Potential Use of Green Nanoparticles as Antimicrobial Agents in Complementary and Alternative Medicine

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SUMMARY

Green nanotechnology significantly contributes to environmental sustainability by producing nanoparticles and nanoproducts without harming the natural environment or human health in jeopardy. This chapter summarizes the green synthesized metallic nanoparticles from plant extracts, bacteria, fungi, and algae for their unique antibacterial properties. Silver, gold, copper, manganese, iron, magnesium, and their oxides have all demonstrated strong antibacterial activity in green synthesis. The antibacterial action of silver, selenium, and palladium is stronger against a variety of well-known gram-positive and gram-negative microorganisms which is discussed in this chapter. Additionally, the general antibacterial mechanism of metallic nanoparticles produced sustainably is addressed. These ecologically friendly methods for producing nanomaterials would make it easier to produce nanoparticles with much improved antibacterial properties and therapeutic efficiency.

INTRODUCTION

Nanotechnologies have the potential to significantly affect the world's major causes of death and disease since they include systems with a diameter that is roughly one thousand of the width of a hair i.e., 1-100 nm (Hulkoti & Taranath 2014). Different kinds of anesthetics, chemotherapeutics, imaging agents, nutritional supplements, and other goods have been approved by the Food and Drug Administration (FDA) as a result of decades of intensive research on nanosystems (Anselmo & Mitragotri 2019). Due to their tiny sizes, huge surface areas with loose dangling bonds, and greater reactivity than their bulk materials, nanoparticles (NPs) have unique and intriguing features (An et al., 2019; Sabourian et al., 2020). Since NPs are often used in environments where people are exposed to them, it is becoming more and more important to develop synthesis methods that exclude dangerous chemical substances. As a result, the green/biological manufacturing of nanoparticles offers a potential substitute for chemical and physical processes (Wu et al., 2020). Although the capability of biological objects that mitigate precursors of metals has been well-known to scientists since the nineteenth century, the pathways are still unknown.

The discovery of an effective green approach employing natural agents for reduction, capping, and stabilization while avoiding the usage of hazardous, expensive chemicals and minimizing energy consumption has increased interest in biological processes among researchers (Rana et al., 2020; Alavi et al., 2022). "Why are green synthesized nanoparticles so intriguing and growing significance today?" is the first query associated with the development of green nanotechnology. NPs created using biological processes are favored over nanomaterials created using physio-chemical processes due to their distinct features (Aboyewa et al., 2021). The consumption of toxic solutions, the production of dangerous byproducts, and material surface irregularities are only a few of the issues that make physio-chemical procedures expensive and problematic (Ijaz et al., 2020). Chemical techniques often consist of many different kinds of chemicals or molecules, which might enhance particle sensitivity and cytotoxicity and impair the well-being of humans and ecosystems (Burlibașa et al., 2020; Parashar et al., 2020). The green nanoparticle synthesis, a bottom-up method, is comparable to the use of chemicals in that it substitutes a costly reducing substance with an extract of organic substance, for example, fruit and vegetable leaves (Chandra et al., 2020; Dikshit et al., 2021), bacteria, fungus, yeast, or algae for

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production of metallic or metal oxide nanoparticles (Ali et al., 2020; Bahrulolum et al., 2021). There is enormous potential for the synthesis of NPs in biological beings (Singh et al., 2018). The environmentally safe, cost-effective, chemically free reduction of metal precursors to their equivalent nanoparticles by green synthesis is suitable for large-scale manufacturing. The required qualities may be obtained in green NPs so that the cellular molecules such as proteins carbohydrates, enzymes, etc. stabilize nanoparticles and also allow their interaction with other molecules consequently improving their antimicrobial activities (Hamida et al., 2020; Salem & Fouda 2021).

