

Recent Advancements and Unexplored Biomedical Applications of Green Synthesized Ag and Au Nanoparticles: A Review

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Abstract: Green synthesis of silver (Ag) and gold (Au) nanoparticles (NPs) has acquired huge popularity owing to their potential applications in various fields. A large number of research articles exist in the literature describing the green synthesis of Ag and Au NPs for biomedical applications. However, these findings are scattered, making it time-consuming for researchers to locate promising advancements in Ag and Au NPs synthesis and their unexplored biomedical applications. Unlike other review articles, this systematic study not only highlights recent advancements in the green synthesis of Ag and Au NPs but also explores their potential unexplored biomedical applications. The article discusses the various synthesis approaches for the green synthesis of Ag and Au NPs highlighting the emerging developments and novel strategies. Then, the article reviews the important biomedical applications of green synthesized Ag and Au NPs by critically evaluating the expected advantages. To expose future research direction in the field, the article describes the unexplored biomedical applications of the NPs. Finally, the articles discuss the challenges and limitations in the green synthesis of Ag and Au NPs and their biomedical applications. This article will serve as a valuable reference for researchers, working on green synthesis of Ag and Au NPs for biomedical applications.

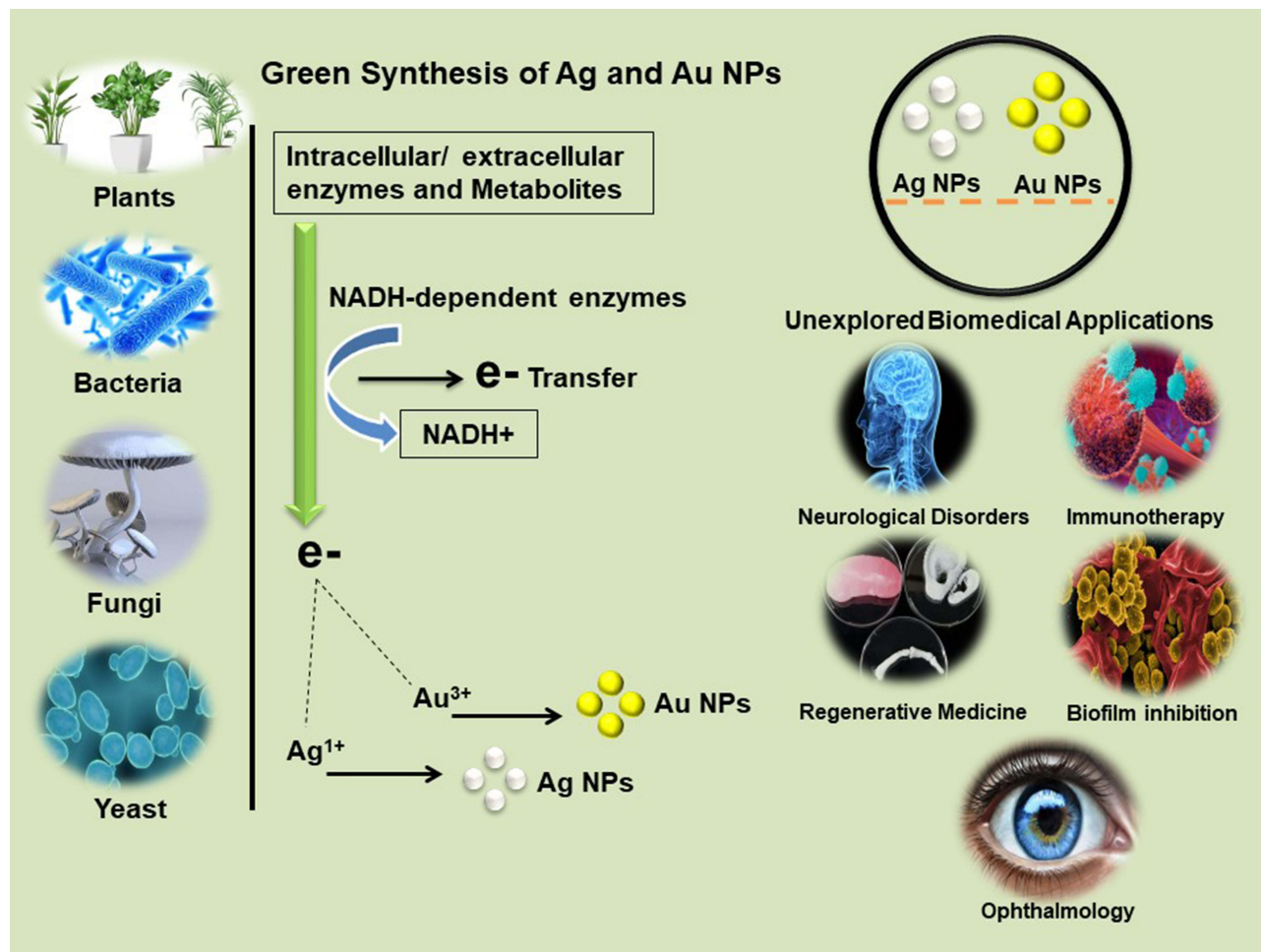
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Introduction

Silver (Ag) and gold (Au) nanoparticles (NPs) have attracted the most interest among the many types of NPs because of their outstanding qualities and diverse applications in biomedicine.¹ Particularly, the green synthesis of Ag and Au NPs is a hot area of research.² This approach uses natural resources including plants, microbes, and other biological components for NPs synthesis.³ Hence, compared to traditional methods, which frequently rely on potentially hazardous components and mechanical processes, this approach has many advantages. Overall, the green synthesis method offers a controlled, biocompatible, and sustainable approach to synthesize NPs with an extensive list of applications.⁴ In the literature, different synthesis approaches are followed for the green synthesis of NPs such as plant-mediated synthesis, microbial synthesis, bio-inspired synthesis, green chemistry approach; microwave-assisted synthesis and ultrasound-assisted synthesis approach (Table 1).

The green synthesis approach for Ag and Au NPs synthesis offers great promise for biological applications. These NPs exhibit unique physicochemical properties at the nanoscale, including high surface-to-volume ratios, improved reactivity, and adaptable optical characteristics. They are suitable for a range of biological applications, such as therapies, drug delivery, biosensing, and diagnostics as a result of their distinctive features.^{3,2} Promising novel possibilities for a range of biological applications have been made possible by the widespread use of eco-friendly procedures for the green synthesis of Ag and Au NPs.^{3,3} In addition, due to their exceptional qualities and capabilities, they serve as valuable tools for the purpose of

Graphical Abstract



diagnosis.³⁴ Similarly, these NPs can also be functionalized with specific biomolecules, like antibodies or DNA probes, enabling them to more specifically bind to pathogens or disease markers, making it easier to recognize them.³⁵ Furthermore, Ag and Au NPs developed by means of green synthesis have antibacterial and anticancer characteristics, making them interesting candidates for therapeutic applications.³⁶ Ag NPs have been the focus of extensive research due to their remarkable antibacterial effects against a number of pathogens, including bacteria, viruses, and fungi.³⁷ On the other hand, Au NPs have drawn interest due to their potential in photothermal therapy and targeted drug delivery.³⁸ Due to their special characteristics, such as their small size and large surface area, green synthesized Ag and Au NPs have been found to offer potential useful tools in the field of drug delivery.³⁹ Additionally, they can also be utilized as effective biosensors because of their excellent sensitivity, selectivity as well as their optical characteristics.⁴⁰ Lastly, when incorporated into tissue engineering scaffolds or hydrogels, these NPs have unique advantages because they preserve the material's structure and can change cellular behavior by encouraging cell adhesion, proliferation, and differentiation.⁴¹

In recent years, Ag and Au NPs have received a great deal of attention for their prospective applications in a variety of biomedical fields. Their individual applications in therapy, tissue engineering, regenerative medicine, and diagnostics have all been explored in various studies. The synthesis and characterization of Ag and Au NPs were the main focus of many earlier studies, but their potential use in biomedical fields was not fully explored. Furthermore, despite individual studies that have provided insightful information, there remains a lack of comprehensive review articles that compile

Table 1 Various Green Synthesis Approaches Employed for the Production of Ag and Au NPs

Synthesis Approach	Source	Classification	Resulting NPs	Size (nm)	Reference
Microbial Synthesis	<i>Bacillus cereus</i>	Bacteria	Ag NPs	45–90	[5]
	<i>Bacillus cereus</i>	Bacteria	Ag NPs	18–39	[6]
	<i>Bacillus subtilis</i>	Bacteria	Ag NPs	15.9–80	[7]
	<i>Bacillus endophyticus</i>	Bacteria	Ag NPs	5–35	[8]
	<i>Nocardiopsis flavescens</i>	Bacteria	Ag NPs	5–50	[9]
	<i>Shewanella loihica</i>	Bacteria	Au NPs	2–15	[10]
	<i>Caldicellulosiruptor changbaiensis</i>	Bacteria	Au NPs	20–60	[11]
	<i>Micrococcus yunnanensis</i>	Bacteria	Au NPs	15–55	[12]
	<i>Fusarium oxysporum</i>	Fungi	Au NPs	20–50	[13]
	<i>T. koningii</i>	Fungi	Au NPs	10–14	[14]
Bio-Inspired Synthesis	<i>Alternaria alternate</i>	Fungi	Au NPs	12–29	[15]
	Raspberry leaves extract	Plant	Ag NPs	NA	[16]
	<i>Hibiscus Tiliaceus</i> flower extracts	Plant	Ag NPs	21–26	[17]
	Banana waste	Plant	Ag NPs	14.1	[18]
Green Chemistry Approach	<i>Sapindus emarginatus</i> pericarp extract	Plant	Ag NPs	5–20	[19]
	<i>Tamarindus indica</i> fruit extract	Plant	Au NPs	500–520	[20]
	<i>Delphinium Chitralense</i> tuber extract	Plant	Au NPs	100–300	[21]
	<i>Ganoderma lucidum</i> extract	Plant	Ag and Au NPs	50 and 40	[22]
	<i>Ganoderma lucidum</i> extract	Plant	Ag NPs	NA	[23]
	<i>Sargassum muticum</i> extract	Plant	Ag and Au NPs	41 and 10.4	[24]
Microwave-Assisted Synthesis	<i>Cornelian cherry</i> fruit extract	Plant	Ag and Au NPs	16 and 19	[25]
	<i>Myristica fragrans</i> leaves extract	Plant	Au NPs	18.7	[26]
	<i>Eupatorium odoratum</i> leaves extract	Plant	Au NPs	10–20	[27]
Ultrasound-Assisted Synthesis	<i>Versicolor</i> and <i>Boletus edulis</i> mushroom extract	Fungi	Ag NPs	82–88	[28]
	<i>Borassus flabellifer</i> fruit extract	Plant	Ag and Au NPs	7–9 and 5–7	[29]
	Corn starch	Plant	Ag NPs	2.9–44	[30]
	Banana leaves extract	Plant	Ag NPs	80–100	[31]

existing literature, comprehend limitations, and provide recommendations for future research despite particular studies that have offered valuable information.⁴²

This review article represents a significant contribution into the field. The article offers an up-to-date and comprehensive review of both Ag and Au NPs potential uses across multiple biomedical fields. It not only evaluates recent research but also indicates unexplored areas for further research, providing scientists and researchers an outline to follow. The article also discusses the classical methods of green synthesis, recent advances, and novel strategies for the green synthesis of Ag and Au NPs, advantages and disadvantages, along with unexplored biomedical applications and future directions.

The research on green synthesis of Ag and Au NPs is increasing day by day due to their unexpected properties and applications. The number of articles published on Ag and AuNPs are increasing continuously since 2010–2023 (Figures 1a and b). Moreover, the number of articles published annually on Ag NPs is more than that of Au NPs which reflects that research on Ag NPs are in more progress than Au NPs.

