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Review Article

Revealing the Health Applications of Gold Nanoparticles for the Cardiovascular System (and in Nerve, Bone, Immune, Skin, and Mental Disorders)

Sudeep Chawla[1†], Nicholas A Kerna[2,3*†], ND Victor Carsrud[4], Kevin D Pruitt[5,6], John V Flores[7,8], Hilary M Holets[7,8], Dabeluchi C Ngwu[9,10], Joseph Anderson II[11] and Nkiru J Obi[12]

[1]*Chawla Health & Research, USA*
[2]*Independent Global Medical Research Consortium, Thailand*
[3]*First InterHealth Group, Thailand*
[4]*Lakeline Wellness Center, USA*
[5]*Kemet Medical Consultants, USA*
[6]*PBJ Medical Associates, LLC, USA*
[7]*Beverly Hills Wellness Surgical Institute, USA*
[8]*Orange Partners Surgicenter, USA*
[9]*Cardiovascular and Thoracic Surgery Unit, Department of Surgery, Federal Medical Center, Umuahia, Nigeria*
[10]*Earthwide Surgical Missions, Nigeria*
[11]*International Institute of Original Medicine, USA*
[12]*Washington University, USA*

***Corresponding Author:** Nicholas A Kerna, (mailing address) POB47 Phatphong, Suriwongse Road, Bangkok, Thailand 10500. Contact: medpublab+drkerna@gmail.com.

†Indicates co-first author

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Abstract

The prospects of healthcare systems and their results may be influenced by nanotechnology. Researchers have recently become very interested in gold nanoparticles (AuNPs) because of their superior physiochemical characteristics. AuNPs exhibit size- and shape-dependent optical and electronic properties and are noncorroding, biocompatible, and amenable to the desired functionalization.

Due to their exceptional qualities, AuNPs have the potential to be used in a wide range of biomedical applications, such as optical bioimaging, targeted drug delivery (TDD), immunoassays, medicinal diagnostics, laser phototherapy of cancer cells and tumors, and genomics. AuNPs bind readily to proteins, antibodies, enzymes, and cytokines. However, particle size may affect how it is distributed throughout the body. AuNPs are FDA-approved metallic nanoparticles that have shown great promise in several medical applications.

To target cancer cells, researchers used nanogold to bind specific antibodies. AuNPs have antioxidant and anti-inflammatory properties that can help with maladies triggered by inflammation and reactive oxygen species (ROS). Also, AuNPs have been claimed to treat rheumatic, mental, neurological, bone, cartilage, cardiovascular, and skin disorders.

Moreover, AuNPs have been shown to boost immunity. This review aims to provide an overview of the historical corporal use of gold throughout the ages—to the present, how AuNPs are synthesized, how they affect human physiology, toxicity, potential positive effects, and their future applications.

Keywords: *Bioimaging; Boost Immunity; Nanotechnology; Reactive Oxygen Species; Targeting Cancer Cells*

Abbreviations

AuNP: Gold Nanoparticle; CAGR: Compound Annual Growth Rate; CAM: Cell Adhesion Molecule; CNS: Central Nervous System; CTAB: Cetyltrimethylammonium Bromide; Dh: Hydrodynamic Diameter; DLS: Dynamic Light Scattering; EC: Endothelial Cell; mTOR: Mammalian Target of Rapamycin; MWPLP: Microwave-Induced Plasma-in-Liquid Process; $NaBH_4$: Sodium Borohydride; NF-κB: Nuclear Factor Kappa B; NP: Nano Particle; PC-12: Pheochromocytoma; PNS: Peripheral Nervous System; ROS: Reactive Oxygen Species; SIMS: Secondary Ion Mass Spectroscopy; TDD: Targeted Drug Delivery; TEM: Transmission Electron Microscopy; TNF-α: Tumor Necrosis Factor Alpha; TOAB: Tetraoctylammonium Bromide; XPS: X-Ray Photoelectron Spectroscopy

Introduction

Gold is classified as a noble metal because it can withstand chemical intervention and is not easily destroyed by acids. Furthermore, gold is strong enough to pass practically unmodified through the digestive tract and readily resist the digesting juices of the human gastric system. This characteristic indicates that it neither damages nor helps the human body in its natural state [1].

