

A review of basic concepts in the field of immunopathological and antioxidant effects of gold nanoparticles

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Abstract: Researchers from a wide range of disciplines have lately been interested in nanoparticles because of their many uses and unique physical, chemical, and biological characteristics. Furthermore, because of their distinct optical, electrical, mechanical, magnetic, and chemical characteristics all of which are a result of their tiny size and huge surface area nanoparticle research has advanced more quickly than that of bulk materials. Gold nanoparticles are one type of metallic nanoparticle that finds utility in cutting-edge technologies such as organic photovoltaics, therapeutic agents, sensory probes, drug delivery in biological and medical applications, electrical conductors, and catalysis. Scientists have long been aware of gold nanoparticles' antibacterial qualities, but the exact mechanism behind this action has remained unknown. By examining this mechanism further, researchers have now demonstrated why gold nanoparticles kill bacteria. Although the method by which certain nanoparticles kill bacteria has long been understood by scientists, it has remained a mystery. However, the use of nanoparticles as an antibacterial agent in commercial, industrial, and medical applications has not been hindered by the lack of understanding of this process. But a deeper comprehension of this antimicrobial substance can increase its potency and open up a variety of uses. Therefore, achieving a breakthrough in the knowledge of how nanoparticles are effective in combating bacteria in the face of the antibiotic crisis is very crucial. Therefore, in this research, the main goal is to review the immunopathological and antioxidant effects of gold nanoparticles against bacterial infection.

Keywords: Immunological, antioxidant, gold nanoparticle, bacterial infection

INTRODUCTION

Particles smaller than 100 nanometers are commonly referred to as nanoparticles. Metal nanoparticles, such gold (AuNPs) and silver (AgNPs), are particularly significant among the various kinds of nanoparticles (1). Because of their special qualities such as their great capacity to absorb and

scatter light, their high compatibility with living things' bodies, and their capacity to interact with biological molecules these materials find extensive use in the biological sciences, veterinary medicine, and agriculture. Researchers' attention has been drawn to the utilization of straightforward, inexpensive, and non-toxic techniques for the manufacture of metal nanoparticles due to their numerous uses (2).

Numerous physical and chemical techniques can be used to produce nanoparticles. In addition to the various uses stated above, gold nanoparticles offer strong antimicrobial and antibacterial characteristics that resist animal pathogenic pathogens. Numerous bacteria are susceptible to the antibacterial effects of gold nanoparticles (3). Gold nanoparticles may be made extracellularly or intracellularly, and the findings of the research that have been done so far show that the extracellularly created nanoparticles have a stronger antibacterial impact than the intracellularly produced ones. They have a far higher capacity to stop the development of pathogenic germs and are created intracellularly. Thanks to technological advancements, gold nanoparticles with appropriate antimicrobial characteristics and good resistance to both gram-positive and gram-negative bacteria may now be produced using a variety of biological techniques.(4)

Today, the need to achieve success in the knowledge of how nanoparticles are effective in combating bacteria in the face of the antibiotic crisis is felt more than ever. Therefore, in this research, the main goal is to review the immunopathological and antioxidant effects of gold nanoparticles against bacterial infection. For this

purpose, after the introduction, the basic concepts in the field of nanoparticles and gold nanowires, immunopathological effects, antioxidants, etc. will be reviewed.

2- Nanoparticles

Researchers from a wide range of disciplines have lately become interested in nanoparticles (diameter 1-100 nm) because of their many uses and unique physical, chemical, and biological characteristics (5). Additionally, because of the special optical, electrical, mechanical, magnetic, and chemical capabilities that come from their tiny size and huge surface area, nanoparticle research has advanced faster than that of bulk

