Green Metallic Nanoparticles: Applications as Immunomodulatory and Anti-Oxidative Agents

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SUMMARY

The goal of any scientific advancement is to improve human health and welfare. While current therapeutic approaches are helpful, there is a need for new methods to produce effective and reliable therapies. Furthermore, society needs new standards for technologies that promote environmental sustainability. Green nanotechnology plays a significant role in this regard by creating nanoparticles and nanoproducts without endangering the ecosystem or human well-being. The nanoparticles of particular interest are gold (Au) and silver (Ag) nanoparticles, that can be synthesized in a controlled size and shape and have been shown to reduce inflammation through cytokine inhibition. Copper (Cu) and selenium (Se), zinc (Zn) and zinc oxide (ZnO) nanoparticles derived from plant extracts have also demonstrated powerful antioxidant capabilities. By using environmentally friendly techniques to create nanomaterials, researchers can generate nanoparticles with significantly enhanced immunomodulatory and antioxidant characteristics, leading to vastly improved therapeutic efficacy.

INTRODUCTION

The study of materials and technologies at the nanoscale, or 10^{-9} meters, is the primary emphasis of the field of nanotechnology. It has significantly advanced several fields, including medical care, energy, as well as environmental sustainability (Grillo et al., 2015). Since they are so small, nanomaterials can have a wide range of forms and sizes and have unique physical and chemical characteristics. As a result, they have been employed in a diverse range of fields including biomedical research, chemical industries, catalysis, cosmetics, electronics, energy science, food and feed, environmental sustainability, healthcare, drug delivery systems, and even clothing (Singh et al., 2018).

In the area of biomedical investigation, nanomaterials offer numerous benefits such as their capacity to affix to biological objects without compromising their functionality, as well as their high surface-to-volume ratio, which facilitates strong bonding with surfactant molecules (Makvandi et al., 2020). Functional nanomaterials with intrinsic physical properties, such as aqueous stability, biocompatibility, interactive functional groups, and adsorptive properties, have opened new possibilities for the development of technologies and their applications in the medical field for both diagnostic and therapeutic techniques, disease control, and prevention (Rizzo et al., 2013).

Depending on their chemical makeup, nanoparticles may be divided into two groups: organic and inorganic. Chemically, organic nanoparticles are identified by the existence of carbon-hydrogen bonds, while inorganic nanoparticles lack such bonds (McClements & Xiao 2017). Inorganic nanosized materials are divided into two categories: metal-based and metal-oxide nanoparticles. Due to their extensive application in a range of fields, such as electronics, optics, medicines, & biology, metal nanoparticle manufacturing has significantly increased in recent years. Typical examples are silver, gold, and iron (Rónavári et al., 2017). Various techniques are used to characterize nanoparticles, such as transmission electron microscopy (TEM) and spectroscopy with ultraviolet-visible wavelengths to determine their size and surface morphology, X-ray photoelectron microscopy (XPS) to analyze their composition, and Zeta-potential to measure their surface charge (Ealia & Saravanakumar 2017).

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SYNTHESIS METHODS

Three different methods such as chemical, physical, and biological could be used for generating nanoparticles. These methods can be top-down or bottom-up. The bottom-up approach involves constructing materials from atoms to clusters to nanoparticles, while the top-down approach comprises downsizing bulk substances to the nanoscale through mechanical or chemical techniques (Ealia & Saravanakumar 2017). Bottom-up synthesis is generally the preferred approach for nanoparticle synthesis as it enables a more controlled environment and facilitates regulation of the morphology and dimensions of the nanoparticles (Escudero et al., 2021). Chemical synthesis of nanomaterials can be proficient by using stabilizing agents, metallic precursors, and reducing agents (both inorganic and organic) through a variety of techniques such as sol-gel, solvothermal, combustion, co-precipitation, microemulsion, and chemical reduction (Wu et al., 2019). Physical techniques are used to create a wide variety of nanoparticles and nanomaterials, including microwave irradiation, chemical vapor deposition (CVD), laser ablation, the soon chemical reduction technique, and plasma which is produced using radio frequency (RF) warming coils (Rajput, 2015).