Methods for Green Synthesis of Ag and Au NPs

Ag and Au NPs are synthesized using environmentally friendly methods to improve environmental sustainability, reduce reliance on hazardous chemicals, and minimize energy consumption. Following are a few well-known green synthesis methods for Ag and Au NPs:

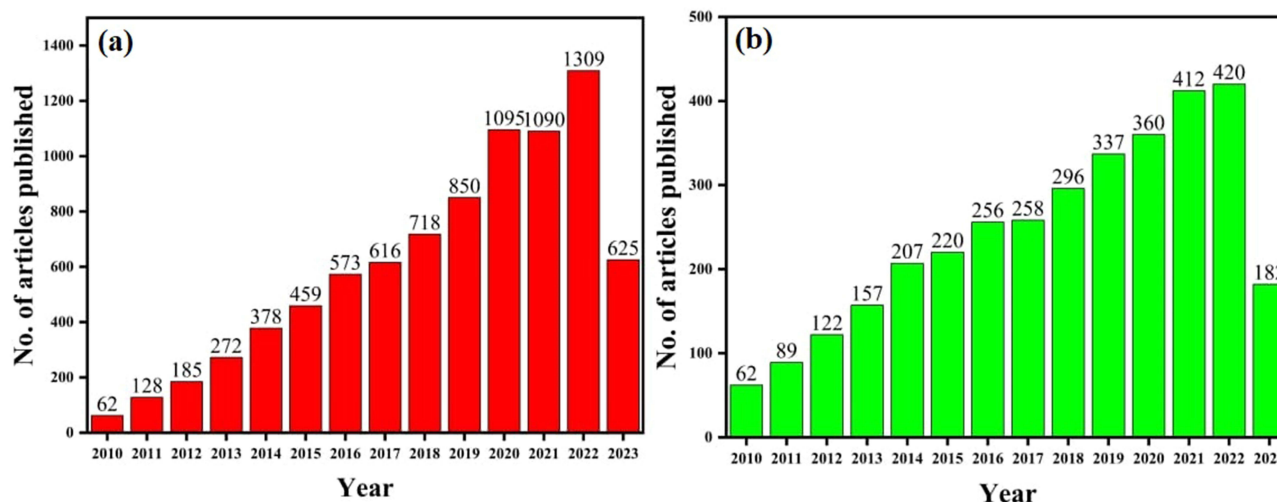


Figure 1 Number of articles published on (a) Ag NPs (b) Au NPs as indicated by the Scopus database at date 25 June 2023 (Searched with a keyword “green synthesis of Ag NPs” and “green synthesis of Au NPs”).

Plant Extracts Mediated Synthesis of Ag and Au NPs

Plant extract-mediated synthesis is a viable and sustainable approach for the green synthesis of Ag and Au NPs. In this technique, NPs are synthesized from a variety of plant components, including stems, leaves, seeds, and flowers, using bioactive chemicals as reducing and stabilizing agents. The utilization of plant extracts has several advantages, such as their easy availability, abundance, as well as the ability to modify the properties of NPs.⁴³ The potential for nanoparticle production in stems, in particular the bark or interior tissues, has been studied. It has been demonstrated that many phytochemicals found within these plant components, especially tannins, alkaloids, and phenolic compounds, which substantially reduce metal ions and promote the development of well-defined Ag and Au NPs.⁴⁴ Leaves are another very often used plant components for the synthesis of Ag and Au NPs. They include large amounts of bioactive compounds such polyphenols, terpenoids, and flavonoids, all of which have strong reducing properties. These compounds are necessary for reducing metal ions and controlling the synthesis of Ag and Au NPs.⁴⁵

Similarly, potential has also been identified with the utilization of different plant seeds for green synthesis of NPs. In seed extracts, proteins, enzymes, and secondary metabolites act as reducing and capping agents to produce Ag and Au NPs. Ag and Au NPs with regulated sizes and shapes have been produced using seed extracts.³³ Another source for production of Ag and Au NPs using plant extracts are flowers. Among the bioactive components included in samples extracted from flower petals and reproductive tissues that aid in reducing metal ions and stabilizing NPs are anthocyanins, flavonoids, and volatile oils. Ag and Au NPs with various morphologies and optical properties have been produced using flower extracts.⁴⁶

Enzymes Mediated Synthesis of Ag and Au NPs

Enzyme-mediated synthesis is a highly effective and ecologically friendly method for synthesizing Ag and Au NPs. Enzymes can operate as biocatalysts in the reduction of metal ions to produce NPs when the reaction conditions are favorable.⁴⁷ Because of their unique catalytic capabilities, enzymes can preferentially attach to metal ions and facilitate their reduction, resulting in the generation of NPs. Reductases, oxidases, and dehydrogenases are frequently used as enzymes in this process due to their ability to transport electrons and speed up the reduction of metal ions through the utilization of co-factors such Nicotinamide adenine dinucleotide (NADH) or Nicotinamide adenine dinucleotide phosphate (NADPH).⁴⁸ The ability of enzyme-mediated synthesis to function at mild conditions, such as neutral pH and room temperature, is one of its advantages. Under typical lab conditions, this technique reduces the amount of energy required and provides simple synthesis. The mild reaction conditions also maintain the enzymes' stability and activity, allowing for effective Ag and Au NPs production.⁴⁹

Other benefits of enzyme-mediated synthesis include the exceptional selectivity of enzymes, which allows for exact control of NPs size, shape, and surface properties. Several studies in the literature support this mechanism. For instance,

research by Wilner et al⁵⁰ demonstrated the role of enzymes in templating the synthesis of AuNPs with defined shapes. Additionally, Schneidewind et al, work explored the enzymatic control of AgNPs size through a specific enzymatic reduction process. These findings collectively highlight the key role of enzymes in providing selectivity and precision in the synthesis of NPs, supporting the mentioned mechanism.⁵¹ Due to their biocompatibility and natural availability, enzymes are suitable for use in biological applications. Lack of hazardous compounds or residues during the synthesis process enhances the biocompatibility of the resulting NPs.⁵² The introduction of additional activities to the NPs is made possible by the adaptability of enzyme-mediated synthesis using various biomolecules and substrates. Enzymes can be developed or altered to include specific peptide sequences or ligands with targeting capabilities or increased stability in biological environments.⁵³

Bio-Waste Materials Mediated Synthesis of Ag and Au NPs

Agricultural waste items such fruit peels, straw, husks, and stalks have attracted a lot of interest due to their affordability and sustainability as a source of bioactive compounds for the development of Ag and Au NPs.⁵⁴ Proteins, phenolic compounds, polysaccharides, and organic acids that serve as reducing and stabilizing agents are just a few of the biomolecules found in these waste products. When biomolecules and metal ions interact, the metal ions are reduced and NPs are created.^{47,55} NPs are produced using the bioactive compounds that have been extracted using extraction methods from the waste materials. The affordability, cost-effectiveness, and ability to modify the properties of NPs are only a few benefits of this synthesis technique.⁵⁶

Microorganisms Mediated Synthesis of Ag and Au NPs

Ag and Au NPs production using microorganism-mediated synthesis has been demonstrated to be an ecologically friendly process. This method makes use of microorganisms such bacteria, fungus, and yeast that effectively reduce metal ions and promote the creation of NPs.^{57,58} Since bacteria contain proteins or enzymes like nitrate reductase, which act as reducing agents and stabilise the NPs, they offer benefits such ease of cultivation, rapid growth, and the ability to be genetically modified to boost the production of NPs.⁵⁹ Fungi, including yeasts and filamentous fungi, produce extracellular enzymes like reductases and cytochrome P450 enzymes, which effectively reduce metal ions and initiate nanoparticle synthesis. Fungi can tolerate a wide range of pH and temperature conditions and are capable of producing NPs in aqueous environments.⁶⁰ Various yeast species, such as *Saccharomyces cerevisiae*, *Candida species*, and *Pichia pastoris*, possess reducing enzymes and metabolites that contribute in metal ion reduction ultimately resulting in the synthesis of NPs.⁶¹ High yields, scalability, and the possibility of intracellular synthesis within yeast cells are only a few advantages of yeast-mediated synthesis.⁶² The yield of Ag and Au NPs synthesis by microbial-mediated green synthesis can vary commonly based on multiple factors, including the specific microorganisms used, reaction conditions, and concentrations of reagents. The yield is often expressed in terms of the concentration (ppm) or mass of synthesized NPs obtained per unit volume or weight of the reaction mixture. For instance, the concentration of Ag and Au NPs was determined by Balakumaran, M. D. et al through ICP-AES analysis. Interestingly, *A. terreus* produced about 214 ppm of AgNPs/litre of culture filtrate when 01 mM silver nitrate was challenged and for AuNPs, it was 196 ppm.⁶³ Lastly, it is important to keep in mind the biosafety factors, which include the choice of non-pathogenic microorganisms, assessment of metal ion sources for possible impurities, and thorough toxicity studies covering cytotoxicity, allergenicity, and long-term impacts.⁶⁴

Mechanisms of Green Synthesis of Ag and Au NPs

Biomolecules-Mediated Reduction

Biomolecules from a variety of natural sources, such as plants, microorganisms, and biowaste products, play an active role in this process by acting as reducing agents. Proteins, enzymes, polysaccharides, phenolic compounds, and organic acids are examples of biomolecules that can reduce metal ions and then generate NPs as a result of their interaction. The precise biomolecules used in this procedure may vary depending on the synthesis technique employed.⁶⁵

Bio-Reduction by Microorganisms

Microorganisms including bacteria, fungi, and yeast hold great promise for speeding nanoparticle creation because they include enzymes or proteins with inherent metal ion reduction capacities.⁶⁶ For instance, nitrate reductase may be

produced by bacteria, whereas cytochrome P450 enzymes and reductases are produced by fungi. The ability of these microorganisms to reduce helps with the transformation of metal ions into NPs.⁶⁷

Phytochemical-Mediated Synthesis

During the synthesis of NPs, phytochemicals from plants, such as flavonoids, polyphenols, terpenoids, and alkaloids, serve as both reducing and stabilizing agents. These phytochemicals must first be extracted using the appropriate solvents in order to create plant extracts or infusions.³³ The plant extracts are then mixed with metal ions, which causes their reduction and the creation of NPs⁶⁸ (Figure 2).

Advantages and Disadvantages of Green Synthesis of Ag and Au NPs

Advantages of Green Synthesis of Ag and Au NPs

The biomedical application of green-synthesized Ag and Au NPs can be attributed to a combination of the inherent properties (antimicrobial properties and biocompatibility) of these materials and the specific characteristics they acquire through the green synthesis process ie better control over size and shape, ease of functionalization, and minimum toxicity.

