the properties of the particles. For example, it may be heat transfer, treatment, catalytic activity, or the dissolution rate [105]. Literature survey has pointed that the particle size can determine the effectiveness of antimicrobial activity of metal nanoparticles [106, 107]. The use of combination therapy with metal nanoparticles has the potential to be a strategy for preventing bacterial resistance to multiple antibacterial agents [108, 109]. More studies are needed to find out if green synthesized nanoparticles have better efficacy over traditionally synthesized nanoparticles or not. Some studies have displayed the same level of antimicrobial effects [110, 111]. The shape of nanoparticles plays major influence on their antimicrobial effects [112]. When antibacterial activity of AgNPs of three different shapes, (spherical, rod-shaped, and triangular) were compared, triangular NPs were found more reactive because of high atom density surfaces and they displayed greater antimicrobial activity [113]. In another study, the size and shape-based antimicrobial activity of fluorescent Ag nanoparticles (1–5 nm) was studied against some Gram-positive and Gram-negative bacteria [114]. It is reported that smaller the particles size, easily they enter the cell and exhibit higher antimicrobial activity. AgNPs could be used for various procedures such as wound dressing, biofilms, bio-adhesives, and coating of certain biomedical materials. Antimicrobial property of TiO_2 is related to the crystal size, shape, and structure [115]. The exact mechanisms in which non-metals present the antibacterial effect is still an area of active investigation. Based on literature review, there are some intrinsic factors that can influence the ability of nanomaterials in reducing or completely eliminating the cells [116].

The pharmaceutical industry has used NPs as a tool to reduce toxicity and side effects of drugs [117]. But while using NPs, certain safety concerns still exist. Numerous NPs seem non-toxic which ultimately has beneficial effects on health [118-121]. Biologically synthesized NPs have been found to be non-toxic or less toxic due to not using external stabilizing agents, hazardous chemicals and solvents during the synthesis process. Hasan et al. [122] compared the morphological, physiological, and biochemical responses of biologically and chemically synthesized iron oxide NPs in *Zea mays*. The biological synthesized iron (FeO) NPs promoted better growth as compared to the chemically derived NPs. Similarly, Anna et al. [123] also observed better growth in (*P. kessleri)*.

4. **Silver nanoparticles as biomaterials in dentistry-** AgNPs have distinctive biological properties and can serve as a novel application in dental restoration, endodontics, implantology, periodontology and oral cancers. AgNPs holds immense potential due to their antimicrobial, antiviral, antifungal actions. AgNPs can prevent biofilm, microleakage and secondary caries. They can improve mechanical properties of restorative materials. They can be used as canal irrigant similar to sodium

hypochlorite. Its use with acrylic resins has shown antifungal property and less chances of denture stomatitis. They can be used for antibiocidal surface coating over titanium implants preventing peri-implantitis. Experiments have revealed that AgNPs possess anticancer activity also. AgNPs based adhesive systems can be used in orthodontic treatments. In vitro research suggested that nanoparticles prevent crack propagation, periodontal diseases and stimulate regeneration. They have been found to be biocompatible with mammalian cells. AgNPs have been found suitable with dental biomaterials, but most of the studies have been done in vitro. In spite of benefits of AgNPs, research on long-term in-vivo results, methods of AgNPs incorporation, characterization and data on its long-term antibacterial action is the needed for its clinical applications [124].

5. Cardioprotection- The medicinal plant or herb neem (*Millingtonia hortensis*) has been used for AgNPs synthesis and significant cardioprotective properties were observed in rats [125]. In low concentrations, silver has been indicated as non-toxic and safe material to humans. It has been assessed as a promising material in pharmaceutical and biomedical uses [126, 127].