Green synthesis

Green synthesis has emerged as a modern approach to nanoparticle production and is gaining popularity due to its benefits compared to conventional physical and chemical techniques. It takes away the necessity for high energy, temperature, or pressure and avoids the use of toxic chemicals (Devatha & Thalla, 2018). Traditional methods that utilize harmful and toxic chemicals can increase the reactivity and toxicity of nanoparticles, this might have a negative influence on both the environment and human health. In contrast, green synthesis generates minimal by-products and is a sustainable, environmentally friendly alternative (Hussain et al., 2016). Green-mediated nanoparticles involve the usage of live organisms such as plants, bacteria, fungi, and algae to produce nanoparticles with reduced toxicity, avoiding the need for chemical or other stabilizing substances (Bandeira et al., 2020). The process begins by combining metallic precursors with aqueous plant extracts or biological agents to create a homogenized solution, which is then subjected to thermal treatment as shown in Fig 1.

This process comprises various stages, such as activation, growth, and termination stages (Bhardwaj et al., 2020; Kumar et al., 2020). Various living entities are utilized in biosynthesis nanoparticle strategies, as described below.

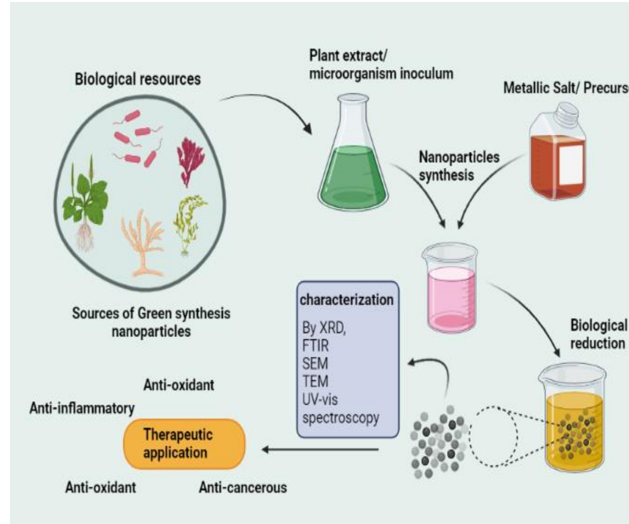

Fig 1. Synthesis of Green metallic Nanoparticles

NP synthesis via bacteria: Bacteria are utilized as "nano-factories" to create a variety of nanoparticles, including metallic nanoparticles, due to their capacity to decrease metal ions (Iravani, 2014). The simplicity of working with bacteria and the availability of interacting pathways inside bacterial cells, which are in charge of producing metallic nanoparticles, are benefits of bacterial synthesis (Fariq et al., 2017). Bacterial cells are capable of producing sustainable nanoparticles on a large scale, and their rapid growth and genetic manipulability make them a desirable option for nanoparticle synthesis. Moreover, bacterial species can tolerate higher concentrations of metallic ions, which further enhances their potential for nanoparticle synthesis (Bahrulolum et al., 2021).

A range of bacterial genera, such as *Escherichia*, *Bacillus*, *Lactobacillus*, *Citrobacter*, *Aeromonas*, *Enterobacter Streptomyces*, *Klebsiella*, *Rhodobacter*, *Plectonemaboryanum*, *Pyrobaculum*, *Rhodopseudomonas*, *Rhodococcus*, *Arthrobacter* and *Geobacter*, have been reported to be used for the biosynthesis of nanoparticles. These bacteria are capable of producing innumerable nanoparticles such as iron, silver (Singh et al., 2016), gold, platinum, selenium, palladium (Song et al., 2017), titanium, and titanium dioxide (Wang et al., 2017).

NP synthesis via fungi: The presence of intracellular enzymes, including NADH-dependent reductase, enables fungi to produce metallic and metallic oxide nanoparticles (Guilger-Casagrande & Lima, 2019). Fungi have a larger biomass and greater surface area for interactions (due to the presence of mycelia) than bacteria, resulting in higher nanoparticle yields. The internal enzymes present in fungi aid in the rapid transformation of metallic salts into nanoparticles, whereas the function of their cell walls is in the uptake and suppression of metal ions to create nanoparticles. Furthermore, fungi possess an advantage over other organisms since fungi have an additional advantage over other organisms as they possess enzymes or proteins on their cell surfaces that can reduce components (Khandel & Shahi 2018).