The availability of an eco-friendly solvent, a suitable reducing agent, and a safe stabilizing component are the three primary criteria that affect the green approach. When using an environmentally friendly approach to create nanoparticles, molecules such as proteins, enzymes, carbohydrates, flavonoids, phenol compounds, etc. typically serve as reducing and stabilizing agents (Sarkar et al., 2020). Equitable growth that meets the needs of future generations produces green synthesis. The use of only naturally occurring ingredients, a reduction in the usage of dangerous reagents and chemical solvents, the stability of the final product, and the simplicity with which the completed goods may be handled and stored are the main benefits of using green chemistry techniques (Nair et al., 2022). Even though there has been a lot of study in nanotechnology, green synthesis is still frequently used to create silver [Ag (Roy et al., 2019)] and gold (Au) nanoparticles (Castillo-Henríquez et al., 2020). However, research has only partially established the biogenesis and potential applications of several metallic and metal oxide nanoparticles (NPs), including those made of iron, copper, manganese, magnesium, and their oxides, among others.

ANTIMICROBIAL POTENCY OF GREEN NANOPARTICLES

Silver nanoparticles

Recent years have seen a substantial increase in interest in the use of silver nanoparticles as an antibacterial agent Tab 1. Silver NPs possess the capacity to cling to bacterial cells' surfaces and damage the cell membrane's lipid bilayer structure. Cell death may occur due to increased membrane permeability, causing the membrane to become leakier. Silver nanoparticles (AgNPs) can modify the electric potential across the bacterial cell membrane, leading to depolarization and membrane breakdown. Consequently, intracellular contents may leak out, ultimately resulting in cell death (Roy et al., 2019). AgNPs can produce reactive oxygen species (ROS) like hydrogen peroxide, superoxide, and hydroxyl radicals, which interact with bacterial cell membranes, causing damage and compromising their integrity (Yin et al., 2020).

In one investigation, the antibacterial activity of AgNPs that were synthesized by *Rheum australe*, *Selinum vaginatum*, and *Berginea ligulata* plant root extract while chemically synthesized AgNPs were prepared from gelatin, polyvinylpyrrolidone (PVP), and polyvinyl alcohol (PVA). The study found that green-synthesized AgNPs using root extracts showed higher antimicrobial activity compared to chemically synthesized AgNPs. Among the plant extracts, *S. vaginatum* is the most effective against *Salmonella enterica typhi* and *Pseudomonas* (*P.*) *aeruginosa* (Chahar et al., 2018). In a different study, AgNPs were made using a leaf extract from *Cestrum nocturnum*, and their antibacterial properties were assessed. The silver nanoparticles showed great antibacterial action against numerous bacterial species, with the maximum activity shown against *Vibrio cholera* (Keshari et al., 2020).

Moreover, it was discovered that generating AgNPs using *Carya illinoinensis* leaf extract was a practical and environmentally friendly method. The AgNPs displayed stronger antimicrobial activity than the leaf extract against both bacteria, with the most notable inhibiting activity seen against Gram-negative bacteria like *E.scherichia* (*E.*) *coli* and *P. aeruginosa*. Such studies suggested that green synthesis of AgNPs using plant extracts is an effective and sustainable method for synthesizing nanoparticles with potential uses in various medical areas (Bakht et al., 2020). AgNPs synthesized using *Lysiloma acapulcense* extract showed high antimicrobial potency against several pathogenic bacteria, such as *E. coli*, *Candida albicans*, *Staphylococcus aureus*, and *P. aeruginosa* (Garibo et al., 2020). Comparative to Grape seed extract alone, grape seed extract-loaded AgNPs were discovered to exhibit strong antibacterial efficacy against several diseases (Al-Otibi et al., 2021). Finally, *Moringa oleifera* leaf extract and AgNPs were observed to have excellent antibacterial activity against many bacteria on cotton fabric (Ibrahim et al., 2021).