materials (6). There are two ways to create metal nanoparticles: top-down and bottom-up. In the top-down approach, metals are reduced through chemical and physical processes to create nanoparticles. Irradiation, laser ablation, and electrochemical steps are examples of physical processes, whereas organic and inorganic reducing agents in aqueous and non-aqueous fluids are examples of chemical processes (7). The use of harmful and non-biodegradable chemicals, as well as high costs and energy consumption, are issues with the top-down approach. Numerous plants and microbes, including bacteria, viruses, yeasts, fungus, and algae, have been employed in the bottom-up method to create safe and affordable nanoparticles. This method is known as green chemistry or biogenic chemistry. Diagnostics, wound healing, medication delivery, molecular imaging, water purification, catalysis, cosmetics, apparel, the food industry, and sunscreens are just a few of the applications for nanoparticles. Additionally, they have anti-inflammatory, anti-coagulant, antiviral, antibacterial, antigenotoxic, antioxidant, anticancer, antidiabetic, analgesic, and antidandruff qualities. A variety of biological materials, including as biomass, fruits, leaves, plants, proteins, seeds, and starches, which function as reducing and capping agents, can be used to biosynthesize nanoparticles because of their unique optical characteristics and stability in aqueous

solutions. In the last 21 years, chemical synthesis has been supplanted by nanoparticle biosynthesis due to its low cost and environmental friendliness. [8]

Gold Nanoparticles

In the last decade, metallic nanocrystals have attracted much attention due to their small size and their potential for use in a wide range of industries and technologies. The oscillation of electrons in the conduction band from one particle's surface to another causes a very significant absorption in noble metals when the particle size exceeds a few tens of nanometers. Surface plasmon absorption is the name given to this oscillation, which exhibits a substantial absorption in the visible spectrum. For decades, artists have been drawn to colloidal gold nanoparticles due to the variety of colors they can create when they interact with light (9–11). Advanced technologies that employ gold nanoparticles include electrical conductors, catalysts, medicinal agents, sensing probes, organic photovoltaics, and drug delivery in biological and medical applications (12).

By altering the size, shape, or aggregation state of gold nanoparticles, their optical and electrical characteristics may be adjusted. Surface plasmon absorption causes colloidal solutions containing nanoparticles to appear bright red. Changing the shape of metal nanocrystals can change their properties and applications. Gold nanoparticles have suitable surface plasmon resonances depending on their size and generally show surface plasmon resonance absorption in the visible region (13).

According to the surface plasmon resonance phenomenon, light in the blue-green region of the spectrum (~450 nm) is absorbed by tiny gold nanoparticles (~30 nm), whereas red light (~700 nm) is reflected, giving the particles a red hue. The

surface plasmon resonance's absorption wavelength changes to longer, redder wavelengths as particle size rises. Solutions become blue or purple as a result of the absorption of red light and the reflection of blue light (Figure 1). The surface plasmon resonance wavelengths go toward the infrared spectrum (4) as the particle size increases approaching the limit, reflecting visible wavelengths and converting the nanoparticles back into brilliant or transparent materials. By altering the nanoparticles' size or form, surface plasmon resonance may be changed. As a result, particles with specific optical characteristics are made for various uses (14).

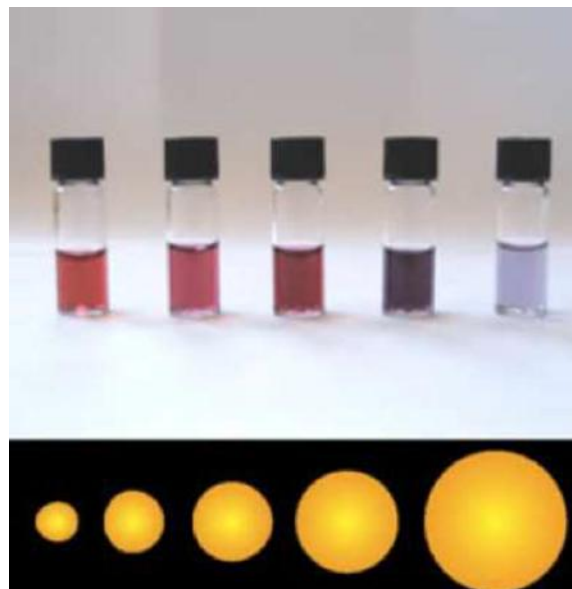


Figure 1. Gold nanoparticle solution in different sizes of gold nanoparticles; the difference in size causes different colors of the solutions.

The number of uses for gold nanoparticles is expanding quickly (15). In addition to the use of nanoparticles in sensors, some other applications of gold nanoparticles include:

Electronics: Gold nanoparticles are intended to be used in electronic devices as conductors. Since the electronics industry has shrunk, nanoparticles have become crucial to the production of chips. Conductors, resistors, and other components of an electrical chip are connected by gold nanoparticles.