Aspergillus fumigates, *Penicillium fellutanum*, *Aspergillus niger*, *Rhizopus stolonifera*, *Aspergillus terreu*, and *Aspergillus flavus* TFR7 are among the fungi that can produce nanoparticles of several metals and metal oxides, such as gold, zinc oxide, titanium dioxide, and silver (Singh et al., 2018).

NP synthesis via plant extract: The potential of plants to produce metallic and metallic oxide nanoparticles has been extensively studied. Plants can also detoxify and accumulate heavy metals, making them a desirable alternative to conventional methods for producing nanoparticles (Hulkoti & Taranath 2014). Plants also offer unique advantages over other biological systems as they are a valuable and renewable source of natural products, including secondary metabolites with antioxidant properties. The process of plant extract-mediated bio-reduction entails combining a metallic salt solution with herbal extractions at ambient temperature, and the response usually concludes in simply a couple of minutes (Singh et al., 2018).

Among the phytochemicals found in botanical extracts are aldehydes, flavones, carboxylic acids, terpenoids, ketones, polyols, amides, and polyphenols, particularly in leaves, as well as biomolecules such as carbohydrates, proteins, and coenzymes, possess strong reduction capabilities for metallic ions and stabilizing nanoparticles. The characteristics of the resulting nanoparticles are impacted by the extract used (Ovais et al., 2018, Mittal et al., 2013).

Using plant extract-assisted methods, the green synthesis approach has successfully synthesized various metallic and metallic oxide nanoparticles. Numerous plants such as *Aloe barbadensis Miller*, *Moringa oleifera*, *Rosa rugosa*, *Dioscorea bulbifera*, *Vitex negundo*, *Terminalia catappa*, *Eucalyptus hybrid*, *Curcuma longa*, *Cinnamomum camphora*, *Cassia fistula*, *Medicago sativa*, *Brassica juncea*, *Camellia sinensis*, *Calotropis gigantean*, *Allium sativum*, *Mucuna pruriens*, and *Mentha piperita*, have been reported to reduce the several metallic and metallic oxide reagents for producing numerous metallic nanoparticles, that include zinc, gold, titanium, palladium, silver, nickel, cobalt, and copper (Iravani, 2011; Mittal et al., 2013).

PHARMACOLOGICAL ACTIVITIES OF GREEN NANOPARTICLES

In recent years, nanomedicine has emerged as a promising field that can revolutionize the medical sector, particularly in the management of chronic illnesses. The generation of environmentally safe nanoparticles is one of the essential elements of nanomedicine which can be derived from biological-based sources (Thiruvengadam et al., 2019). The antibacterial, antitumor, antidiabetic, anti-inflammatory, and antioxidant besides immunomodulatory capabilities of these nanoparticles have been discovered to have multiple beneficial impacts. This makes them highly versatile and potentially useful in treating a broad range of medical conditions (Saratale et al., 2020). A fascinating and exciting field of study that has the potential to completely alter how chronic diseases are treated is the use of metal nanoparticles produced through green synthesis.

Silver nanoparticles

Metal nanoparticles, especially silver nanoparticles (Ag-NPs), are created using the "green synthesis" technique, which is gaining popularity because of their exceptional characteristics. AgNPs are intensively researched due to their distinctive characteristics, such as their photonic, catalytic, sensing, antioxidant, immunomodulatory, and antibacterial activities (Rahman et al., 2019). Agarwal et al. (2019) have testified that silver NPs can legitimately reduce cytokine production, mast cell, and lymphocyte infiltration, pro-inflammatory gene expression such as NF-κB, and induce apoptosis in inflammatory cells, indicating their anti-inflammatory effects. Furthermore, research has shown that silver NPs are capable of inhibiting the generation of reactive oxygen species (ROS) and nitric oxide (NO) in inflammatory cells shown in Fig 2., (Ameen, et al., 2023).