Polyvinylpyrrolidone which was commonly used as a capping or stabilizing agent in conventional synthesis of NPs. However, it can be non-biodegradable and may have potential long-term environmental impacts such as genotoxic effects as reported by Nymark, Penny et al.⁶⁹ Cetyltrimethylammonium Bromide is used as a surfactant in some conventional synthesis methods. It can be associated with toxicity and environmental concerns to marine life.⁷⁰ The green synthesis of Ag and Au NPs possesses a number of advantages over conventional approaches. First of all, it is an environmentally friendly approach that minimizes the use of hazardous chemicals and decreases the effects of NPs production on the environment.⁷¹ Secondly, by using abundant and renewable natural resources like plants, microorganisms, and bio-waste materials as ingredients for the production of NPs, encourages sustainability and renewability.⁷² Furthermore, considering that they use low-cost starting materials as well as simple reaction conditions, green synthesis approaches are inexpensive.⁷³ Additionally, they work at mild reaction conditions, such neutral pH and ambient temperature, which saves energy while keeping laboratory procedures simple.⁷⁴ With the use of green

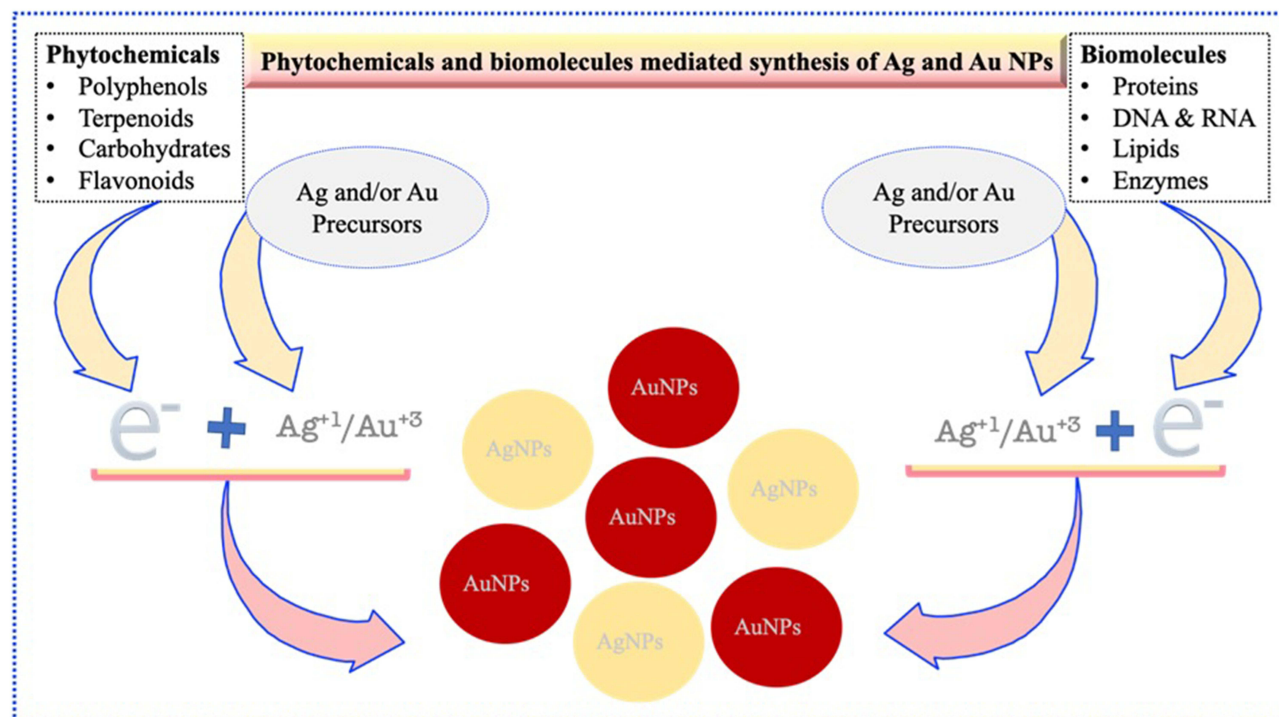


Figure 2 Phytochemicals and biomolecules act as reducing and capping agents. These molecules donate electron(s) to Ag^+ and/or Au^{+3} ions. The Ag^+ and/or Au^{+3} ions are reduced to their corresponding neutral atoms. The Ag and Au atoms nucleate to form Ag and/or Au NPs. Subsequently, the capping agents (phytochemicals or biomolecules) in the reaction mixture stabilize the NPs.

synthesis, NPs may possess their size, shape, and morphology precisely controlled, providing specific features that improve their performance in certain applications.⁷⁵ Lastly, Ag and Au NPs synthesized through green approaches frequently exhibit excellent biocompatibility, making them suitable for various biomedical applications including drug delivery, imaging, and biosensing.⁷⁶

Disadvantages of Green Synthesis of Ag and Au NPs

Green synthesis techniques may yield fewer NPs than conventional methods, which limits their potential for large-scale manufacturing.⁷⁷ Green synthesis techniques usually require longer reaction times due to the relatively slow reduction process, which may delay the synthesis process.⁷⁸ Additionally, as they include complex reaction processes and a number of factors that must be carefully optimized in order to produce the necessary nanoparticle characteristics, green synthesis approaches require substantial testing and knowledge.⁵⁷ Moreover, it can be technically challenging and time-consuming to extract and purify bioactive compounds from natural sources, such as plants or microbes, in order to synthesize high-purity NPs. While green synthesis techniques enable precise control of some aspects, such as size, shape, and surface chemistry, it can be more challenging to achieve so for other features, such as crystallinity.⁷⁹

Emerging Development and Novel Strategies for the Synthesis of Ag and Au NPs

In order to improve the effectiveness, scalability, and functionality of the synthesis of Ag and Au NPs, ongoing research and novel approaches are continuously being developed (Table 2).

Microwave-Assisted Synthesis

Microwave irradiation is now able to be used to quickly and very efficiently produce NPs. It enables more rapid reaction kinetics, reduces the necessary reaction time, and improves the yield of NPs synthesis. Additionally, the shape and size of the resulting NPs may be precisely controlled using this technique, making it very attractive for large-scale production.⁸⁰ Precursor ions, a reducing agent, and a stabilizing agent are first combined in a reaction mixture to produce Ag and Au

Table 2 Emerging Strategies for the Synthesis of Ag and Au NPs

Synthesis Method	Description	Reference
Microwave-assisted synthesis	Utilizes microwave irradiation to rapidly and effectively produce NPs, resulting in quicker reaction kinetics, shorter reaction time, increased yield, and precise control over size and shape.	[80]
Plant-mediated synthesis	Utilizes plant extracts or chemicals from plants as reducing and stabilizing agents to synthesize NPs, offering a sustainable and eco-friendly approach with the potential for unique nanoparticle characteristics.	[81]
One-Pot synthesis	Simultaneously stabilizes and reduces metal ions in a single reaction vessel, optimizing the synthesis process by eliminating multiple steps, resulting in increased productivity, faster reaction times, and better control over nanoparticle characteristics.	[82]
Bio-inspired synthesis	Mimics biological and natural processes by using biomolecules as catalysts or templates for nanoparticle synthesis, allowing for precise control over size, shape, and surface chemistry, leading to customized characteristics and improved functionality.	[83,84]
Electrochemical synthesis	Utilizes electrochemical technologies to synthesize NPs, either directly on conductive surfaces or in solutions, by carefully controlling electrode voltage and current density, enabling scalability and precise control over size, shape, and composition of NPs.	[85]
Templated synthesis	Guides nanoparticle production using templates or scaffolds, which can be biological structures, self-assembling materials, or porous substances, allowing for the construction of complex nanostructures with control over size, shape, and dispersion.	[86,87]
Micro-fluidic synthesis	Utilizes micro-fluidic platforms at the micro scale level to achieve excellent control over reaction conditions and mixing dynamics, resulting in better control of nanoparticle synthesis, quick mixing, consistent heat transfer, and accelerated mass transfer, enabling the production of monodisperse NPs with high repeatability.	[88,89]
Hybrid and composite NPs	Combines multiple materials or incorporates functional components to produce hybrid and composite NPs, offering versatility, synergistic effects, enhanced stability, and multifunctionality, with applications in catalysis, sensing, and energy storage.	[90]

NPs using a microwave.⁹¹ Microwave heating enables metal ions to reduce rapidly and uniformly, which promotes the development of small clusters or nuclei.⁹² As more metal ions are reduced and deposited onto the surfaces of these clusters, which will keep expanding, the stabilizing agent regulates growth and prevents agglomeration. Once the necessary size has been achieved, the reaction is stopped and the NPs are filtered to get rid of byproducts or unreacted substances. By altering the reaction conditions, size control can be achieved.⁹³

Plant-Mediated Synthesis

Plant extracts or compounds derived from plants are utilized in plant-mediated synthesis to produce NPs. Utilizing a range of plant species, including medicinal herbs and herbal extracts, is a sustainable and environmentally friendly approach.⁹⁴ Additionally, the phytochemicals found in plants are capable of imposing unique properties on the resulting NPs. In the process of producing Ag and Au NPs by plants, plant extracts can serve as both reducing and stabilizing agents. Selecting and harvesting plant material that contains bioactive compounds is the first step in the process. The metal ions are subsequently reduced and Ag and Au atoms are formed when the plant extract is combined with precursor ions of Ag and Au. These components act as nucleation sites during the development of NPs. At the precise point of their production, the NPs are stabilized by the bioactive components in the plant extract. To remove any impurities, the synthesized NPs are inspected and thoroughly cleaned.^{32,95}

One-Pot Synthesis

The production of Ag and Au NPs in a single reaction vessel is a faster and more efficient approach known as “one-pot synthesis.” Preparing a reaction mixture comprising a stabilizing agent, a reducing agent, and Ag and Au precursors is the first step in the process. Metal ions must first be reduced by the reducing agent to generate Ag and Au atoms, which act as the nucleation sites for the production of NPs. The stabilizing agent controls the development process to prevent agglomeration and ensure the stability of NPs. The resultant NPs are next scrutinized and cleaned of any impurities.^{96,97}

Bio-Inspired Synthesis

Bio-inspired synthesis uses biological and natural processes to mimic the synthesis of NPs. Examples of biomolecules that can be modified to serve as catalysts or templates for the production of NPs include peptides, DNA, and proteins.⁹⁸ The size, shape, and surface chemistry of the NPs can be carefully controlled to produce customized properties and enhanced functioning.⁸³ Bio-inspired synthesis of Ag and Au NPs draws inspiration from nature to create NPs using biological entities or processes. In this method, natural sources like plants, microbes, or biomolecules are chosen and their special qualities such as reducing or stabilizing agents are used to promote the production of NPs. The bio-inspired source interacts with the Ag and Au precursor ions, reducing them and consequently producing NPs as a result. The specific chemicals or enzymes present in the bio-inspired source act as a nucleation, growth, and stabilization guidance for the process. The resulting NPs can be further modified for specific uses in a variety of areas after being characterized. A sustainable and ecologically friendly way to create NPs, bio-inspired synthesis offers the potential for modified nanoparticle properties and a wide range of applications.^{99,100}

Electrochemical Synthesis

For the production of NPs, a variety of electrochemical technologies may be employed. By carefully controlling the electrode voltage and amount of current, NPs can be generated directly on conductive surfaces or in solutions. Due to the precise control it allows over nanoparticle size, shape, and composition, electrochemical synthesis is feasible for industrial-scale production.⁸⁵ Ag and Au NPs may be produced electrochemically in an electrochemical cell where metal ions are reduced at the cathode to produce NPs.¹⁰¹ An electrolyte solution including an Ag and Au salt is first developed, then the electrochemical cell is assembled. By generating a potential difference between the anode and the cathode, which also triggers the nucleation and growth of NPs on the cathode surface, metal ion reduction is accelerated. Nanoparticle development can be regulated and stabilized by adding chemicals to the electrolyte. The resultant NPs are assessed and processed to remove impurities.¹⁰²

Templated Synthesis

In templated synthesis, the synthesis of NPs is controlled by the application of templates or scaffolds. These replica templates could be biological, self-assembling, or made of porous substances. Templated synthesis, allowing for control

over nanoparticle size, shape, and dispersion, enables the production of complex nanostructures with desired functionality.⁸⁶ Templated synthesis of Ag and Au NPs involves using templates or frameworks to guide the formation and control the properties of the NPs. Choosing a template and modifying its surface is the first step in the process. The template is then treated with metal ions, which proceed through reduction and growth to produce NPs. After synthesis, the template is removed in order to isolate the NPs. The characterized templated NPs can be used for a number of biomedical applications.¹⁰³

Micro-Fluidic Synthesis

Micro-fluidic platforms provide exceptional control over reaction conditions and mixing dynamics at the micro scale.¹⁰⁴ Quick mixing, constant heat transfer, and faster mass transfer are advantages of this technique, which improves control over the synthesis of NPs. Microfluidic synthesis can produce monodisperse NPs with excellent uniformity.⁸⁸ In order to accurately regulate the flow, mixing, and reaction conditions for nanoparticle synthesis, Ag and Au NPs are synthesized utilizing microfluidic devices. First, the precursor solutions are added to the microfluidic apparatus, where they mix and react to produce NPs. Through the enclosed microfluidic environment, nucleation, growth, and nanoparticle properties are better controlled. Once the synthesized NPs have been gathered and purified, stabilizing agents may be used to prevent agglomeration.¹⁰⁵

Hybrid and Composite NPs

Hybrid and composite NPs incorporate valuable components or combine various materials to improve efficiency. These NPs' synergistic actions, improved stability, or multifunctionality make them particularly versatile. Energy storage, sensing, and catalysis are among the uses for hybrid and composite NPs.⁸⁶ Ag and Au NPs are combined with other materials to create hybrid and composite NPs that possess novel properties and functionalities. The required components are integrated throughout the synthesis process using techniques like surface functionalization, co-reduction synthesis, or core-shell synthesis. These techniques enable the systematic incorporation of different components into the nanoparticle structure. The resulting NPs are carefully scrutinized and modified for specific applications including energy conversion, sensing, imaging, and drug delivery. The incorporation of various materials provides a wide range of alternatives because of the synergistic effects and unique combination of properties exhibited by hybrid and composite NPs. This opens up new possibilities for innovative applications in various industries.⁹⁰

Biomedical Applications of Green Synthesized NPs

Green synthesized NPs have displayed potential in various biomedical fields such as drug delivery, tissue engineering, diagnostics, cancer therapy, ophthalmology, and dental care (Figure 3).