6. Wound care and healing application- A very important area for application of AgNPs is the treatment of wound infections caused by opportunistic microorganisms. The main goal is rapid tissue repair processes, accompanied by maximum restoration of functionality and minimum scar formation. The wound healing includes various stages such as blood coagulation, inflammation, cell proliferation, and matrix and tissue remodeling. Antibacterial and bactericidal properties of silver make it suitable for wound healing. It was found that doses of silver nanoparticles (non-toxic) synthesized by bacteria *Bacillus cereus* and *Escherichia fergusonii* promoted the collagen formation and epithelisation. It slowed down angiogenesis and the length of epithelization termination in rats [128]. Data were also revealed on biomaterials for improving wound healing such as modified cotton fabrics, bacterial cellulose, and chitosan [129-132]. Biopolymers combined with nanoparticles (antimicrobial, and anti-inflammatory) have great potential in wound healing. It is particularly useful in the management of diabetic foot ulcers (DFUs), which is related to high amputation rates and clinical costs [133]. Dai et al. developed an antimicrobial peptide-AgNPs composite and tested its wound healing properties in vivo on a diabetic rat model. They demonstrated improved wound healing without side effects, indicating a wide-spectrum activity without inducing bacterial resistance [134]. AgNPs increases the effectiveness against multi-drug-resistant organisms [135]. Prevention of microbial accumulation is very important in rapid wound management and to avoid high costs of antibiotics [136]. In vivo; a reduction of the bacterial burden and fast wound healing by silver-containing dressings was demonstrated, [137]. Several products with silver nanoparticles, such as bandages, gauzes, sutures, plasters, many creams and ointments can be prepared for wound healing application [138]. Silver treated textile materials and surgical sutures demonstrated improved wound healing in vitro, indicating a positive effect of silver for cell migration and proliferation [139-141]. Silver and silk proteins combination (improved antibacterial properties and tissue regeneration) is opening new options for development of completely natural wound dressing biomaterials [142]. This application for wound dressing biomaterials requires multidisciplinary research involving biotechnologists, clinicians, wound care professionals for further progress in wound care [143].

7. Larvicidal and antiplasmodial activity- The spread of many diseases by mosquito vectors is one of the most serious problems in many countries. The most typical diseases are dengue fever (A. aegypti) and malaria (A. stephensi). Mosquitoes are vectors for transfer of zika virus, yellow fever, japanese encephalitis, and many other diseases. Since effective drugs, and vaccines, are not available against these diseases, controlling the mosquito population in their breeding areas can be an alternative for controling these diseases. It has been demonstrated that silver nanoparticles obtained from extracts of various plants and microbial cultures have larvicidal, pupicidal, and adulticidal toxicity for A. albopictus and A. aegypti [144-148]. AgNPs penetrate the exoskeleton of young mosquitoes, and then bind to cell enzymes and DNA. Decrease in membrane permeability may cause cell function loss and cell death [149,150]. AgNPs' may have direct impact on the pathogen Plasmodium falciparum and other plasmodia [151-153].

8. Anthelmintic activity- Contact with the soil as well as travel to tropical regions abundant with different parasites results in human infections of various types of helminths. The most anthelmintic drugs act on target proteins and regulation of parasite neurons and muscles, resulting in paralysis, starvation, immune attack, and expulsion of the worm. However, such drugs may have a limited activity spectrum in different types of worms and generate drug resistance [154]. The concentration-dependent nature of silver nanoparticles in such bioactivity manifestation using plant extracts has been indicated [155-157]. It is assumed that the lethal effect in worms is achieved by inhibiting glucose uptake and the presence of components such as glycosides, tannins, and saponins in the packaging of nanoparticles [158,159]. These phytochemicals can attach to free proteins in the gastrointestinal tract or glycoprotein on the parasite's cuticle and cause death.

9. Leishmanicidal activity- Leishmaniasis is another health problem transmitted to humans by sand flies [160]. Leishmaniasis is closely linked to poverty, poor sanitation, malnutrition, and other diseases affecting the immune system. This disease is mainly observed in underdeveloped and war-torn countries around the world. Although, various strategies for the registration and treatment of this disease have been made, there is no anti-leishmaniasis vaccine. Traditional leishmaniasis treatment uses toxic and poorly tolerated expensive drugs which have already developed resistance. Here, the use of silver nanoparticles has potential for solving this problem. Leishmanicidal activity is based on the generation of ROS, latency in G0/G1 phases of the cell cycle, and inhibition of trypanothione/trypanothione reductase enzyme system [161-163]. "Green" AgNPs from plant extracts with activity against Leishmania can be a new hope in managing this health problem.