A variety of plant extracts such as *Svensonia hyderobadensis, Amaranthus retroflexus, Teucrium polium, Azadirachta indica, Syzygium aromaticum, Melia dubia, Rosa damascene, Piper nigrum, Viburnum opulus, Punica granatum,* and *Solanum nigrum* a green production of silver nanoparticles has been described (Simon et al., 2022). In research from Chirumamilla et al. (2022), the anti-inflammatory qualities of silver nanoparticles made from *Solanum khasianum* were assessed using a technique for stabilizing the membrane of human red blood cells. The study's findings suggested that silver nanoparticles may be used as an anti-inflammatory pharmaceutical component since they demonstrated better anti-inflammatory efficacy than leaf extract.

Subsequently, silver NPs were created using fruit extract from the *Viburnum opulus*, and their anti-inflammatory capabilities were investigated. These nanoparticles showed a

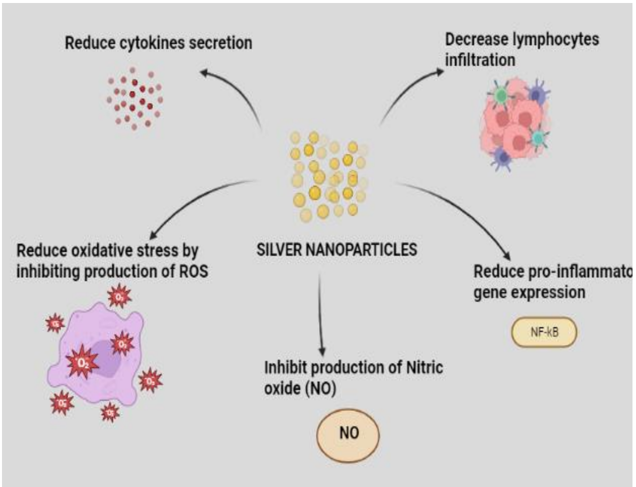

Fig 2. Schematics illustration of antioxidative and anti-inflammatory effect of silver nanoparticles.

dual effect on the release of inflammatory cytokines, initially increasing the production of IL-1α afterward ultraviolet B exposure but decreasing it after 48 hours. *In vivo*, the nanoparticles exhibited anti-inflammatory effects by reducing paw edema in rats with carrageenan-induced hind paw edema. The extract that was employed for making nanoparticles demonstrated antioxidant activity by inhibiting the production of nitric oxide, peroxides of lipids, and superoxide anions. In addition, Alkhalaf et al. (2020) reported that *Nigella sativa-mediated* AgNPs have promising anti-diabetic effects by mitigating hyperglycemia, modulating inflammatory biomarkers, and restoring antioxidant status.

Correspondingly, the recent study found that topical treatment with AgNPs produced from cyanobacteria *Phormidium* species reduced the creation of ROS, fostered the creation of cytokines IL-10, as well as kept IL-6 significantly lower throughout contrasted with the positive control in terms of the wound rehabilitation process. The study suggested that AgNPs have potent wound-healing properties due to their efficient antioxidant property and modulation of cytokines involved in wound healing (Younis et al., 2021). The studies showed that green-synthesized AgNPs have valuable therapeutic potential for treating inflammation by modulation of cytokines and efficient antioxidant properties and may serve as effective therapeutic agents for the management of health disorders.

Gold nanoparticles

By preventing the synthesis of pro-inflammatory cytokines, gold nanoparticles (AuNPs) can reduce inflammation which can be achieved by interfering with the signaling pathways that regulate cytokine expression, or modulating the activity of immune cells that produce these cytokines (Cai et al., 2022). Additionally, gold nanoparticles can modulate oxidative stress and cellular signaling pathways that contribute to inflammation. These processes can help reduce inflammation and promote tissue healing (He et al., 2022).

The anti-inflammatory properties of gold nanoparticles made from green synthetic materials have been shown in several researches in various experimental models of inflammation, including asthma (Yi et al., 2020), and colitis (Sunayana et al., 2020). Gold nanomaterials synthesized using *Vitex negundo* leaf extracts exhibited strong antioxidant activity, exceeding that of the *V. negundo* extract. Additionally, these AuNPs displayed significant anti-inflammatory effects, as demonstrated by their ability to inhibit cyclooxygenase 2, and lipoxygenase, in addition to xanthine oxidase in both *in vivo* research using Swiss albino mice and *in vitro* research utilizing HeLa cells, carrageenan-induced paw edema, and writhing testing (Sunayana et al., 2020). Another investigation has demonstrated that the use of gold NPs synthesized by *Mentha piperita* in rats with asthma resulted in a reduction of inflammatory markers such as PLA2, IgE, and IL-4, along with an improvement in lung pathology. Moreover, the nanoparticles were found to increase the IFN-γ/IL-4 ratio, which indicates a shift toward Th1 immune response (Yi et al., 2020).