Drug Delivery Systems

Green synthesized NPs can be modified with ligands or antibodies that specifically target diseased cells or tissues. This targeted accumulation improves the efficacy of drug delivery, minimizes off-target effects, and enhances therapeutic outcomes¹⁰⁶ (Table 3). Additionally, they can be engineered for carrying drugs on their surface or within their structure. Drug release can be modulated through modification of nanoparticle composition, size, and surface properties, resulting in sustained and controlled release profiles that extend therapeutic effects and minimize the frequency of drug administration.¹⁰⁷ Furthermore, Green synthesized NPs protect drugs against environmental factors including light, heat, and moisture attributable to their modified surface characteristics and stabilizing agents. The integrity of the drugs is improved, and the shelf life is extended.¹⁰⁸ Green synthesized NPs, particularly those made from bioactive chemicals or plant extracts, increase the solubility and bioavailability of natural or herbal medicines. As a result, they can be effectively utilized as a source of delivery and used in the field of drug delivery sciences.¹⁰⁹

Furthermore, they can also be designed as multifunctional platforms that can deliver multiple drugs simultaneously. This provides avenues for combination therapy, so that multiple drugs or therapeutic agents can be administered together to effectively target numerous pathways or disease sites.¹¹⁰ In addition, these NPs also have imaging properties, acting as contrast materials in MRI, CT, or fluorescence imaging procedures, which facilitate non-invasive visualization and monitoring of drug delivery mechanisms, disease progression, and therapy response. They are able to combine therapeutic and diagnostic

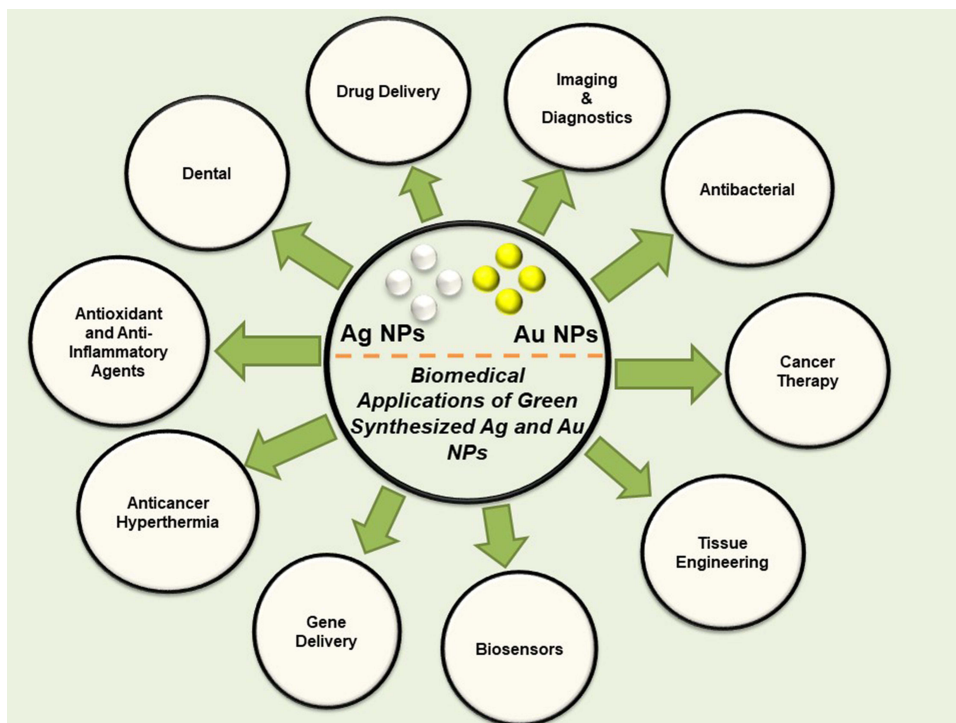


Figure 3 Biomedical Applications of Green Synthesized Ag and Au NPs.

features to develop theranostic platforms. These technologies enable simultaneous drug delivery and imaging, enabling real-time drug distribution monitoring, personalized therapy, and treatment efficacy evaluation.¹³⁶

Saha et al physically attached a number of antibiotics, including ampicillin, kanamycin, and streptomycin, to non-functionalized spherical AuNPs with a diameter of roughly 14 nm. Consequently, compared to their free form, conjugated antibiotics demonstrated greater stability and bacterial growth suppression.¹³⁷ Methotrexate, a folic acid analog, is primarily utilized as a cytotoxic anti-cancer drug. It was conjugated to 13 nm colloidal Au NPs to interfere with the metabolism of folate in cancer cells. According to the study reports, the quantity of AuNP-conjugated methotrexate in tumor cells was higher than that of free methotrexate after the drug’s carboxylic groups were able to interact with the surface of Au NPs during the overnight incubation. Similarly, compared to free methotrexate, the conjugated version had a cytotoxic effect that was 07 times greater in Lewis lung cancer animal models.¹³⁸

Table 3 Summarized Overview of Biomedical Applications of Green Synthesized NPs

Application	Description	References
Drug Delivery	<ul style="list-style-type: none"> Green synthesized NPs with ligands or antibody modifications enable targeted delivery of drugs to specific cells or tissues. Precise control over composition, size, and surface characteristics allows controlled drug release. Green-synthesized NPs enhance drug stability and shelf life. Green synthesized NPs improve solubility and bioavailability of natural or herbal drugs. Potential for co-delivery of multiple therapeutic agents. Non-invasive imaging capabilities for visualization. Biocompatibility and reduced toxicity compared to conventional methods. 	[110,111]
Medical Imaging and Diagnostics	<ul style="list-style-type: none"> Green synthesized NPs serve as contrast agents in various medical imaging techniques. Fluorescent properties enable visualization of cellular processes. Generation of acoustic waves for high-resolution imaging. Functionalized Green synthesized NPs for biosensors and diagnostic assays. Real-time monitoring of drug distribution and treatment response. Portable diagnostic devices for rapid on-site testing. 	[112,113]

(Continued)

Table 3 (Continued).

Application	Description	References
Antibacterial Agents	<ul style="list-style-type: none"> • Antibacterial properties of Green synthesized NPs particularly silver (Ag) or copper (Cu) NPs. • Disruption of bacterial cell structures and inhibition of growth. • Broad-spectrum activity against Gram-positive and Gram-negative bacteria. • Synergistic effects with conventional antibiotics. • Inhibition of biofilm formation and disruption of existing biofilms. • Incorporation into delivery systems for improved efficacy. • Lower toxicity to mammalian cells. • Eco-friendly synthesis methods. 	[114,115]
Cancer Therapy	<ul style="list-style-type: none"> • Targeted delivery of anticancer drugs using modified Green synthesized NPs. • Improved drug stability, solubility, and bioavailability. • Green synthesized NPs as imaging agents for early cancer detection and treatment monitoring. • Hyperthermia induction for localized cancer cell destruction. • Photosensitization in photodynamic therapy. • Enhanced effectiveness of radiotherapy. • Biocompatible and eco-friendly properties. 	[116]
Tissue Engineering	<ul style="list-style-type: none"> • Green synthesized NPs as carriers for controlled drug delivery in tissue engineering. • Functionalization with bioactive molecules and growth factors. • Biodegradability and integration with host tissue. • Inherent bioactive properties for regeneration and reduced inflammation. • Promotion of angiogenesis and prevention of infections. • Potential for better tissue regeneration and repair. 	[117–119]
Biosensors and Diagnostics	<ul style="list-style-type: none"> • Physicochemical properties of Green synthesized NPs enable sensitive biosensors. • Functionalization with biorecognition elements for selective binding. • Specific detection and quantification of biomolecules, pathogens, or chemical compounds. • Non-invasive visualization and monitoring of biological processes. • Real-time monitoring of air, water, or soil quality. • Environmental sustainability and public health benefits. 	[120,121]
Gene Delivery	<ul style="list-style-type: none"> • Green synthesized NPs as safe and biocompatible vehicles for gene delivery. • Efficient cellular uptake and release of transferred genes. • Surface modifications and targeting molecules for site-specific delivery. • Protection and stability of genetic material. • Reduced risk of long-term accumulation or adverse effects. • Sustainability and biocompatibility advantages. 	[122]
Anticancer Hyperthermia	<ul style="list-style-type: none"> • Green synthesized NPs for localized hyperthermia in anticancer treatments. • Selective absorption and conversion of light into heat. • Minimization of harm to healthy tissues and cells. • Synergistic effects with chemotherapy or immunotherapy. • Reduced toxicity and personalized therapeutic effects. • Precise regulation of temperature increase within the tumor region. 	[123–127]
Antioxidant and Anti-Inflammatory Agents	<ul style="list-style-type: none"> • Green synthesized NPs as eco-friendly antioxidant and anti-inflammatory agents. • Scavenging of free radicals and reactive oxygen species. • Reduction of oxidative stress and prevention of cellular damage. • Decreased release of inflammatory mediators and cytokines. • Protection against oxidative damage and inflammation-induced injury. • Targeted delivery and reduced systemic toxicity. • Synergistic effects with other antioxidants or anti-inflammatory agents. 	[128–132]
Dental Applications	<ul style="list-style-type: none"> • Green synthesized NPs for oral health and dental treatments. • Antimicrobial activity against oral pathogens. • Inhibition of microbial growth and prevention of dental caries, periodontal diseases, and oral infections. • Enhanced mechanical properties of dental materials. • Controlled drug delivery for localized treatment. • Visualization and diagnostic capabilities. • Improved dental restoration longevity and reduced risks of secondary caries. 	[33,133–135]

Imaging and Diagnostics

In the field of healthcare, Green synthesized NPs have a number of uses as potential imaging and diagnostic tools. They can be utilized in medical imaging procedures as contrast agents. These NPs improve the visibility of particular tissues or structures

through modifying their surface properties, assisting in the precise identification and characterization of diseases.¹³⁹ They are useful tools for fluorescence-based imaging since they may be engineered to exhibit fluorescence qualities. These NPs emit light at particular wavelengths that make it possible to see cellular functions and spot alterations brought on by disease.¹⁴⁰ These NPs generate acoustic waves when exposed to laser light, which may be recognized and turned into high-resolution images to make it easier to see biological structures.¹¹²

Additionally, ligands or antibodies can be used to functionalize Green synthesized NPs to make biosensors and diagnostic procedures. Through their interactions with target molecules like disease indicators, these NPs enable the sensitive and accurate identification of diseases using a variety of diagnostic procedures. Similarly, combining therapeutic and diagnostic functions play a role in theranostics. In order to optimize patient outcomes, medical professionals can evaluate therapy response, modify doses, and personalize medicines with the use of these NPs.¹⁴¹ Furthermore, Green synthesized NPs have been incorporated into portable diagnostic tools, allowing for rapid on-site testing. At the point of care, these technologies quickly and accurately diagnose patients by identifying specific disease markers or infections in samples.¹⁴²