Palladium nanoparticles

Palladium nanoparticles (PdNPs), according to studies, have the potential to be used in biological applications because of their antibacterial characteristics. The incorporation of *Urtica* extract in combination with a green methodology is a viable strategy to improve the therapeutic capabilities of palladium nanoparticles (PdNPs). Indicating its prospective utility as an antibacterial agent in biomedical applications, the PdNPs-*Urtica* demonstrated strong antimicrobial activity against gram-negative bacteria (Gulbagca et al., 2021). Another work described employing *Solanum nigrum* leaves (SNL) extract as a reducing and capping agent in the green production of gold, silver, and palladium nanoparticles. Palladium nanoparticles created by SNL were discovered to have powerful antibacterial characteristics and may find use in health and medicinal domains (Vijilvani et al., 2020). The application of *Saudi* *propolis* extracts against, *Basella alba*, *Tabernaemontana divaricate,* and *Allium fistulosum,* was found to be an effective and environmentally friendly method for biosynthesizing PdNPs. These PdNPs demonstrated a potent bactericidal activity against various microorganisms (Al-Fakeh et al., 2021; Vinodhini et al., 2022).

Additionally, *Rosmarinus officinalis* leaf extracts mediated PdNPs showed promise for creating effective antibacterial agents against *S. aureus, S. epidermidis, E. coli,* and *Micrococcus luteus*. Overall, this study suggested that PdNPs could be synthesized using natural products and have the potential for use in developing new and effective antimicrobial agents (Rabiee et al., 2020). PdNPs can produce ROS, including hydroxyl and superoxide radicals, which can harm bacterial cells by inflicting oxidative stress. Consequently, the cell membrane and other cellular components are damaged, which ultimately causes cell death. The structure and functionality of bacterial membrane proteins can also be altered by PdNPs, which can result in membrane breakdown, increased permeability, and the leaking of intracellular contents. The physical contact of PdNPs with the lipid bilayer of bacterial cell membranes might ultimately result in damage and the loss of membrane integrity, which will ultimately result in cell death (Singh et al., 2020).

Copper nanoparticles and its oxides

Plant extracts are frequently used to generate copper nanoparticles (CuNPs). The amine and carboxyl groups of bacteria interact with copper-containing nanoparticles, or elevated Cu^{2+} levels of ions can result in the production of ROS, which can lyse microbial cells (Akintelu et al., 2021). CuNPs were made using extracts of the roots of *Salvia officinalis* and leaf extracts from six commonly accessible plants, including *Avicennia marina, Rosa rubiginosa, Azadirachta indica, Eucalyptus camaldulensis, Datura stramonium, Murraya koenigii* (Asghar et al., 2020). Excellent antibacterial action of CuNPs has been observed in testing data against Gram-positive and Gram-negative bacteria of different types as they are capable of a very high surface capacity owing to their tiny diameter, which allows for effective interaction with microorganisms. The SEM pictures reveal that CuNPs synthesized from *A. indica* exerted a bactericidal effect by altering the morphology of the cell membranes of bacteria (Kamçi et al., 2022).

One of the unused byproducts of the plant *Zea mays L.* is dry husk extract. However, it has been demonstrated that they are an excellent source of several phytochemicals, including flavonoids, saponins, alkaloids, and glycosides, among others. For the first time, an easy, environmentally friendly, green synthesis method was used to produce red-colored cubed CuO nanoparticles. According to the research, CuO NPs are excellent at combating bacteria *like S. aureus, P. aeruginosa, E. coli,* and *B. licheniformis* (Nwanya et al., 2019). *Aerva javanica* plant leaf extracts or the outer layer of *Allium cepa* are being employed in many pieces of research to reduce and cap CuO nanoparticles. These nanoparticles were reported to have more antibacterial action against Gram-negative pathogens than Gram-positive pathogens, especially at concentrations of 200 g/mL. This may be owing to Gram-negative bacteria having a less dense cell wall than Gram-positive bacteria; as a result, the easier infiltration of NPs by the weaker wall leads to cell lysis (Amin et al., 2021). However, researchers employ *Allium cepa* in herbal remedies to combat resistant bacteria as they have antimicrobial properties against both gram-positive and gram-negative organisms (Kenneth & Nwodo 2023).