Gold nanoparticles possess the ability to scavenge free radicals and safeguard cells from oxidative stress, which can cause different ailments such as cardiovascular disease, Alzheimer's, and cancer (Al-Radadi, 2022). Further research is necessary to comprehensively comprehend the underlying mechanisms and enhance the characteristics of gold nanoparticles for their therapeutic applications.

Zinc and zinc oxide nanoparticles

Immunomodulatory effects of zinc oxide (ZnO) nanoparticles have been demonstrated through their synthesis using plant extracts or microorganisms, wherein they regulate cytokine production and increase phagocytosis activity (Kumar et al., 2020). Zinc nanoparticles synthesized using plant extracts or microorganisms have been demonstrated to neutralize free radicals and prevent lipid peroxidation, and antioxidant properties, which can lead to cellular damage. Zinc nanoparticles synthesized by *Withania somnifera*, demonstrate efficient antioxidant activity in DPPH (2,2-diphenyl-1-picrylhydrazyl) assay (Dhabian et al., 2021). Zinc oxide nanoparticles (NPs) made from a variety of plant extracts, such as the *indica* species *of Azadirachta*, *Murraya koenigii*, *Hibiscus Rosa-Sinensis, the oleifera Moringa*, and *Tamarindus indica*, have demonstrated considerable radical scavenging efficacy in an *in-vitro* investigation. The *Tamarindus indica* extract used to make ZnO nanoparticles demonstrated noteworthy antioxidants which may help reduce toxicity Rehana et al. (2017).

Selenium nanoparticles

Selenium (Se) NPs are a versatile and valuable micronutrient that has garnered interest in various fields since they are less toxic, have excellent bioavailability, and have biological processes such as antioxidant, anti-inflammatory, antitumor, and antibacterial activities (Hosnedlova et al., 2018). It is a crucial component needed for several biological enzymes and amino acids, including thioredoxin reductase, glutathione peroxidase, and superoxide dismutase. These enzymes are effective in scavenging free radicals and safeguarding cells against oxidative damage (Riaz and Mehmood 2012). Selenium nanoparticles (Se-NPs) are extensively employed as nutritional supplements and exhibit significant potential as drug nano-carriers in the medical field. The incorporation of phytochemicals during the green synthesis process can additionally boost the bioactivity, biocompatibility, and target binding of Se-NPs (Nikam et al., 2022).

Several bacterial species, including *Lactobacillus*, *Bifidobacterium*, *Klebsiella pneumonia*, *Rhodospirillum rubrum*, *Thaurea selenatis, and Pantoea agglomerans*, were utilized when synthesizing SeNPs (Torres et al., 2012; Menon et al., 2019; Alipour et al., 2021). Additionally, plant extracts from *Aloe vera* leaf, *Vitis vinifera*, *Emblica officinalis*, *Withania somnifera*, *Diospyros montana*, *Zingiber officinale*, *Moringa peregrina*, *Allium sativum*, *Mentha*, and *Matricaria recutita* used the sodium selenite as a basis for the formation of SeNPs Rajeshkumar et al. (2021). A review published in 2021 by Rehman et al. reported that biogenically synthesized SeNPs possess the potential to act as an antirheumatic agent. This is achieved through the activation of natural antioxidant defenses and the reduction of inflammatory indicators, radical plus non-radical species. The effectiveness of SeNPs is dependent on their concentration and size. Moreover, the use of ginger extract-mediated selenium NPs has also been shown to improve renal inflammation-induced impairment in rats by exhibiting anti-inflammatory properties mediated by antioxidants (Zahran et al., 2017).

SeNPs biosynthesized by *Lactococcus lactis* were found to have antioxidant and anti-inflammatory properties, reducing oxidative stress and inflammation in porcine intestinal epithelial cells and maintaining intestinal barrier integrity (Xu et al., 2019). The research by Pandiyan et al. (2022) synthesized the SeNPs by the *Thymus vulgaris* extract and reported its *in-vitro* anti-oxidant and anti-inflammatory properties.