Lee et al used the hepatitis B virus (HBV) core protein as a scaffold for developing ultrasmall AuNPs with a particle size of 1.4 nm. Both subcutaneous and deep-tissue tumors in living mice were significantly affected by these AuNPs in terms of MRI and magnetic hyperthermia therapy.¹⁴³ The absorption cross-section of AuNPs is thousands of times greater than that of popular chemical dyes like indocyanine green or rhodamine-6G. AuNPs have been effectively employed as molecularly targeted contrast agents for PAI in animal models due to their exceptional performance. Larger diameter AuNPs, however, are not well eliminated by the kidney, which restricts their use in clinical settings.¹⁴⁴ Consequently, the development of particular ultrasmall AuNPs for PAI is required. AuNPs with particle diameters of roughly 5 nm and 40 nm were coupled to a monoclonal anti-EGFR (epidermal growth factor receptor; EGFR) antibody by Sokolov et al and utilized to identify cancer cells. The findings demonstrated that the 5 nm AuNPs retained the same PA signal as the 40 nm AuNPs and exhibited high near-infrared absorption. Due to their incredibly small diameter, the 5 nm AuNPs surprisingly demonstrated exceptional tissue penetration and in vivo clearance ability. These findings showed that ultrasmall AuNPs would be a practical in vivo solution for sensitive PAI of cancer cells.¹⁴⁵

Antibacterial Agents

Green-synthesized NPs, including Ag NPs, possess inherent antibacterial properties. They have the ability to damage bacterial cell structures, inhibit bacterial growth. In a study, *Escherichia coli* strains were subjected to 10:1 reaction mixture mediated green synthesized Au NPs of *Macadamia* nut shell extract, upon antibacterial assessment the zone of inhibition was increased 2 times in comparison to crude extract (Figure 4).^{146,147} In addition, Ag and Au NPs are capable of eliminating bacteria because of their capacity to penetrate bacterial cell walls, interact with internal components, produce reactive oxygen species (ROS), impair membrane integrity, and inhibit vital cellular functions.¹⁴⁸ Additionally, both Gram-positive and Gram-negative bacteria are susceptible to the antibacterial effects of green synthesized NPs, because they have a broad-spectrum antibacterial coverage. Due to their effectiveness towards a variety of bacterial species, including frequently encountered pathogenic strains, they are effective for treating bacterial infections.¹⁴⁹ Additionally, they exhibit synergistic effects when used in combination with conventional antibiotics. Combination therapy minimizes the dose of antibiotics required, reduces the incidence of antibiotic resistance, and improves antibacterial activity.¹¹⁴

The “Bacterial biofilms” are a significant problem in antibacterial drug resistance and represent significant challenge in the treatment of bacterial infections due to antibiotic resistance.¹⁵⁰ Green synthesized NPs have demonstrated potential in preventing the formation of new biofilms and destroying those that already exist, making bacteria more sensitive to antibacterial treatments. For instance, the biofilm production by *L. Monocytogenes* and *S. marcescens* was inhibited by Au NPs synthesized from extract of *Trachyspermum ammi* (Figure 5).¹⁵¹ Furthermore, these NPs can be incorporated into a number of delivery systems, such as hydrogels, coatings, and NPs loaded with conventional antibiotics. These delivery methods enable NPs and antibiotics to be delivered for an extended period of time at the infection site, enhancing their antibacterial properties and reducing the frequency of administration.¹⁵² When it comes to toxicity studies, these NPs exhibit lower toxicity to mammalian cells compared to conventional antibacterial agents, making them potentially safer for therapeutic use.¹⁵³

Flavonoid glycerin was utilized by Alsamhary et al as a capping and reducing agent during the synthesis of AuNPs. Furthermore, an evaluation was conducted on the antibacterial activity of synthetic AuNPs against opportunistic bacterial pathogens responsible for respiratory tract infections. Research on bacteria has verified that AuNPs have broad-spectrum

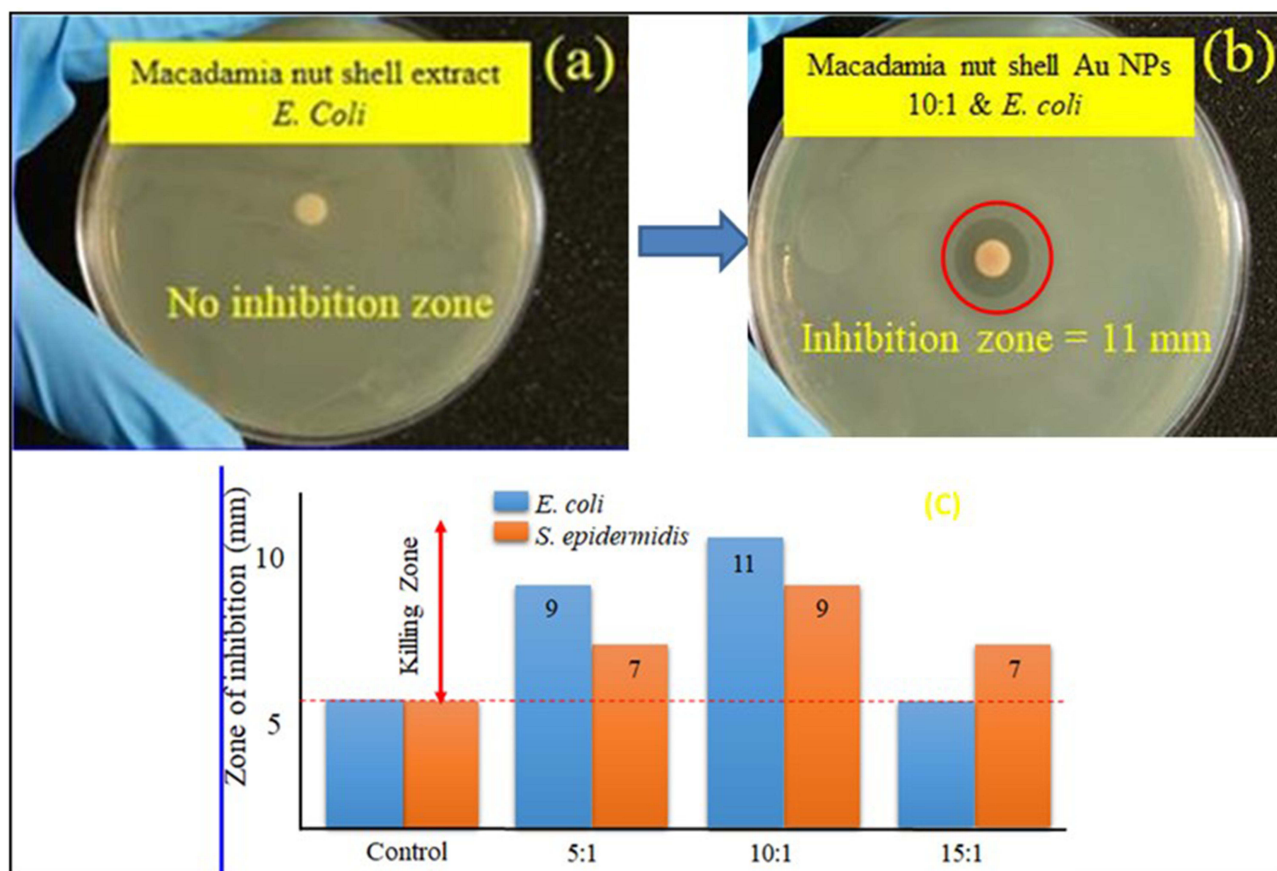


Figure 4 A representative petri dish sample of sterile disc and plant extract alone (a), *Escherichia coli* subjected to 10:1 reaction mixture mediated green synthesized Au NPs (b), and (c) indicative outcomes for the antibacterial assessment (The zone of inhibition was increased 2X).

Notes: Reprinted from Dang H, Fawcett D, Poinern GEJ. Green synthesis of gold nanoparticles from waste macadamia nut shells and their antimicrobial activity against *Escherichia coli* and *Staphylococcus epidermidis*. *International Journal Of research in medical sciences*. 2019;7(4):1171–1177. Creative Commons. ¹⁴⁶

antibacterial action against both Gram-positive and Gram-negative tested bacteria.¹⁵⁴ A novel method of developing AuNPs with glucosamine functionalization was described by Govindaraju et al. During the study, a laser and UV light were applied to AuNPs. The findings showed that compared to pure AuNPs, functionalized AuNPs and AuNPs exposed to UV and laser light demonstrated enhanced antibacterial properties.¹⁵⁵ According to Bajaj et al, free metal nanoparticles and natural peptides with AuNPs at the end exhibited lower antibacterial and antifungal effects than those with AuNPs at the end. It was shown that the antibacterial effect of AuNPs encapsulated with the cationic peptide (1-His1-Arg-OMe) surpassed that of conventional antibiotics.¹⁵⁶ Additionally, a family of nonantibiotic drugs including mercaptopuridine-coated AuNPs have been shown to have bactericidal and broad-spectrum antibacterial effects on multidrug resistant bacteria and superbugs.¹⁵⁷

AuNPs based on polyvalent amino sugars were presented by Yang et al as therapeutic option for wounds infected with super bacteria. Polyvalent amino sugar-based AuNPs were produced by modifying AuNPs with d-glucosamine (GluN). Au-GluN not only has exceptional super bacterial infection wound healing properties but also does not damage red blood cells outside of the body.¹⁵⁸ A number of studies have demonstrated that AuNPs, cefotaxime, and ciprofloxacin work against all strains of *Salmonella*. Conventional antibiotics encourage the production of reactive oxygen species, which kills bacteria, but AuNPs disrupt the equilibrium of cations. *Salmonella* cells undergo apoptosis as a result of this mechanism.¹⁵⁹ Long-term resistance to MDR bacteria is an urgent issue in healthcare, and Li et al found that cationic and hydrophobic functionalized AuNPs can successfully inhibit the growth of 11 clinical MDR isolates, including Gram-negative and Gram-positive bacteria, providing a promising strategy for antibiotic resistance.¹⁶⁰ Dextrose-coated AuNPs (D-AuNPs) were the subject of a study by Badwaik et al on their antibacterial properties. The research demonstrated the effectiveness of D-AuNPs against both Gram-positive and Gram-negative bacteria, as well as their bacteriostatic and bactericidal properties.¹⁶¹ AuNPs with chitosan,

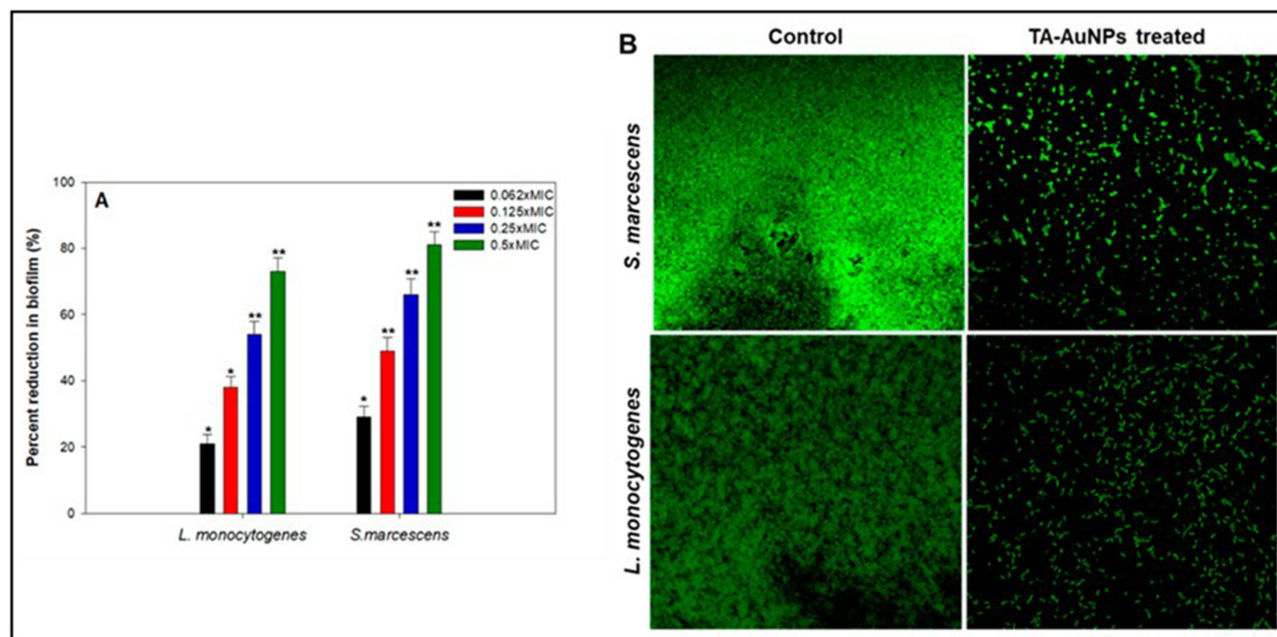


Figure 5 (A) Effect of sub-MICs of TA-AuNPs on biofilm formation. *Denotes significance at $p \leq 0.05$ and **Denotes significance at $p \leq 0.005$. **(B)** Confocal laser scanning microscopic images of *L. Monocytogenes* and *S. marcescens* biofilm in the absence and presence of $0.5 \times$ MICs of TA-AuNPs (Gold NPs synthesized from extract of *Trachyspermum ammi*). The biofilm production was inhibited by TA-AuNPs.