10. Antioxidant activity- Silver phyto-nanoparticles obtained from extracts of flower *Hyacinthus orientalis* and *Dianthus caryophyllus* (oriental hyacinth and garden clove) have high antioxidant activity [164]. Salari et al. demonstrated that AgNPs synthesized using aqueous *Prosopis farcta* fruit extract were excellent free radical "cleaners" [165]; a similar effect were found in vitro for aqueous extract of black Currant pomace [166], apple extract [167], leaf extracts of *Elephantopus scaber* [168], *Indigofera hirsuta* [169], and *Tinospora cordifolia* [170]. The most popular used and rapid methods for estimating antioxidant activity are the ABTS (2, 2-Azino-bis (3-ethylbenzthiazoline-6-sulfonic acid radical) and DPPH (1, 1-diphenyl–2–picrylhydrazyl radical) assays [171]. The high antioxidant potential of silver nanoparticles was shown for aqueous solution of spice mixture (garlic, ginger, and cayenne pepper) [172]. Antioxidant activity of the nanoparticles may be associated with different types of functional groups from the spice mixture that were responsible for reducing and capping the AgNPs. Similar results were obtained in other studies against DPPH and ABTS [173]. Various substances in plant extracts (polyphenols, enzymes, alkaloids, etc.) can donate hydrogen to free radicals and thus disrupt the free radical chain reaction. Silver nanoparticles synthesized by purple sweet potato root extract (*Ipomoea batatas* L.) had radical scavenging activity in vitro. Sweet potato root extract is full of glycoalkaloids, polyphenols, and anthocyanins acting as free radical scavengers and AgNP-capping by these molecules can be great antioxidants [174]. According to Elemike et al. antioxidant capacity of AgNPs was due to the phenolic compounds, terpenoids, and flavonoids in plants that let nanoparticles act as singlet oxygen quenchers, hydrogen donors, and reducing agents [175]. Shriniwas et al. suggested that the higher antioxidant activity of AgNPs from *Lantana camara* leaves may be associated with the predominant adsorption of the antioxidant substances from the extract to the surface of the nanoparticles [176]. Thus, high antioxidant phyto-nanoparticle activity may be associated with the specific capping of AgNPs specifically for medicinal plants, whose extracts contain a variety of antioxidant substances (polyphenols, flavonoids, etc.).

11. Anticancer activity- Many side effects in "classical" cancer therapy and their poor tolerance is a reason for searching new drugs of natural origin. Silver nanoparticles are potential agents for cancer diagnosis and therapy. Silver nanoparticles can induce apoptosis-dependent programmed cell death in the absence of the p53 tumor suppressor. A higher cytotoxicity was observed against cancer cells compared to non-cancer fibroblasts [177]. The cell cycle has a complex series of signaling pathways for the cell growth, DNA replication and division. Due to mutations in cancer cells, uncontrolled cell proliferation takes place. Thus, the most important stages of the cell cycle - DNA synthesis (S), Gap2/mitosis (G2/M), Gap1 (G0/G1), and subG1 are the main arrest points [178]. Al-Sheddi et al. showed that AgNPs produced by the plant *Nepeta deflersiana* had the ability to induce apoptosis and cell death by cell necrosis HeLA by stopping the sub G1 cell cycle [179]. Silver nanoparticles were found to induce apoptotic pathway by generating free oxygen radicals that displayed antitumor, antiproliferative, and antiangiogenic effects in vitro [180]. Silver nanoparticles influence the integrity of membranes by inducing different apoptotic signaling genes in mammalian cells, leading to programmed cell death [181]. It is well known that the high level of ROS can damage mitochondrial membranes, leading to toxicity [182].