Tab 1. A review of the green synthesized NPs and their biological applications

Nanoparticle	Source	Size	Application	References
Silver	*Piper nigrum*	~40-100 nm	Inhibition of TNF-α, IL-1β and 6 (IL-1β and IL-6).	Mani et al., 2015
	Punica granatum L.	~10 nm	Exhibit free radicals scavenging and potent antioxidant activity	Khorramiet al., 2019
	Cotyledon orbiculate	~10nm	Inhibiting the secretion of pro-inflammatory cytokines such as TNF- α, IL-6, and IL-1β	Tyavambiza et al., 2021
	Syzygium cumini	~47 nm	Show antioxidant and anti-inflammatory effect	Chakravarty et al., 2022
Gold	*Mentha piperita*	~10 nm	Decreased phospholipase A2, immunoglobulin E, interleukin 4, and total protein, increased interferon-γ/interleukin 4 ratios; exhibited the anti-inflammatory effect	Yi et al., 2022
	Extract of *Vitex negundo*	20–80 nm	Strong antioxidant, free radical scavenger, displayed robust anti-inflammatory activities by inhibiting cyclooxygenase 2 and lipoxygenase	Sunayana et al., 2020
	Hylocereus polyrhizus	25.31 nm	Show anti-inflammatory, anti-Alzheimer, and antioxidant activity against various in vivo cell lines	Al-Radadi 2022
Zinc	*Withania somnifera*	-	Potent anticancer as well as antioxidant activity	Dhabian et al., 2021
Zinc oxide	Stem extract of *Rubia cordifolia*	20.07 nm	Possess immunomodulatory effects by regulating the production of cytokines and increasing phagocytosis activity	Negi, 2018
	Root extract of *Polygala tenuifolia*	33.03-73.48nm	Dose-dependently exceptional anti-inflammatory action by decreasing cyclooxygenase 2, interleukins (1β, 6), and tumor necrosis factor α.	Nagajyothi et al., 2015
	The aqueous seed extract of *Caesalpinia crista*	34.67nm	Dose-dependent antioxidant activity, Radical scavenging activity	Donga & Chanda 2022

Copper nanoparticles

Due to their distinct physical, chemical, and biological characteristics, copper nanoparticles (Cu NPs) have become an attractive contender for biomedicine and might be used in a variety of applications. These nanoparticles were found to have a variety of therapeutic effects, including anti-allergic, cancer prevention, analgesic, and antibacterial activity, making them a crucial topic of study in the biomedical industry (Saranyaadevi et al., 2014). By controlling enzymes like superoxide dismutase (SOD), oxidases, and peroxidases that reduce the formation of free radicals and uphold homeostasis, copper as well as zinc can reduce oxidative stress. (Asadi et al., 2017). Similar to this, it has been demonstrated that Cu nanoparticles can effectively reduce oxidative stress caused by ROS (Ghadi et al., 2018).

Copper nanoparticles have been synthesized using various plants and their extracts, such as *Punica granatum* (Kaur et al., 2016), *Calotropis procera* (Harne et al., 2012), *Capparis spinosa* (Khatami et al., 2020), *Ocimum sanctum* (Sadanand et al., 2016), *Eucalyptus* (Kolekar et al., 2015), and *Cinnamom zeylanicum* (Sarwar et al., 2021). Copper nitrate or copper sulfate are typically used as precursors for these biosynthesis processes, which can vary in their physical and chemical processing methods. In recent work, circular Cu-NPs with a typical particle dimension ranging from 50 to 100 and 100-200 nm were fabricated using aqueous leaf extract from *Aegle marmelos correa* and showed in-vitro anti-inflammatory activity. The study suggested that Cu-NPs exert anti-inflammatory and anti-oxidative effects by stabilizing the lysosomal membrane and preventing the release of lysosomal enzymes, reducing oxidative damage, and modulating iron levels, which prevented further tissue damage (Angajala et al., 2014). Other studies have also reported the positive antioxidative and anti-inflammatory properties of copper nanoparticles mediated by *Adhathoda vasica* and *Cardiospermum halicacabum*, which was found to be dose-dependent (Thariny et al., 2020; Chandra et al., 2020).

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