Treatment 2: Gold nanoparticles are excited and produce heat when they are absorbed at wavelengths between 700 and 800 nm. This allows the targeted malignancies to be destroyed by the nanoparticles.

Transport of medicinal substances 3. The surface of gold nanoparticles can also be coated with therapeutic substances. Hundreds of molecules can fit inside gold nanoparticles due to their high surface area to volume ratio (16).

Immunological effect of gold nanoparticles

The immunological characteristics of colloidal metals, particularly gold, have piqued the curiosity of researchers since 1920 (17). The immunological properties of gold were probably related to immunogenicity due to physicochemical (non-specific) properties, which was proposed by Mr. Boudet.

He asserted that the compounds' physicochemical characteristics and their colloidal condition are the primary determinants of their immunogenic and antigenic qualities. After a lot of work, Zilber was also able to use colloidal gold to agglutinate (adhesion, binding of antibodies to insoluble antigens, and production of precipitates or clots) serum. Furthermore, some studies have demonstrated that the body produces more antibodies in response to hard antigens and colloidal metals. Additionally, by attaching to colloidal particles, some haptens can promote the formation of antibodies (18). Useful information on the impact of colloidal gold on the nonspecific immune response has been gathered in one of the greatest research ever carried out. Specifically, the leukocyte content in 1 milliliter of blood rose dramatically (from 9900 to 19800) two hours after rabbits had an intravenous injection of 5 milliliters of colloidal gold. On the other hand, multinuclear forms had a notable rise (from 4700 to 14900) while mononuclear forms experienced a minor decline (from 5200 to 4900). It should be mentioned that following the colloidal metal injection, these outcomes were no longer seen. Researchers' interest in the immunological characteristics of colloids will, however, decline as immunology advances and certain components of Burdett's idea are refuted. However, research into enhancing the immune response by antigens adsorbed to colloidal particles continues with the design of various adjuvants (compounds effective in increasing the immunogenicity of weak immunogens). It has now been proven that antibody production is enhanced by agents such as proteins, polysaccharides and certain synthetic polymers with extensive structures and high immunogenicity. On the other hand, a significant portion of low molecular weight physiologically active substances (hormones, vitamins, antibiotics, analgesics, etc.) can only elicit a mild immune response. In order to get over this restriction with the conventional techniques for producing antibodies in vivo, agents like haptens are chemically attached to large molecular weight carriers (often proteins) that enable the synthesis of certain antisera. Nevertheless, these antisera frequently contain antibodies directed against the carriers' antigenic features. Japanese researchers successfully produced antibodies against glutamic acid using colloidal gold particles as carriers in a study they published in 1986(19). Subsequent research employed the same technique to generate antibodies against haptens and hard antigens, including capsid peptides of hepatitis B and C viruses, influenza, α-amino peptides, actin, antibiotics, azobenzene, AB-peptides, Yersinia surface antigens, gastroenteritis viruses (diarrhea and vomiting), quinolinic acid, biotin, recombinant peptides, lysophosphatidic acid, endostatin, Yersinia surface antigens, Yersinia, and tuberculin.

Antioxidants

Natural or artificial compounds known as antioxidants have the potential to stop or slow down the harm that oxidants, such as reactive oxygen and nitrogen species, free radicals, and other unstable molecules, do to cells (20). According to Halliwell and Gutteridge, an antioxidant is any chemical that inhibits,

slows, or completely eradicates oxidative damage to a target molecule. A chemical must be active at low concentrations (phenolic antioxidants tend to become prooxidants at high concentrations), have a high enough concentration to render the target molecule inactive, react with oxygen or nitrogen free radicals, and produce a reaction product that is less harmful than the scavenged radical in order to be classified as an antioxidant. Since various antioxidants protect distinct molecular targets and react with different reactive species, at different places, and through diverse processes, there is no such thing as a universal antioxidant. Generally speaking, antioxidant defense can be supplied by endogenous processes (production of intracellular enzymes, such as superoxide dismutases, superoxide reductases, peroxiredoxins, glutathione peroxidases, catalases, and peptides; or extracellular antioxidant defense of transferases, albumin, urate, and glucose; low molecular weight agents, such as bilirubin, α-keto acids, melatonin, lipoic acid, coenzyme Q, and uric acid; or by supplementing deficiencies through food (vitamins C, E, A, D, riboflavin, thiamine, niacin, pyridoxine, carotenoids, flavonoids, polyphenols, amino acids, folic acid, phytoalexins, metals selenium, iron, zinc, and magnesium)(20, 21).