Selenium nanoparticles

The microdilution technique was used to test the antibacterial activity of *Abelmoschus esculentus*, *Urtica dioica* (stinging nettle), and orange peel waste aqueous extract-generated selenium (Se) nanomaterials against microbes like *S. aureus* and *S. mutans*, and *E. coli* and *Pseudomonas aeruginosa*. Due to the significantly negative charge of Gram-negative one's bacterial cell membranes in contrast to that of Gram-positive microbes, nanoparticles have a greater propensity to adhere to the exteriors of Gram-positive bacteria to cause bacterial cell destruction (Ghaderi et al., 2022; Hashem & Salem 2022; Salem et al., 2022). For a sustainable, cost-effective, and environmentally acceptable method, SeNPs were also green-synthesized using a baker's yeast isolate (*Saccharomyces cerevisiae*). *E. coli*, *Aspergillus fumigatus*, *Staphylococcus aureus*, and *Aspergillus niger* were among the food-borne pathogens that SeNPs exhibited promising antibacterial efficacy (Salem, 2022). *Penicillium crustosum*, an endophytic fungal strain, was used in an alternative green production of Se nanoparticles. Experimental data showed that Se-NPs had stronger antibacterial effects against microbes (bacteria) that were dose-dependent (Fouda et al., 2022).

Manganese nanoparticle and its oxides

Green chemistry's cost-effective, low-toxic, biocompatible, and environmentally acceptable method for producing manganese oxide nanoparticles (MnO NPs) involves in reduction and stabilization of manganese metal by the use of plant extracts (Ahmad et al., 2022). In a study, the disc diffusion method was used to assess the antimicrobial potential of curcumin-stabilized Mn NPs against *E.coli* and *S. bacillus* besides *S. aureus* (gram-negative) and *Bacillus subtilis* and the inhibition zone was compared to Chloramphenicol and observe that *Curcumin* mediated MnNPs had superior antibacterial properties to curcumin for all bacteria (Jayandran et al., 2015).

Tab 1. Review of Green metallic nanoparticles and their anti-microbial efficacy.

Nanoparticle	Biological resources	Size	Application	References
Ag	*Berginea ligulate, Selinum vaginatum, Rheum austral*	5-15 nm, 20-50 nm, 10-30 nm	*Salmonella enteric typhi, Pseudomonas aeruginosa*	Chahar et al., 2018
	Cestrum nocturnum	20nm	*Vibrio cholera*	Keshari et al., 2020
	Carya illinoinensis	12-30nm	*Escherichia coli, Pseudomonas aeruginosa*	Bakht et al., 2020
	Lysiloma acapulcensis	5nm	*Escherichia coli,*	Garibo et al., 2020
	Grape seed	91.89nm	*B. subtilis, E. coli, P. aeruginosa, S. aureus,*	Al-Otibi et al., 2021
	Moringa oleifera	15-25 nm	*S. aureus, E. coli,*	Ibrahim et al., 2021
Pd	*Urtica*	7.44 ± 1.94 nm	*L. pneumophila, P. aeruginosa, E. coli,*	Gulbagca et al., 2021
	Solanum nigurum	21.55nm	*E. coli*	Vijilvani et al., 2020
	Saudi Propolis	3.14 -4.62 nm	*B. subtilis, K. pneumoniae, C. albicans, S. aureus, E. coli*	Al-Fakeh et al., 2021
	Allium fistulosum, Tabernaemontana divaricate, Basella alba	2-5nm	*E. coli, S. aureus*	Vinodhini et al., 2022
	Rosmarinus officinalis	15 - 90 nm	*S. epidermidis, S. aureus, E. coli, M.lutens*	Rabiee et al., 2020
CuO	*Eichhornia Crassipes*	9.1 nm	*E. coli, S. typhi, B. subtilis*	Saligedo et al.,2023
Cu	*Moringa oleifera*	35.8–49.2 nm	*E. coli, K. pneumoniae, S. aureus and E. faecalis*	Das et al., 2020
	Millettia pinnata	23±1.10 nm	*B. subtilis, E. coli, P. aeruginosa, S. aureus*	Thiruvengadam et al., 2019
Se	Orange peel waste (OPW)	16–95 nm	*S.aureus, P. aeruginosa*	Salem et al., 2022
	Withania somnifera	45– 90 nm	*E. coli, P. aeruginosa, S. aureus*	Alagesan & Venugopal 2019
	C. bulbosa tuber	55.9 nm	*E. coli, B. subtilis*	Cittrarasu et al., 2021
Au	*Djulis (Chenopodium* formosanum) shell	24 ± 17 nm	*S. aureus, E. coli*	Chen et al., 2019
	Artemisia absinthium (wormwood)leaf	13.40 nm	*S. aureus, Aeruginosa strains, S. pyogenes, E. coli*	Keskin et al., 2021
	Macroalga *Sargassum muticum* (SM)	10.4 ± 1.2 nm	*Staphylococcus aureus*	González-Ballesteros et al., 2020
	panchagavya (PG)	53.29 nm	*E. coli, K. pneumoniae, B. subtilis*	Sathiyaraj et al., 2021
Fe	*Azadirachta Indica* leaf	96-110 nm	*E. Coli, P. aeruginosa, S. aureus*	Devatha et al., 2018
	Chlorophytum comosum leaf	246 nm	*Staphylococcus aureus*	Ardakani et al., 2021
FeO	*Withania coagulans*	16 ± 2 nm	*S. aureus* and *P. aeuroginosa*	Qasim et al., 2020
	Laurus nobilis L.	8.03 ± 8.99 nm	*Listeria monocytogenes,* *Aspergillus flavus* and *Penicillium spinulosum*	Jamzad & Bidkorpeh 2020
	Psidium guajava	1 - 6 nm	*Escherichia coli, Staphylococcus aureus*	Madubuonu et al., 2020