Antitumor activities of AgNPs have been described: toxicity against tumor cells of HepG2 (human hepatocellular carcinoma) [183,184] and MCF-7 (invasive human breast ductal adenocarcinoma) [185]. It was found that the induction of apoptosis of HT29 cells (human colon cancer) can occur due to DNA fragmentation by silver nanoparticles [186]. It has been shown that the process of apoptosis can be realized via the degradation of lysosomes during autophagy, increasing the programmed cancer cells' death [187]. Similar results for Jurkat cells were obtained in vitro. Activation of caspase-3 and condensation/fragmentation of chromatin were observed in tumour cells treated with silver nanoparticles, which led to cell death due to the apoptotic process [188]. Antitumor effect was found for A549 cells (human adenocarcinoma) [189], HeLa cells [190], HCT116 (human colon carcinoma), MCF-7 (human breast adenocarcinoma), PC3 (prostate cell line), and A549 (lung carcinoma cell line) [191]. The most common biofactory for the production of AgNPs is plants, specially those for which anti-cancer properties are already known. However, other organisms are also used for synthesis of nanoparticles, for example, fungi *A. fumigatus* [191, 192]. So due to powerful anti-carcinogenic properties and very low toxicity, AgNPs are promising anticancer medicines.

12. Antidiabetic activity- α-amylase and α-glucosidase are key enzymes in carbohydrate metabolism. These enzymes breakdown carbohydrates to monosaccharides, resulting in increased blood glucose levels. Amylase inhibitor, jointly with starchy foods, reduces the usual upturn in blood sugar. AgNP's are represented as alpha-amylase inhibitors in many studies in vitro and in vivo [193-197].

13. Anti-inflammatory activity- In vitro, silver nanoparticles have anti-inflammatory effect due to TNF-α, interferons, and interleukin 1, inhibition of COX-2 and MMP-3 expressions. They reduce the activity of TNF-α, (involved in inflammatory processes) [198-202]. AgNPs from the Piper nigrum extract were shown as selective cytokine inhibitory agents for IL-1β and IL-6 [203]. AgNPs using European cranberry bush fruit extracts were developed and their anti-inflammatory effect was identified both in vitro (on HaCaT cell line, exposed to UVB radiation) and in vivo (on acute inflammation model in Wistar rats) that could be used for the treatment of inflammation [204]. Silver nanoparticles from European black elderberry (*Sambucus nigra*) fruit extracts demonstrated an anti-inflammatory feature in vitro on HaCaT cells exposed to UVB radiation, in vivo on the acute inflammation model, and for humans on psoriasis damage. In vitro, the anti-inflammatory effects of functionalized AgNPs were indicated by the decrease in cytokine production induced by UVB irradiation, and in vivo, the pre-administration of AgNPs reduced the edema and cytokine levels in the tissues early after the induction of inflammation [205]. Synergistic effect of polyphenols and silver nanoparticles for the manifestation of anti-inflammatory activity is known. Polyphenols have good anti-inflammatory activity in the treatment of psoriasis [206]. AgNPs produced using *Clinacanthus nutans* aqueous leaf extract have good analgesic and muscle relaxant properties, and can act as an analgesic agent [207]. Specific targeting of skin macrophages and suppression of inflammatory mediators may contribute to a substantial enhancement in therapeutic results [208].

14. Anti-alzheimer activity- Alzheimer's disease is associated with AChE. AgNPs could be new acetylcholinesterase inhibitors. Silver nanoparticles interact with the AChE protein, inhibiting its activity. It indicates the affinity of the nanoparticles with cholinesterase. The lithophilicity of the nanoparticles and hydrophobicity environment of the enzyme ChE molecule provide this interaction [209].