Depending on how they work, antioxidants can be categorized into two groups:

(1) Preventive antioxidants, which delay or prevent the first generation of radical species, hence interfering with the initiation process.

(2) Chain-breaking antioxidants, which compete with diffusion processes to decrease auto-oxidation by reacting with radicals more quickly than they do with the oxidizable substrate. In addition to direct antioxidants, indirect antioxidants are substances that can boost the effectiveness of biological systems' endogenous antioxidant defenses while lacking antioxidant activity themselves.

There are two broad categories into which antioxidant nanoparticles may be divided:

(1) nanoparticles having inherent antioxidant qualities.

(2) Antioxidant-functionalized inert nanoparticles.

The latter can take several forms, including passive carriers that can carry and release tiny molecule antioxidants (e.g., nanocapsules, nanotubes, or mesoporous materials) or a core containing antioxidants covalently linked to the surface (e.g., in the case of magnetic nanoantioxidants) (Figure 2).

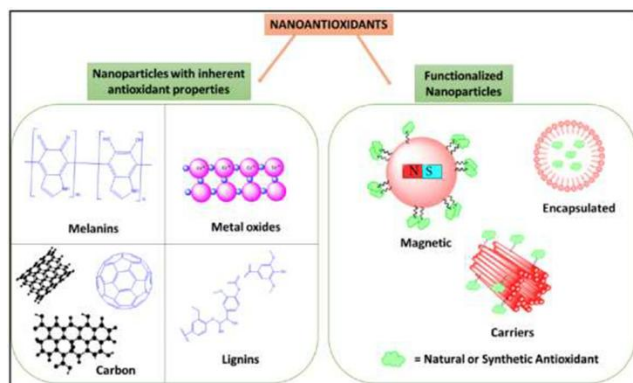


Figure 2. Nanoantioxidants, which are nanoparticles having antioxidant properties (22)

Current instances of nanomaterials that have been employed for their antioxidant properties

Antioxidant nanoparticles that are intrinsic

Metal oxides are the basis for the most prevalent nanoparticles with inherent antioxidant qualities. Because cerium oxide may cycle between the Ce^{3+} and Ce^{4+} ionic states, cerium oxide nanoparticles have been employed as effective antioxidants. Certain cerium atoms have electrons in their 4f orbitals because the nanoparticle's surface lacks oxygen atoms. Since not all cerium (IV) atoms undergo conversion to cerium (III), a redox pair is formed when cerium with three and four positive charges are present on the surface at the same time (23).

Even while metal nanoparticles are good antioxidants, their long-term usage may have negative environmental effects. Biodegradable nanoparticles can be used to lessen this issue. Numerous studies have been carried out to investigate the potential of lignin, a polymeric polyphenol, as a natural antioxidant. Its solubility in organic solvents is restricted, nevertheless. As a result, several techniques are employed to raise its hydroxyl group concentration and decrease its molecular weight. There aren't many papers on the relatively recent studies to obtain and analyze lignin nanoparticles. Numerous biologically derived nanoparticles, including melanin nanoparticles, have been demonstrated by advances in nanotechnology to be strong antioxidants on their own. For instance, these compounds have anti-inflammatory, wound-healing, and anti-ischemic properties. Additionally, polydopamine has the ability to scavenge the combined impacts of hydroperoxyl and alkylperoxyl radicals. The reduction of the ortho-quinone moieties in polydopamine by a reaction with

•HOO is the primary mechanism that explains this antioxidant activity.

Melanins' inherent biocompatibility and biodegradability are drawing more and more interest from the fields of nanomedicine, nanocosmetics, and hygiene. In order to produce polyserotonin and alumeelan dihydroxynaphthalene, respectively, a form of nitrogen-free melanin, nanoparticles based on the ethoxidation of serotonin (5- hydroxytryptamine) and 8,1-dihydroxynaphthalene have been devised and developed, drawing inspiration from polydopamine

nanoparticles.