Notes: Reprinted from Perveen K, Husain FM, Qais FA, et al. Microwave-assisted rapid green synthesis of gold nanoparticles using seed extract of *Trachyspermum ammi*: ROS mediated biofilm inhibition and anticancer activity. *Biomolecules*. 2021;11(2):197. Creative Commons.¹⁵¹

ethylene glycol chitosan, and poly(γ glutamic acid) caps were developed by Inbaraj et al, researchers also assessed and described the particles' catalytic and antibacterial properties. Each of the three artificially functionalized AuNPs exhibits a characteristic antibacterial action.¹⁶² Wang et al developed stable daptomycin Au nanoflowers in moderate lab conditions by using daptomycin (Dap) micelles as a template and reducing agent. Under near-infrared light illumination at 808 nm, Dap-AuNPs suppressed the growth of bacterial strains and cancers.¹⁶³

Cancer Therapy

In the field of cancer therapy, Green synthesized NPs demonstrate great promise as innovative approaches to addressing cancer-related issues. They can be modified to bind specifically to cancer cells or tumor markers using certain ligands or antibodies. With this targeted strategy, chemotherapy drugs can be delivered precisely, enhancing their accumulation at the tumor site while reducing their toxicity to healthy tissues.¹⁶⁴ Additionally, Green synthesized NPs enhance the stability, solubility, and bioavailability of anticancer drugs by encapsulating it. This avoids challenges related to conventional chemotherapy via enhancing drug efficacy, extended drug release pattern, and improved therapeutic outcomes.¹⁶⁵ Moreover, they can act as imaging agents to help with early cancer detection, precise tumor location, and tracking effectiveness of the therapy.¹¹³ These NPs preferentially absorb and convert light spectrum into heat when exposed to near-infrared light, which leads to localized hyperthermia and the destruction of cancer cells while minimizing harm to healthy tissues.¹⁶⁶

Green synthesized NPs offer a viable route for anticancer hyperthermia, offering cutting-edge strategies to treat cancer by localized heating.¹⁶⁷ Gold or carbon-based NPs are two examples of NPs made via green synthesis that have special photothermal characteristics.^{112,168,169} These NPs selectively absorb near-infrared light when exposed, transforming it into heat and producing reactive oxygen species (ROS) that can specifically destroy cancer cells while causing minimal amounts of damage to healthy surrounding tissues, enhancing the effectiveness of anticancer treatments (Figure 6).¹⁷⁰ They can also be designed to release heat in a regulated manner, allowing for exact control of the elevation in temperature within the tumor area. Similarly, they can also be used in combination with chemotherapy or immunotherapy to achieve synergistic effects. As a result of their relative safety and ecologically friendly nature, Green synthesized NPs exhibit a lower impact on healthy cells and tissues.¹⁷¹

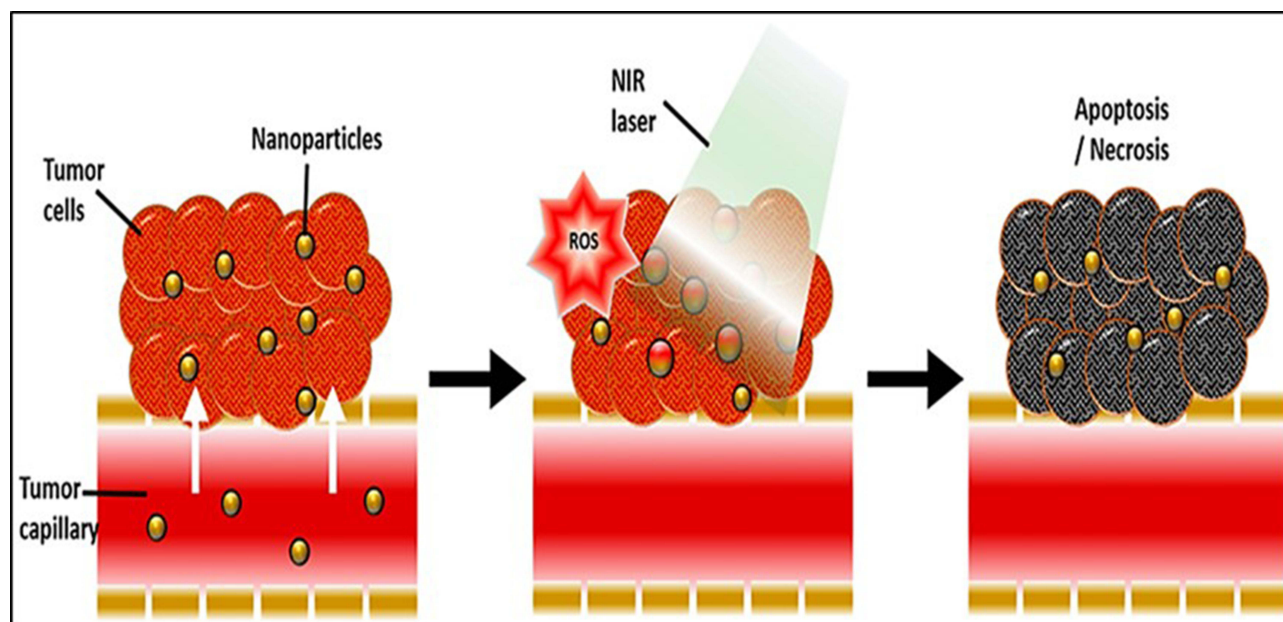


Figure 6 When exposed to near-infrared light (NIR laser), Au NPs selectively absorb and convert light into heat, resulting in localized hyperthermia and generation of ROS resulting in selective apoptosis/necrosis of cancer cells.

Notes: Reprinted from Kim HS, Lee DY. Near-infrared-responsive cancer photothermal and photodynamic therapy using gold nanoparticles. *Polymers*. 2018;10(9):961. Creative Commons.¹⁷⁰

AuNPs with a size range of 8–15 nm have the potential to be produced in large quantities using the hydroethanolic extract of Brazilian Red Propolis and its components. AuNPs exhibited a dose dependent cytotoxic action in T24 and PC-3 cells. The compounds with the highest in vitro cytotoxic impact were AuNP dichloromethane and AuNP extract. Furthermore, pathways connected to apoptosis promoted the cytotoxicity of biogenic nanoparticles. A surface plasmon resonance (SPR) band was visible in AuNPs at 535 nm.¹⁷² AuNPs and carboxymethylcellulose were combined to create a nanocomposite (ACMC-AuNPs). CMC-AuNPs showed the lowest IC₅₀ values ($2.56 \pm 0.19 \mu\text{g/mL}$) in MCF-7 cells, indicating a potent cytotoxic action. In cells treated with CMC-AuNPs, the percentage of overall apoptosis was $38.81 \pm 1.99\%$, while the control group had $0.61 \pm 0.022\%$. The results lead to conclude that these CMC-AuNPs' anticancer effect is caused by increasing caspase-8 and -9 activity and lowering VEGFR-2 levels, which in turn trigger necrosis and apoptosis in breast cancer cells. In accordance with cell cycle, CMC-AuNPs also stopped the cell cycle at the G₁/G₀ phase.¹⁷³

Tissue Engineering

Green synthesized NPs demonstrate promise as tissue engineering tools, offering innovative approaches to improve tissue regeneration and repair. They have the potential to be used in tissue engineering as controlled drug delivery platforms. They may contain growth factors, cytokines, or drugs that will release locally in a sustained and controlled manner to promote tissue regeneration and regulate the healing process. In order to direct cellular behavior and tissue development, they can also be functionalized with bioactive compounds or growth factors. In addition to minimizing their adverse effects on cells and tissues and promoting better integration with the host tissue, they disintegrate over time, avoiding the need for removal. The green synthesis method makes use of elements from the natural world; these NPs also include built-in bioactive qualities like anti-oxidant, anti-inflammatory, antibacterial, or angiogenic activities. These features assist tissue engineering by improving vascularization, promoting regeneration, and lowering inflammation and infection susceptibility.¹⁷⁴ Green-synthesized NPs can be used as imaging agents to track and monitor tissue engineering structures. They might utilize imaging probes to offer real-time monitoring of implanted scaffolds, cell behavior, and tissue growth. As a result, the regeneration process may be enhanced and tissue engineering techniques' efficacy may be assessed.¹⁷⁵

Yi et al proposed that AuNPs may interact mechanically with proteins in the cytoplasm and extracellular matrix to activate the p38 MAPK signaling pathway, which in turn causes the up-regulation of osteogenic genes and the down-regulation of

adipogenic genes. This mechanism explains how AuNPs induce osteogenic differentiation.¹⁷⁶ On the other hand, Zhang et al proposed that AuNPs raised the degree of ERK phosphorylation/total ERK and that the ERK/MAPK pathway is activated during the differentiation and mineralization of primary osteoblasts.¹⁷⁷ AuNPs at 20 nm are more efficient than those at 40 nm. In addition to promoting skeletal muscle regeneration and repair, activation of this pathway can increase myoblast adhesion and proliferation.¹⁷⁸ Mahmoud et al examined the effects of several nanostructures on bone marrow-derived mesenchymal stem cells (BM-MSCs) in order to determine their capacity to induce osteogenic development. They studied Hydroxyapatite NPs, AuNPs, Chitosan NPs, Gold/hydroxyapatite NPs, and Chitosan/hydroxyapatite NPs. AuNPs and Au/HA-NPs have the most significant impact among all.^{179,180} AuNPs improved the bone development of adipose-derived stem cells (ADSCs) at 30 and 50 nm in size, according to Ko et al.¹⁸¹ Li et al discovered that GNP size and shape influenced the osteogenic differentiation of hMSCs by controlling Yes-associated protein (YAP) activation through a comparison of multiple GNP forms and sizes.¹⁸² There were concentration-dependent relationships found in the study of superparamagnetic iron oxide (SPIO)-Au core-shell nanoparticles for stimulating osteogenic differentiation of MC3T3-E1 cells.¹⁸³

Biosensors and Diagnostics

With the development of green-synthesized NPs, biosensors and diagnostics have encountered an enormous evolution, providing new possibilities for the precise and sensitive detection of various analytes. Green synthesized NPs have special physicochemical characteristics that raise the sensitivity of biosensors. With excellent precision and sensitivity, they can detect analytes at low concentrations due to their large surface area to volume ratio, adjustable optical qualities, and significant signal amplification abilities. Biorecognition components like antibodies, enzymes, DNA, or aptamers can be used to functionalize them. These components allow for the selective binding and recognition of target analytes, resulting in highly specialized biosensors that are capable of precisely identifying and measuring a variety of biomolecules, pathogens, or chemical substances. The aforementioned parts enable the selective binding and recognition of target analytes, providing highly specialized biosensors that are capable of precisely identifying and measuring a variety of biomolecules, pathogens, or chemical substances.¹⁸⁴ Additionally, they enable non-invasive visualization and monitoring of biological processes, disease progression, and therapy response because of their unique optical and magnetic features. They can be incorporated into sensor platforms for continuous monitoring of the quality of the air, water, or soil, assisting in preserving the environment and protecting public health.^{113,185}