15. Application in medical equipments- AgNP coating is used in catheters to prevent biofilms [210, 211]. Medical dressings with silver nanoparticles are used in burns, chronic ulcers, pemphigus, and toxic epidermal necrolysis [212]. AgNPs are used in creation of orthopedic and orthodontic implants, dental instruments, and bandages, as well as medical clothing to avoid bacterial infections [213-215]. Central venous catheters (CVC) are widely used for providing intravenous fluids, drug delivery, and nutritional support in critically ill patients. So they should be clean and resistant to microbial contamination. It was found that catheters with silver nanoparticles coating were non-toxic and capable of preventing infectious complications [216, 217]. In catheter (surfaces coated with AgNPs), an inhibitory effect was found against both Gram-positive (coagulase-negative staphylococci) and Gram-negative microorganisms [218, 219].

Major Challenges

A large number of studies have reported the green synthesis of metallic NPs using various biological sources (bacteria, fungi, and yeast and many plants). However, challenges persist, limiting their large-scale production and applications. Some of the major challenges during the synthesis are discussed here. Optimization studies on reactants (plant extract, microbial inoculum, medium composition, etc.) and process parameters (temperature, pH, agitational speed, etc.) are required to control the size and shape of the NPs. Research is required to be focused on improving various physicochemical characteristics of NPs for specific use. The involvement of each metabolite of plant extract and cellular components of microorganism in the synthesis of NPs should be fully analyzed. Scale-up of NPs production for commercial purposes using green synthesis methods is highly needed. Optimizing all reaction parameters for high yield, stability, less reaction time is required. Green synthesis methods may be cost-effective in comparison to the conventional methods for the large-scale production of NPs. The separation and purification of NPs from the reaction mixture needs to be refined. Toxicity of the NPs on plants and animals is necessary before expanding their applications in diverse fields. Genetically modified microorganisms (with the ability to produce greater quantity of enzymes, proteins, and bio molecules) could further enhance the biosynthesis as well as the stability of NPs. Thus, the low toxicity, low production cost, and multiple uses of metallic nanoparticles make them suitable for solving various biomedical problems.

The prospective medical applications of NPs obtained using a wide variety of biological materials are extremely large, and the number of publications increasing rapidly on this topic is. A Vast variety of materials used for biosynthesis of silver nanoparticles with knowledge in the biosynthesis, mechanism and their influence on living organisms, will undoubtedly find new areas of applications in near future [220].

Conclusion and future prospects

The present review focuses on the green synthesis of metal NPs derived from plants and their biomedical applications. Green synthesis is a clean, non-toxic, and eco-friendly approach for metallic NPs synthesis as compared to other conventional (physical and chemical) methods. A wide range of plant materials (extract of stems, leaves, fruits, seeds, and bark etc.) and microorganism (bacteria, fungi, actinomycetes, etc.) have shown great potential for synthesis of various metal and metal oxide NPs (viz., Au, Ag, Pt, Pd, Ni, Se, Cu, CuO, and TiO_2). The size and shape of NPs depends on various experimental parameters such as reaction time, reactant concentration, pH, temperature, aeration, salt concentration, etc. Different characterization techniques such as UV-VIS spectroscopy, FTIR, XRD, SEM, TEM, EDX, and AFM have been used to determine shape, size, and morphology of biosynthesized NPs. However, several factors, viz., bioavailability, cellular interactions, biodistribution, and biodegradation, adverse reactions, toxicity etc. need to be addressed.

The accumulation of these nanomaterials in the environment and biological systems may lead to undesired consequences (DNA, membrane, mitochondrial damage and protein misfolding). Additional research is required for safety, use and disposal of products containing metallic nanoparticles. In this review paper we have provided in-depth details of green synthesis and their real world biomedical applications. Green synthesis procedures will benefit researchers involved in this emerging field of nanobiotechnology. It is expected that in near future more and more biomedical applications will emerge using green synthesis nanobiomaterials. It may take time until we can say that commercially available silver nanomaterials are truly safe for application both in everyday life and medical practice. This article also points researchers to other appropriate opportunities where metallic nanobiomaterials can be used.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

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