By evaluating their photothermal characteristics, drug loading and release, and biocompatibility, polyserotonin nanoparticles—which are derived from the oxidative polymerization of the well-known neurotransmitter serotonin—were utilized as potential nanomaterials for cancer treatment. On the other hand, by radical scavenging, synthesized alumeelan nanoparticles demonstrated radiation protection in human skin cells.

Nanoparticles with a Function

The chemicals utilized for the surface of functionalized nanoparticles have a significant impact on their antioxidant qualities. Antioxidants, whether synthetic or natural, are typically used to do surface functionalization (24).

The kind of agent and a list of nanoparticles are displayed in Table 1. It has also been suggested recently to functionalize nanoantioxidants using barrier nitroxides affixed to their surface. A family of stable radicals known as nitroxides, which are produced from tetramethylpiperidinoxyl, have great stability in water and air, exhibit antioxidant activity, are non-toxic in lab settings, and are readily synthesized into various nanoantioxidants.

Table 1 . List of some nanoparticles and the type of agent (24, 25)

Nanoparticle Type	Agent Type
Gold	Glutathione
Magnetite	Carotenoids
Silicon Dioxide	Gallic Acid
Hallwaysite Nanotubes	Curcumin
Silica Particles	Rosmarinic Acid
Silica Nanospheres	Caffeic Acid
Hallwaysite Nanotubes - Trolux	a-Tocopherol Analogs

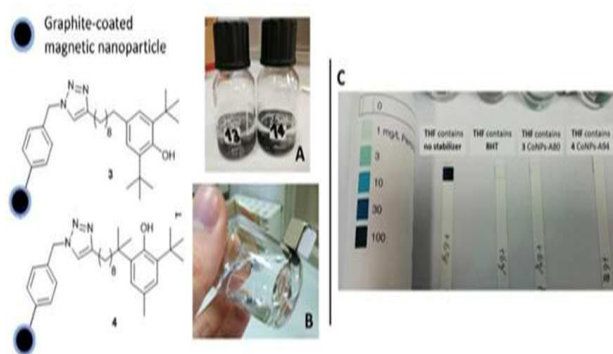


Figure 3. Peroxide test strips (C) and nanoantioxidants 3 and 4 suspended in tetrahydrofuran (A) and retrieved using a neodymium magnet (B) demonstrate that peroxide generation is absent in the antioxidant-containing sample and the reference butylated hydroxytoluene (26).

Methods for determining antioxidant activity

Various techniques and tests are used to determine the antioxidant activity (or capacity) of materials from various origins (27). The chemistry-based concept of antioxidant capacity has been applied to numerous scientific domains, including biology, medicine, and nutrition (27, 28). Stated differently, the ability of molecules to scavenge free radicals is referred to as antioxidant capacity. Some of the methods used in determining antioxidant activity are listed in Table (2).

Table 2. Methods for assessing antioxidant capacity

Method	Principle	Final Product Determination
DPPH	Reaction with an organic radical	Colorimetry
FRAP	Reaction with Fe ³⁺	Colorimetry
ORAC	Reaction with peroxy radical by AAPH	Fluorescence Loss
Inhibition assay	Fenton-like system (CO ₂ +H ₂ O ₂)	Colorimetry
Lipid peroxidation	Enzyme-based biosensors for measuring total phenolic content	Electroanalytical Evaluation
Biosensors	Reaction of noble metal salt (Au, Ag) with an antioxidant compound	Colorimetry

Gold nanoparticles' antioxidant properties and skin protection as a secure cosmetic component

Gold nanoparticles are utilized in cosmetics, particularly as anti-inflammatory, anti-aging, and skin wound disinfectants. Numerous causes, such as pollution, exposure to ultraviolet (UV) radiation from the sun, cigarette smoke, etc., can harm the skin. The generation of reactive oxygen species is caused by

these elements. Reactive oxygen species have the capacity to seriously harm proteins, DNA, and cells. Therefore, it causes skin aging by upregulating the production of matrix

metalloproteinases that break down collagen and elastin. Giving the skin an extra supply of antioxidants is crucial for assisting it in protecting itself (29).