Using the disk-diffusion agar method, the anti-microbial potential of the *AbutiIon indicum* mediated MnO NPs was assessed on bacterial species such as *Bordetella bronchiseptica, E. coli*, *Bacillus subtilis* and *S. aureus* comparable to that of the conventional antibiotic (Iqbal et al., 2018). In a different investigation, well diffusion and Bauer-Kirby techniques were used to investigate the anti-microbial activation of MnO NPs alone or in combination with nine antibiotics against *K. pneumonia*, *E. coli,* and *P. aeruginosa*. The MnO NPs showed strong action against these microbes (Saod et al., 2022).

Magnesium nanoparticles and its oxides

From a medical perspective, creating biocompatible magnesium oxide nanoparticles (MgO NPs) utilizing green chemistry would be beneficial. The biological production of MgO NPs has not received much attention (John Sushma et al., 2016). In a previously published investigation, the anti-microbial activity of MgO NPs against Gram-positive (*S. aureus*, *S. pneumoniae*) and Gram-negative (*S. typhi, E. coli*) bacteria. The *Rhizophora lamarckii* derived MgO NPs produced promising antibacterial action against *S. aureus*. According to studies, MgO NPs' antibacterial action triggers the production of ROS-like O_2, which leads to bacterial lipid peroxidation (Tang et al., 2014). In general, MgO NPs made through green synthesis can be excellent for anti-pathogenic activity with the best performance for biomedical applications since they are biocompatible and environmentally benign materials (Farani et al., 2023).

Gold nanoparticles

Gold nanoparticles (AuNPs) have gained wide popularity in biomedical applications for antimicrobial delivery owing to their ease of production, low toxicity, and unique physicochemical characteristics making them a preferred material for biological applications (Iqbal et al., 2016). Novel, affordable, and environmentally friendly gold nanoparticles (Au NPs) were created by using the green approach from various plants such as *Indigofera tinctoria* (Vijayan et al., 2018), *Sargassum muticum* (González-Ballesteros et al., 2020) *Artemisia absinthium* (Keskin et al., 2021) and *P*anchagavya

(Sathiyaraj et al., 2021) and their anti-microbial activities against different pathogens were observed. The research by Vijayan et al. (2018) observed the antibacterial and anti-fungal efficacy of the gold nanoparticles synthesis by *Indigofera tinctoria* leaf extract against the *Bacillus pumilis* and *Staphylococcus aureus*, *Pseudomonas species and Escherichia coli*, *Aspergillus fumigatus* and *Aspergillus niger* (fungi). Their results suggested good antimicrobial efficacy against *Pseudomonas s.p* and *Escherichia coli* compared to the *Bacillus pumilis* and *Staphylococcus aureus* possibly due to the presence of the peptidoglycan layers in their cell wall.