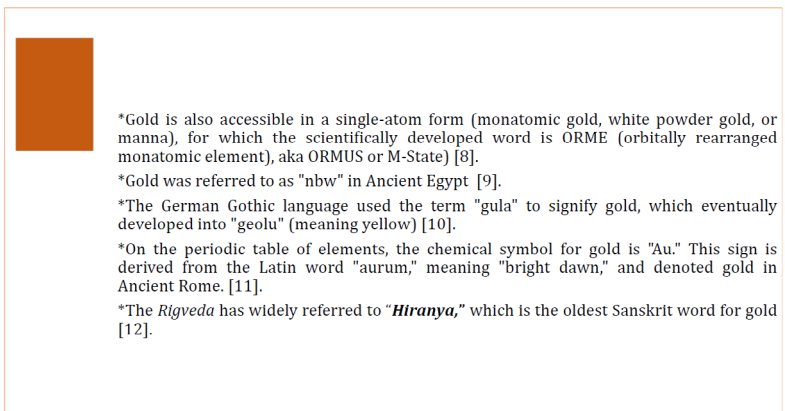
Generally, gold is considered a symbol of immortality [2]. Since ancient times, it has been regarded as the 'elixir of life' [3]. The first records of colloidal gold can be found in monographs written by Chinese, Arabian, and Indian researchers, who obtained colloidal gold as early as the fifth and fourth centuries BC [4]. The Chinese and Indians used it to treat male impotence, epilepsy, syphilis, rheumatic disease, and tuberculosis [5].

In 3000 BCE, Egyptians consumed gold to purify the mind, body, and spirit because they thought it was the skin and flesh of the gods and a doorway to immortality [6]. Even Cleopatra is believed to have used a 24-karat gold face mask while sleeping every night to keep her appearance young [1]. At the height of the Renaissance, noblemen in Europe's Middle Ages decorated food at banquets and weddings with gold leaf to impress their guests.

This custom included bread, oysters, quail, and carp. After meals, gold-covered almonds were served in Renaissance Venice in the belief that gold would strengthen the heart and protect against rheumatoid arthritis. Later, this belief proved valid to a certain extent [6].

According to *Quinta Essentia Auri*, Paracelsus wrote about the curative properties of gold quintessence, *Quinta Essentia Auri,* which he detected by reducing gold chloride by vegetable digging in alcohols or oils. He utilized the "potable gold" to treat various mental illnesses, including syphilis. Giovanni Andrea, a contemporary of his, used "aurum potabile" to treat those suffering from leprosy, plague, epilepsy, and diarrhea.

In 1583, the alchemist David de Planis-Campy, who served as the doctor to Louis XIII of France, promoted his "longevity elixir," a colloidal solution of gold in water [7]. The philosopher and physician Francisco Antonii wrote the first treatise on colloidal gold that has survived to this day. It was published in 1618 [4]. The following graphic shows other names for gold that have been used since ancient times [8-12].



In Pricker (1996), *Medical Uses of Gold Compounds: Past, Present and Future,* Nicholas Culpepper advised a gold cordial in the New Pharmacopoeia of the 17th century to treat diseases induced by a reduction in vital spirits, such as depression, dizziness, fever, and fainting [13].

However, Robert Koch found in 1890 that gold cyanide was poisonous to tuberculosis bacillus *in vitro*. Although gold cyanide appeared unsuccessful against tuberculosis *in vivo*, this finding provided the basis for clinical gold use. Furthermore, it prompted research into this precious metal's biological activities and effects on many diseases.

In this respect, Jacques Forestier demonstrated in 1929 that ionic gold compounds reduce joint discomfort in individuals with rheumatoid arthritis and can occasionally lead to total remission [14].

Even though gold has a long history, the "revolution in immunochemistry" that arose by using AuNPs in biological investigations did not begin in 1971. At that time, British researchers Faulk and Taylor revealed a technique of antibody conjugation with colloidal gold. This technique enabled direct electron microscopy imaging of the surface antigens of salmonellae. Research began with biospecific markers—colloidal gold coupled with immune cells and other molecules—in several disciplines of medicine and biological sciences [4]. Remarkably, the gold's physiochemical characteristics change when it is reduced to nanoscale size [2].

Numerous studies have been conducted over the past 40 years using AuNPs to identify biomacromolecules in biochemistry, microbiology, immunotherapy, cytology, plant physiology, and other fields [4].

Discussion

AuNPs: Properties and synthesis

AuNPs are not the same as bulk gold. Bulk gold is an inert yellow solid, but AuNPs are a wine-colored solution with antioxidant capabilities. The formation of AuNP networks and the interactions between the particles are crucial in determining the characteristics of these nanoparticles. AuNPs come in various shapes, including irregular, sub-octahedral, nanotriangles, nanorods, icosahedral multiple-twined, decahedral, multiple-twined, tetrahedral, hexagonal platelets, spherical, octahedral, and nanoprisms [15]. They also have various diameters, ranging from 1 nm to 8 m. AuNPs have a wide range of physical and chemical characteristics. Figure 1 depicts the general features of AuNPs [16].