Green gold nanoparticles made from *Hubertia ambavilla* extract have been studied for their possible use as a cosmetic component. Their effects on normal human fibroblast cells and antioxidant activity have also been assessed. The outcomes of scientific investigations and studies show that nanoparticles have the potential to be used as a material in cosmetic applications. Gold nanoparticles may efficiently scavenge free radicals and are non-toxic to skin and fibroblast cells. They also shield skin cells and fibroblast cells from UV-A ray damage. According to OECD criteria, gold nanoparticles are neither poisonous, phototoxic, nor genotoxic, and green gold nanoparticles are a viable element for cosmetic applications, according to regulatory testing conducted to assure their safety as ingredients in cosmetics (29).

Antibacterial effect of gold nanoparticles

Although the antibacterial properties of gold nanoparticles have been identified by scientists, the mechanism of this process has been a mystery. Recently, researchers have shown why gold nanoparticles kill bacteria by further investigating this process. The physical mechanism that enables gold nanoparticles to efficiently kill bacteria has been discovered by researchers after reviewing previous studies on the antibacterial impact of these particles. Wider uses in the medical realm may result from this discovery. It has long been known by scientists that certain nanoparticles have the ability to kill germs, but the exact process is still unknown. Although this lack of knowledge hasn't stopped nanoparticles from being employed as antibacterial agents in commercial, industrial, and medical settings, a deeper comprehension of this antibacterial chemical may increase its efficacy and lead to new uses (30, 31).

In light of the antibiotic crisis, a breakthrough in our knowledge of how nanoparticles fight bacteria is essential. As a result of medication abuse and usage, bacteria that are resistant to antibiotics are evolving. According to earlier research on the antibacterial properties of gold nanoparticles, these particles have a physical mechanism that allows them to degrade bacterial cell walls and kill the germs. By creating perfectly spherical gold nanoparticles in the lab, they were able to identify this process. In order to determine which shape was better at killing bacteria, they also examined nanoparticles in the form of stars. The nanoparticles examined in these investigations were all around 100 nanometers in diameter, despite their various forms. After creating the nanoparticles, the researchers investigated their interactions with real bacteria. They discovered that the bacteria were destroyed by these nanoparticles. Assuming that a physical process was in charge of breaking down the cell wall and eliminating the bacteria, the team performed a number of simulations. According to the simulation, the nanoparticles pushed against the cell wall and

caused it to break. They found that the bacterial wall deformed till it burst due to the mechanical action of the gold nanoparticles pushing against it. Additionally, the study found that the spherical nanoparticles were more efficient and caused faster bacterial harm. They ascribed this to the fact that spherical nanoparticles are more "willing" than star-shaped ones to interact with the cell membrane surface (30, 31).

The research into the antibacterial effect of gold nanoparticles, which was accompanied by the unique use of various modeling methods, could help biologists and materials scientists understand how nanoparticles kill bacteria. This, in turn, might help create effective strategies to protect humans from microorganisms that cause a wide range of diseases (30, 31).

Conclusion

The studies conducted in this article showed that gold nanoparticles are very valuable materials that can have very diverse applications in many important industries in the near future. This highlights the importance of paying attention to them and the need for more extensive research in this field. One of the important issues that raises the use of these materials in the antibacterial effect of gold nanoparticles. In other words, gold nanoparticles have been proposed as one of the most popular compounds in the antibacterial effect of gold nanoparticles due to their unique properties. Many methods of synthesizing gold nanoparticles allow us to obtain them with desired architecture and specifications. In addition, their ability to be functionalized and modified on the surface, their bioavailability and their justified immunological properties are other reasons for their use in the field of veterinary medicine. By using carriers such as gold nanoparticles, the antigenic properties of weak antigens can be increased to stimulate the immune system in the animal's body to create an immune response. The abundant and diverse physicochemical properties of gold nanoparticles have separated them from other nanoparticles and they can be hoped for especially in drug delivery, modulation and regulation of the angiogenesis process, and as agents that destroy bacteria and even tumors under heat induction conditions. The destruction of bacteria and tumors using gold nanoparticles is not limited to one method, and in addition to photothermal therapy, photodynamic therapy, and radiofrequency destruction, there are various methods for expanding research. However, there are still no detailed reports of the mechanism of action of gold nanoparticles in this area and more research needs to be done.

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