For the purpose of identifying multiple allergy protein types on a single strip, the multiplex lateral flow immunoassay offers a viable platform. The red and blue colors were represented by the SPR bands of spherical and desert rose-like AuNPs, which were detected at 525 nm and 620 nm, respectively.¹⁸⁶ AuNPs were functionalized with two distinct capture proteins, and each form was responsible for identifying a single allergen. Spherical and desert rose-like AuNPs could, respectively, reveal the presence of casein and hazelnut proteins in biscuits and hazelnut flowers using the multi-chromatic lateral flow test probes. Compared to the traditional enzyme-linked immunosorbent assay and polymerase chain reaction (PCR), this approach was both quicker and less expensive. Finding the allergic DNA is an additional strategy for treating food allergies. Hybridization chain reaction was used by researchers since it did not require expensive equipment or enzymes.¹⁸⁷ AuNPs-based techniques have the potential to offer a simple and easy detection method. For instance, Ochratoxin A (a toxic mycotoxin) detection using semi-quantitative and visual methods based on Au nanorod color shift has been described.¹⁸⁸ Free antibodies that would not bind to the test line were occupied if zearalenone was present in the sample. In the scenario that zearalenone was not present, unbound antibodies would attach to the antigen coated on the test line. In this instance, red conjugation would occur on the test line due to functionalized AuNPs' affinity for free antibodies. In contrast, when zearalenone was present, it did not exhibit any color. Zearalenone detection's limit of detection was 5 ng L⁻¹. In order to easily detect zearalenone and aflatoxin B1 simultaneously, two types of identifiable Au nanoclusters were linked by aflatoxin B1 aptamer and zearalenone aptamer, respectively.¹⁸⁹

L-proline-modified Au nanoclusters, which emit blue light, and bovine serum albumin-modified Au nanoclusters, which emit red light can be used as detectors for aflatoxin. According to Di Nardo et al, aflatoxin B1 and type-B fumonisins can be detected immediately using a multiplex lateral flow immunoassay that is based on a single test line labeled with both antigens. Aflatoxin B1 and type-B fumonisins, respectively, were targeted by two different types of AuNPs. After synthesizing the nanoparticles using a sodium citrate-induced tetrachloroauric acid reduction, red spherical AuNPs with a mean diameter of around 30 nm and an SPR band at 525 nm were coupled with an aflatoxin-specific

antibody. Antibody specific to type-B fumonisins was used to connect blue desert rose-like nanoparticles. These nanoparticles, which have an SPR band at 620 nm and a mean diameter of roughly 75 nm, were synthesized using a seed-mediated growth technique. Aflatoxin B1 would competitively bind to red AuNPs upon their addition, preventing them from adhering to the test line. The test line displayed blue nanoparticles that resembled desert roses. Blue desert rose-like nanoparticles were unable to conjugate to the test line in samples contaminated with type-B fumonisins. The test line had a red appearance. A color loss on the test line would occur if aflatoxin B1 and type-B fumonisins were present at the same time. On the other hand, in the event that neither of the pollutants was present, the test line would be purple. Additionally, this method's validity was put to the test. In 30 blank samples, there were no false positive results, and in 60 fortified samples, there were no false negative results. Furthermore, every positive sample was accurately identified. Through a red-green-blue data evaluation, the relative standard deviation was found to range between 1.5% and 5.9%. It might be quickly, easily, and affordably applied to cereal-based foods.¹⁹⁰ Moreover, an another study by Valentini and Pompa states that *Listeria monocytogenes* can be taken up by many antibody-coated AuNPs, resulting in the formation of dimers, trimers, or multi-aggregates of AuNPs. Using dynamic light scattering, the amount of *Listeria monocytogenes* could be measured; 35 colony-forming units (CFU) mL⁻¹ were found in PBS, while 22 CFU g⁻¹ were found in samples of lettuce. Gastrointestinal disorders can be brought on by the spore-forming, Gram-positive bacterium *Bacillus cereus*, which is present in both food and soil. Although gel electrophoresis-based detection and the PCR assay are frequently employed, they are both time-consuming and labor-intensive.¹⁹¹ AuNPs and asymmetric PCR were utilized to find the living cells' ssDNA in order to accurately determine the concentration of *Bacillus cereus*.¹⁹²

Gene Delivery

In terms of safety, biocompatibility, and sustainability, green synthesized NPs have been regarded as a viable and creative method for gene delivery. These NPs can be modified to effectively transfer genetic material into target cells due to their biocompatible nature, indicating that they are less likely to trigger adverse consequences or provoke immune responses.¹⁹³ Additionally, surface modifications are occasionally used to facilitate effective cellular absorption and the release of transferred genes within the cells.¹⁹⁴ Furthermore, adding specific ligands and targeting molecules to their surfaces facilitates the transport of genes to the desired site. It significantly improves the specificity and efficacy of gene transfer by making it possible to deliver genes selectively to appropriate cells. Targeted gene delivery improves the therapeutic potential of gene-based treatments and minimizes off-target effects.¹⁹⁵

A drug delivery nanopatform mediated by AuNPs was developed to co-deliver doxorubicin and siRNA targeting polo-like kinase 1 (PLK1). Polyethyleneimine was applied to AuNPs to help PLK1 assemble on the surface. A pH-sensitive linker containing a thiol group at one terminal end was used to load doxorubicin onto nanoparticles for controlled release. In a cancer therapy model, the lowered IC50 value clearly showed the synergistic effect of combination drugs and gene administration over individual delivery.¹⁹⁶ A gold nanovehicle that is highly effective in delivering doxorubicin hydrochloride and siRNAs in combination with chemotherapy and photothermal treatment was developed using dsDNA and MMP-2 cleavable peptides, modified with AS1411 aptamer. According to the results, targeted gene silencing and tumor inhibition were achieved with this combined treatment. A synergistic effect that promoted the eradication of long-lived tumors and an enhanced survival rate of mice were noted after nearly a month of treatment with Au-siRNA-PAA-AS1411 nanoparticles loaded with DOX, given once every three days. In comparison to the passive genetic therapy group, which showed a 30% tumor inhibition ratio and a 0% survival rate, the combined genetic, chemotherapeutic, and photothermal treatment group demonstrated more than 90% tumor inhibition ratio (tumor signal) and an approximately 67% survival rate.¹⁹⁷

Antioxidant and Anti-Inflammatory Agents

Green synthesis techniques use sustainable production techniques and natural resources like plant extracts or biological components.¹⁹⁸ This aspect aligns with eco-friendly values and promotes the development of environmentally conscious antioxidant and anti-inflammatory agents. By providing novel applications as antioxidant and anti-inflammatory agents, Green synthesized NPs shows potential for managing oxidative stress and inflammation.¹⁹⁹ These NPs can scavenge free radicals and reactive oxygen species, minimizing oxidative stress and the cellular damage linked to many diseases. They

also control the amount of cytokines, chemokine's, and other inflammatory mediators released, which lowers inflammation and its adverse effect.²⁰⁰

Studies have demonstrated that AuNPs have antioxidant applications, since they can efficiently scavenge DPPH free radicals in a shorter period of time. This may be the result of AuNPs' capacity to neutralize DPPH free radicals by donating electrons or hydrogen ions.²⁰¹ Green synthesized AuNPs were reported to have a greater capacity to scavenge free radicals than an extract of the same plant that did not contain nanoparticles.²⁰² Dipankar and Murugan also reported an association of a similar nature. This might be the result of antioxidants (such polyphenols) in the plant extract adhering to the AuNPs' surface. This might be the result of antioxidants (such polyphenols) in the plant extract adhering to the AuNPs' surface.²⁰³ In addition to their ability to scavenge free radicals like DPPH, AuNPs have also been shown to scavenge ABTS and nitric oxide. This makes them a viable option for the cosmetics industry, where they can be employed in the formulation of anti-aging creams and sunscreens.²⁰⁴ It further raises the likelihood that AuNPs will be extremely useful in the key fight against cancer and liver illnesses as an antioxidant agent.

Dental Applications

Green synthesized NPs indicate promise in a variety of dental applications, providing revolutionary options for dental health and treatment operations. Utilizing biocompatible and non-toxic ingredients, green synthesis techniques guarantee the safety and compatibility of NPs with oral tissues.²⁰⁵ These NPs have antimicrobial activity against bacteria, fungi, and viruses which cause tooth decay, periodontal disease, and oral infections in humans.²⁰⁶ This antimicrobial activity effectively inhibits microbial growth. Dental materials like resin composites and dental cement benefit from the addition of Green synthesized NPs since it increases their mechanical qualities, durability, and longevity while lowering the possibility of subsequent cavities or restoration failure.²⁰⁷

Caries is a dental condition where the enamel is broken away by the action of acidogenic organisms such as lactobacillus and *Streptococcus mutans* (*S. mutans*). Either salivary malfunction or a diet high in carbohydrates are the causes.²⁰⁸ Because of their nanosize, AuNPs have a greater surface area that facilitates increased interaction with both organic and inorganic molecules. Hernández Sierra et al assessed the effects of zinc oxide nanoparticles (ZnPs), AgNPs, and AuNPs on *S. mutans*, as well as their bacteriostatic and bactericidal properties. AgNPs (0.0976 to 100 µg/mL), AuNPs (0.192 to 197 µg/mL), and ZnPs (3.90 to 4000 µg/mL) were the three nanoparticle concentrations that were studied. Using the liquid microdilution approach, the minimum inhibitory concentration (MIC) was determined. The findings demonstrated that, compared to AuNPs and ZnPs, AgNPs exhibited better antibacterial action at lower concentrations.²⁰⁹ Park et al investigated the impact on *S. mutans* at low plasma temperatures using AuNPs (30 nm). Bacterial viability stains and colony-forming unit counts (CFU) were used to calculate the survival rate. The study's findings demonstrated that the addition of AuNPs enhanced *S. mutans*' ability to be killed by low-temperature plasma. This may be the result of AuNPs increasing plasma energy and stress toward *S. mutans*' cell walls.²¹⁰ Elgamily et al evaluated the antibacterial activity of Chlorhexidine gluconate-CHX (0.2%) and NanoCare (AuNPs and AgNPs) against *S. mutans*. Both NanoCare and CHX disinfection shown a considerable reduction in the number of bacteria when tested against Gram positive cariogenic bacteria (*S. mutans*), while CHX demonstrated a significantly greater rate of bacterial inhibition. This could be because NanoCare's gold ions, which are released from AuNPs, reduce the disinfectant's antibacterial efficacy. Nonetheless, it demonstrated that, in contrast to conventional agents, the innovative addition of AuNPs to the cavity disinfectant might enhance the material's antibacterial activity and reduce the incidence of secondary caries.²¹¹

Advantages of Biomedical Applications of Green Synthesized Ag and Au NPs

Ag and Au NPs synthesized using green synthesis approach provide a number of benefits over conventional NPs in biomedical applications. Utilizing plant resources, natural extracts, or other ecologically friendly techniques, green synthesis techniques reduce the consumption of hazardous chemicals and encourage sustainability.^{43,212} Secondly, Ag and Au NPs synthesized by green synthesis approach frequently demonstrate excellent biocompatibility, indicating their compatibility with biological systems.²¹³ In comparison to their counterparts made using conventional synthesis methods, NPs synthesized via green synthesis techniques frequently use non-toxic or low-toxic ingredients.^{214,215} Au NPs synthesized through green synthesis approach possess better stability, allowing them to hold onto their characteristics and effectiveness for longer periods of time.