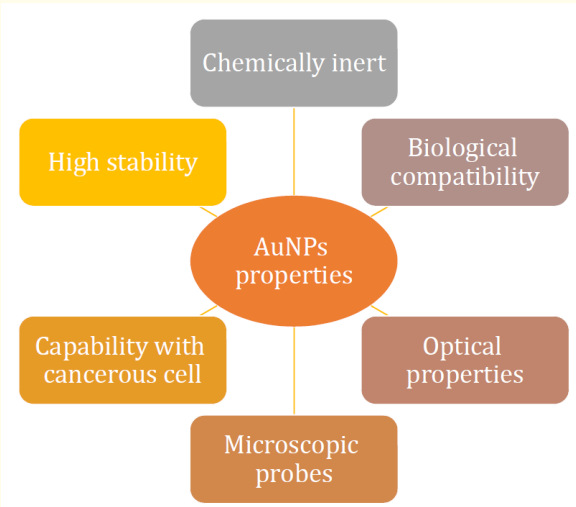


Figure 1: *Properties of AuNPs [16].*

The modern era of AuNP synthesis began more than 150 years ago with the work of Michael Faraday, perhaps the first to recognize that colloidal gold solutions varied in their properties from bulk gold. Over the past 50 years, reliable and high-yielding techniques have been established for generating AuNPs, including those with round and quasi forms. The resultant AuNPs have distinctive characteristics, including size- and shape-dependent optical and electrical features, large surface area to volume fraction, and surfaces easily altered with ligands containing functional groups such as thiols, phosphines, and amines that have an affinity for gold surfaces. Using these functional groups to bind the ligands, other moieties such as oligos, peptides, and monoclonal antibodies can offer even more activity [17,18].

Physical, chemical, or biological methods create AuNP from the bottom-up or the top-down (Figure 2) [19]. The top-down technique uses physical and chemical processes to manufacture the desired sizes from the bulk material. In contrast, the bottom-up method employs chemical ways to combine essential components in the production of nanostructure systems [5].

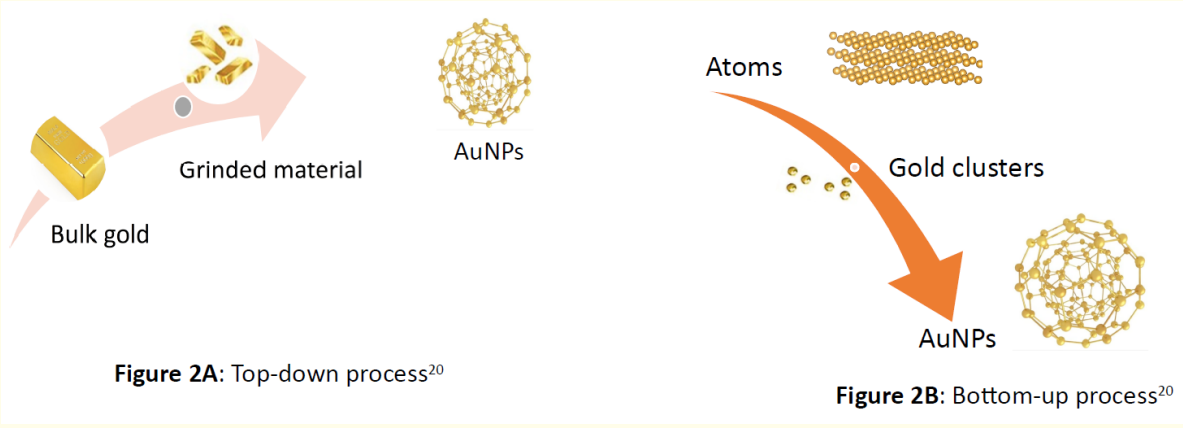


Figure 2A: Top-down process[20]

Figure 2B: Bottom-up process[20]

Figure 2: *Top-down and bottom-up approaches for the synthesis of AuNPs. Figure 2A: Top-down process, Figure 2B: Bottom-up process. Adapted from [20].*

The Turkevich and Brust approach is the most frequently employed bottom-up procedure, in which metal salts are reduced to generate spherical monodisperse AuNPs with diameters ranging from 10 to 20 nm. Sodium citrate salts are commonly utilized to stabilize AuNP during synthesis and function as a reducing agent. The process was further adjusted by altering the citrate to gold precursor concentration ratio, yielding AuNP with diameters ranging from 15 to 150 nm. In many cases, citrate has been replaced as a reducing agent by ascorbic acid, amino acids, cetyltrimethylammonium bromide (CTAB), sodium borohydride, and UV radiation [5,19,20]. However, specific chemical-reducing agents are poisonous [19].