Iron nanoparticles and their oxides

Eucalyptus robusta leaf aqueous extract was used to synthesize iron nanoparticles (FeNP), which showed antibacterial action against *Pseudomonas aeruginosa*, *Escherichia coli*, *Bacillus subtilis and S. aureus* (Vitta et al., 2020). The production of ROS, such as hydroxyl (OH^-) radicals and singlet oxygen (O^{2-}), which contribute to bacterial death, and particle accumulation in the cytoplasmic region are among the mechanisms for the anti-bacterial potential of iron nanoparticles. The ability of a nanoparticle to penetrate and accumulate within a bacterial cell wall improves with nanoparticle size which enables the inhibition of bacterial growth (Devatha et al., 2018).

Laurus nobilis L. extract was used to make (Fe_2O_3) nanoparticles in the hematite phase. Characterization methods employed included EDS, SEM (scanning electron microscope), TEM, and spectroscopy showed that nanoparticle size ranged from 8.03-8.99 nm. The outcomes demonstrated that the nanoparticles displayed anti-fungal efficacy against *Penicillium spinulosum*, *Aspergillus flavus*, and *Listeria monocytogenes* (Jamzad & Bidkorpeh 2020). In another study, hexahydrate ferric chloride ($FeCl3.6H2O$) was combined with papaya (*Carica papaya*) extract to produce nanoscaled iron oxide particles (FeO NPs) in ambient settings. According to Bhuiyan et al. (2020), FeO NPs synthesized nanoparticles show dose-dependent antibacterial properties, with the highest effect observed for *S. aureus* and the lowest effect for *Klebsiella spp*. The inhibition zone for *S. aureus* increased with an increase in dose, while *Klebsiella spp*. exhibited resistance at lower doses but showed an inhibition zone at a higher dose. Additionally, the nanoparticles showed moderate effects on *E. coli* and *Pseudomonas* spp. with inhibition zones observed at a dose of 30 mg/ml.

PROPOSED ANTIMICROBIAL MECHANISM OF NANOPARTICLES

Nanoparticles produced using green synthesis might be used in the production of antimicrobial substances. Although research on the antibacterial mechanism of green-synthesized nanoparticles is still ongoing, it is thought that these tiny particles may collaborate with microbial cells in a variety of manners as shown in Fig 1.

The membrane of microbial cells being damaged is one of the key approaches. The nanoparticles may adhere to the cell membrane and compromise its integrity, allowing vital cellular components to seep out and finally causing cell death (Nisar et al., 2019). Another process involves the production of reactive oxygen species (ROS) in microbial cells. These ROS have the potential to oxidatively damage biological elements such as proteins, lipids, and DNA, which can result in cell death. It has been demonstrated that green nanomaterials may produce ROS through a number of different methods, such as the formation of singlet oxygen (O^{2-}) and hydroxyl radicals ($OH\cdot$) (Jamdagni et al., 2018). Additionally, nanoparticles produced during green synthesis may obstruct microbial cell signaling pathways, which are crucial for the survival and proliferation of microbial cells. By attaching to major signaling molecules or by changing the regulation of genes engaged in these pathways, these nanoparticles can interfere with signaling pathways (Singh et al., 2020).

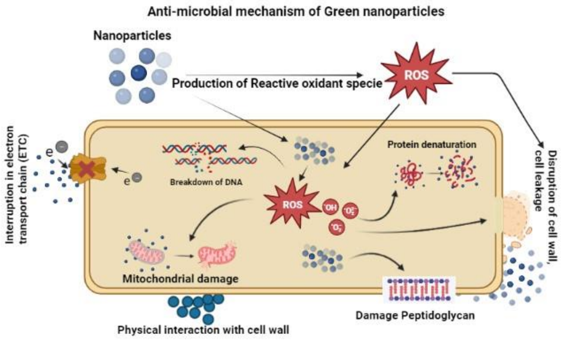

Fig 1. Anti-microbial mechanism of Green Nanoparticles

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