For NPs to be reliable and effective in biological applications, this stability is essential.^{2,216} Green-synthesized Ag and Au NPs also offer the advantage of tunable properties.²¹⁷

Ag and Au NPs, particularly those synthesized via a green synthesis procedure, exhibit antibacterial properties. Due to their ability for inhibiting the growth of many bacteria and pathogens, these NPs are helpful for applications such as wound healing, infection control, and antibacterial coatings.²¹⁸ Additionally, they can also be functionalized with biomolecules like antibodies, peptides, or enzymes to improve their selectivity and targeting.^{122,219} Furthermore, they can be used in a variety of scenarios, including cancer therapy, wound healing, biosensing, tissue engineering, and diagnostics.^{220,221}

Unexplored Biomedical Applications and Future Directions

As previously mentioned, green-synthesized Ag and Au NPs have demonstrated significant potential in a variety of biological applications, but there are still a number of unexplored possibilities (Figure 7). In order to further advance the fields of biomedical engineering and medicine, these disciplines present interesting future applications for environmentally friendly synthesized Ag and Au NPs.

Neurological Disorders

Green synthesized Ag and Au NPs could be effective in treating neurological disorders. Due to their ability to target neural pathways and to cross the blood-brain barrier (BBB), drugs can be precisely administered to the brain while using them.²²² Future research in this domain might concentrate on using these environmentally friendly NPs as drug delivery systems for neurological diseases like Alzheimer's, ALS, Huntington's disease, Motor Neuron disease, and Parkinson's

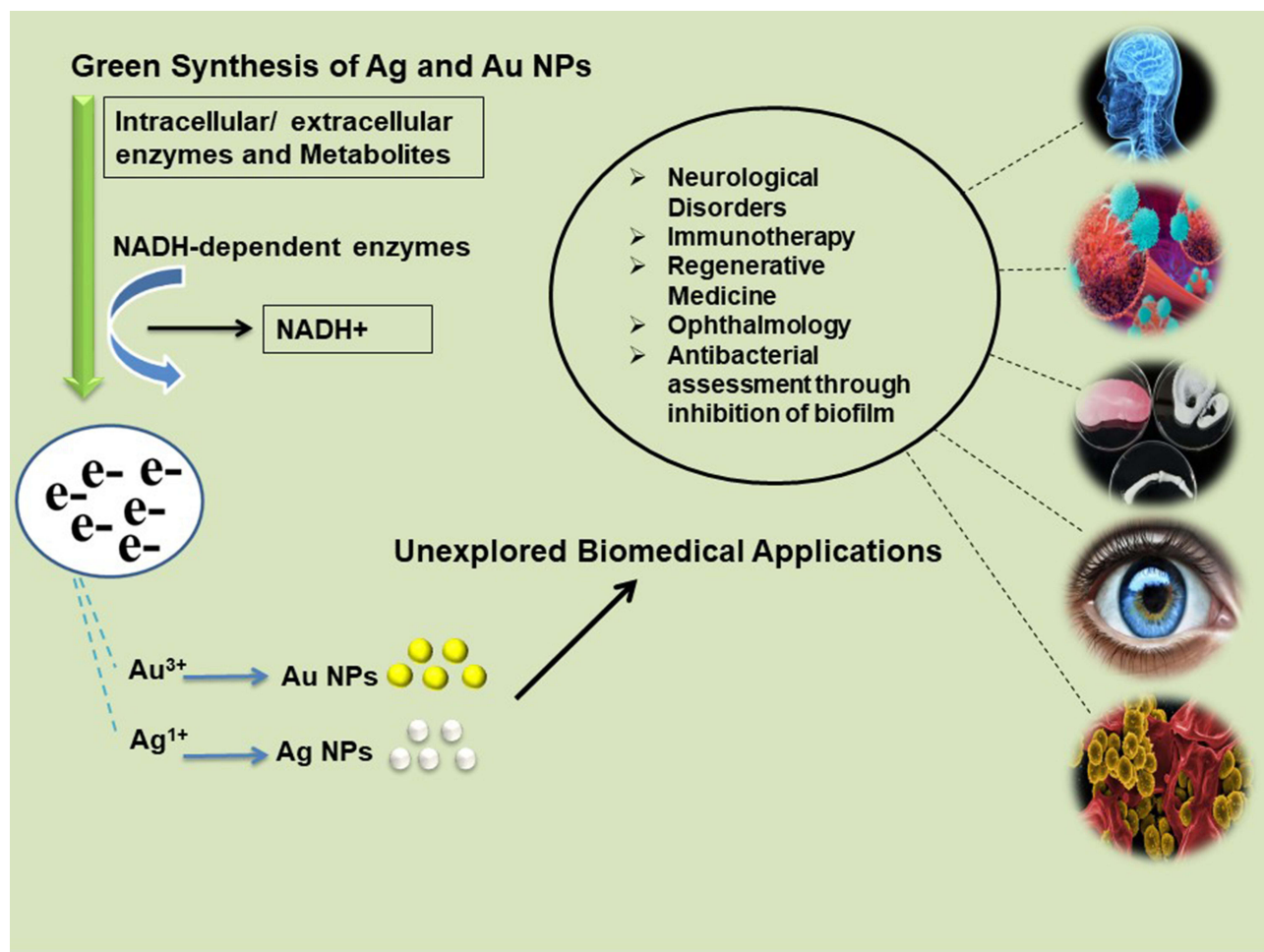


Figure 7 Unexplored biomedical applications of Green Synthesized Ag and Au NPs.

disorders. In addition, future studies should also focus on utilizing green synthesized Ag and Au NPs in order to uncover the effects of these NPs in reducing the oxidative stress and inflammation linked to neurodegenerative conditions.

Immunotherapy

Green synthesized Ag and Au NPs are potentially helpful in immunotherapy, particularly for the treatment of cancer. These NPs may function as vaccine or immunostimulatory drug delivery systems, enhancing the immune response to tumors and enhancing therapeutic outcomes. Their unique properties allow for the targeted delivery of drugs, which could improve the accuracy and potency of immunotherapeutic treatments.^{223,224} Future studies should focus on co-delivery of Ag and Au NPs along with immuno-stimulatory drugs and vaccinations for promoting therapeutic results.

Regenerative Medicine

Green-synthesized Ag and Au NPs could help in the development of regenerative medicine procedures. For the purpose of promoting cellular development, differentiation, and tissue regeneration, they can be included into the scaffolds or matrices used in tissue engineering.²²⁴ Future research in this area must combine tissue engineering scaffolds and matrices with Ag and Au NPs to explore their regeneration potential. Future studies might look into their ability to modify the stem cell microenvironment and promote stem cell proliferation and differentiation.

Ophthalmology

The use of Ag and Au NPs produced by green synthesis in ophthalmology is an area that needs more research. These NPs may be assessed for the delivery of specific drugs to the eye as well as for the treatment of eye infections, glaucoma, macular degeneration, and other ocular diseases.^{225,226} Future studies may also enable imaging and diagnosis of many ocular diseases using the optical properties of Ag and Au NPs.

Antibacterial Assessment Through Inhibition of Biofilm

Ag and Au NPs produced by green synthesis have shown promise in inhibiting biofilm formation and disrupting existing biofilms, rendering bacteria more susceptible to antibacterial agents.¹⁵⁰ However, there are many bacterial strains showing resistance to antibiotics due to formation of biofilm around their colonies. Future research should concentrate on using green synthesized Ag and Au NPs to combat different bacterial strains that form biofilms, including *Methicillin-resistant Staphylococcus aureus (MRSA)*, *Extended-spectrum β -lactamase (ESBL)-producing Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Vancomycin-resistant Enterococcus (VRE)* and *Candida* biofilms. In addition, Green synthesized Ag and Au NPs should also be researched as drug delivery vehicles for the delivery of conventional antibiotics.

Potential Impact of Green Synthesized Ag and Au NPs on Cellular and Molecular Processes

There are several ways that Ag and Au NPs might enter the human body, but the most common ones are through the skin, intravenous injection, oral delivery, and inhalation. Ag and Au NPs come into touch with a variety of biological components, including proteins, lipids, polysaccharides, and nucleic acids, once they are within the body. The distribution of these NPs in various organs or tissues can be influenced by the interaction between ubiquitous proteins and NPs, forming protein corona.²²⁷ The inherent characteristics of proteins and Ag/Au NPs may alter as a result of their interaction.²²⁸ Significantly, the contact can cause a number of physiological alterations, such as changes in bound protein structure, complement activation, blood clotting, and protein aggregation.²²⁹

A comprehensive examination into the intricate mechanisms regulating the interplay between green-synthesized Ag/Au NPs and molecular and cellular activities is a multidisciplinary challenge. The first emphasis will be centered on figuring out the exact mechanisms by which these nanoparticles enter cells, exploring mechanisms like endocytosis or direct membrane penetration. Moreover, the intracellular environment should then be examined, with a focus on the location within cellular compartments or organelles. Beyond the point of cellular entry, researchers should study the

mechanisms and the manner in which vital cellular processes are altered, focusing for how this affects metabolism, homeostasis, proliferation, and differentiation.

Challenges and Limitations in Green Synthesized Ag and Au NPs for Biomedical Applications

There are a number of issues that need to be resolved before Ag and Au NPs synthesized through green synthesis approach could potentially be utilized successfully in biological applications. Firstly, natural extracts or plant materials used in green synthesis processes might cause differences in the characteristics of individual batches of NPs. For large-scale manufacturing and commercialization, it is essential to achieve repeatable nanoparticle characteristics and consistent synthesis techniques.²³⁰ Secondly, Green synthesis techniques may not always provide for exact control of the NPs' size and form. To maximize their qualities and guarantee reliable performance in biomedical applications, homogeneity in particle size and shape is essential.²³¹ The first step in the extraction of natural compounds (NCs) include sample preparation, procedure selection, and a thorough review of the literature. Researchers are primarily concerned with reducing the interference of undesired compounds that might coextract with the targeted compounds during the extraction of NCs from biological materials. While many extraction techniques have been developed in addition to the current classical extraction approach (conventional extraction methodology), scientists are still working to create a single, universal technique for removing NCs from biological materials. A major hurdle in green synthesis methodologies is the technical complexity of extracting and purifying bioactive chemicals from natural sources. By addressing these complexities in our discussion, we aim to offer a more nuanced understanding of the practical obstacles associated with the utilization of green synthesis methods, fostering a comprehensive view for researchers and practitioners in the field.²³² Furthermore, under certain conditions, such as changes in pH or temperature, green-synthesized Ag and Au NPs may aggregate or become unstable. For their biological uses, it is essential that they remain stable over long periods of time and under physiological settings.²³³ Moreover, additional surface alterations or functionalization may be necessary to improve the stability, biocompatibility, and targeting abilities of green NPs. To customize NPs for particular biological applications, effective and reliable technologies for surface modification must be developed.^{234,235} Green synthesized NPs are often thought to be less harmful than conventionally synthesized NPs, however further investigations on their long-term toxicity and biocompatibilities are still required. It's important to assess how they affect biological systems and any potential negative effects in the long term.^{236,237} Last but not the least, it can be difficult to scale up the production of Ag and Au NPs produced through green synthesis approach to fulfill the needs of biomedical applications. The development of scalable and affordable production techniques that maintain the fundamental characteristics of NPs is essential for their widespread applications.²³⁸

Conclusion

The utilization of Ag and Au NPs made through green synthesis in biomedical applications is extremely promising. These NPs have several benefits, including biocompatibility, reduced toxicity, improved stability, adaptable characteristics, antibacterial activity, surface functionalization, therapeutic efficacy, and imaging capabilities. In a number of domains, including drug delivery, tissue engineering, diagnostics, cancer treatment, ophthalmology, and dental care, these NPs have already demonstrated promising results. However, employing Ag and Au NPs synthesized through green synthesis has drawbacks and limitations. Future studies should focus on overcoming limitations and paying attention to the underexplored biomedical uses of Green Synthesized Ag and Au NPs.

In conclusion, Ag and Au NPs produced via green synthesis method offer potential uses in the realms of science and biomedicine. These have a variety of uses, distinctive characteristics, eco-friendly synthesis approaches, and serve as valuable nanotools to be utilized in healthcare and medicine. Even if there are still challenges and limitations, more research, collaboration, and technological advancements will clear the way for their successful integration. The ability of green synthesized NPs to overcome these challenges and explore unknown biomedical spaces will transform biomedical research, improve healthcare outcomes, and bring novel treatment options in near future.

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Disclosure

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