Greener methods have been utilized in synthesizing AuNPs to eliminate hazardous chemical-reducing agents, such as the microwave-induced plasma-in-liquid process (MWPLP) and green nanotechnology. MWPLP generates metallic nucleation of nanoparticles (NPs) using microwaves, requires no reducing agents, and requires extremely little energy [21]. Alternatively, green nanotechnology creates biogenic AuNPs using natural substances derived from microbes and plants as reducing agents. Green nanotechnology is believed to be more environmentally friendly, making it more acceptable for biomedical applications [19].

Brust and Schriffin made a breakthrough in AuNP synthesis in 1994 when they created AuNP stabilized with organic soluble alkanethiol using a biphasic reduction process that included tetraoctylammonium bromide (TOAB) as a phase transfer reagent and sodium borohydride ($NaBH_4$) as a reducing agent. Adjusting the reaction parameters, such as the gold-to-thiol ratio, reduction rate, and reaction temperature, produces low-dispersity AuNPs that range in size from 1.5 to 5 nm [22-24].

Top-down procedures often produce nanoscale materials by processing larger macroscale structures with processes like lithography. Sonochemical, microwave, and photochemical-based approaches are some of the more frequently used physical synthesis techniques. For synthesizing AuNPs, a recently discovered process employs N-cholyl-L-valine as a self-reducing and stabilizing agent to be combined with natural sun irradiation.

The size and form of AuNP generated may be altered by varying the ratio of Au^{3+} to NaValC ions, the amount of solar irradiation, the pH, and the duration of the reaction. A novel production approach was recently devised in which aqueous [$AuCl_4$] is irradiated with 532 nm nanosecond laser pulses to make 5 nm monodisperse AuNP without the need for capping agents or additives, thus removing the danger of contamination by leftover chemicals.

Compared to previous techniques that use 800 nm femtosecond laser irradiation, which often results in the formation of nanoparticles as large as 40 nm, 532 nm nanosecond laser irradiation produces a more uniform monodisperse of AuNP of 5 nm diameter [19,20].

AuNPs: Effect on human physiology

As a result of their outstanding physiochemical characteristics, AuNPs have attracted the attention of many researchers. Moreover, AuNPs are biocompatible and noncorroding and have size- and shape-dependent optical and electrical characteristics. These exceptional features of AuNP suggest that they have enormous potential for use in a wide range of biomedical applications (for example, *in vitro*/*in vivo* bioimaging, contrast enhancement of X-ray computed tomography, targeted drug administration, diagnosis, plasmonic biosensing, colorimetric sensing, gene transportation, tissue regeneration, photoinduced treatment, and oncotherapy) (Figure 3) [2].

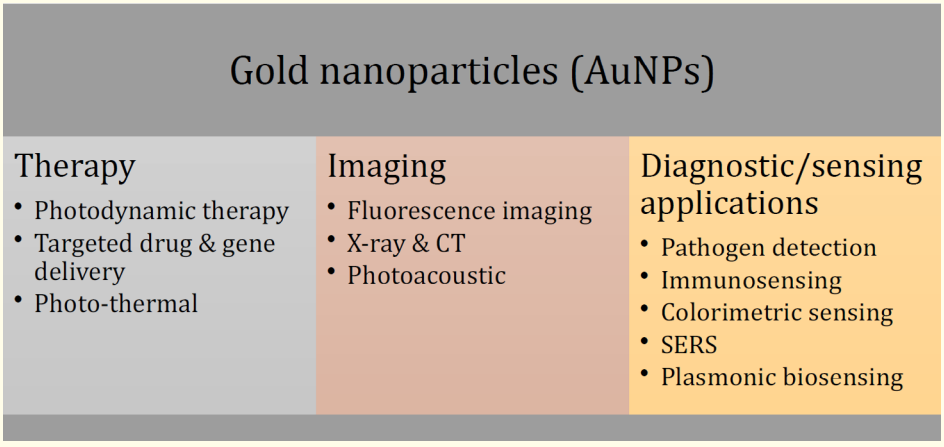


Figure 3: *Applications of AuNPs. Adapted from [2].*

AuNPs can cross the blood-brain barrier, aid in functional recovery after spinal cord injuries, stimulate electrical activity, and cause calcium transients within neurons, all of which point to their potential role in modifying neuronal behavior [25].

When used as a drug delivery technique for the brain, AuNPs offer a few advantages over other nanoparticles. Their capacity to attach to various functional groups, including thiol, amine, and disulfide groups, as well as their stability, simplicity of functionalization, and size manipulation, among other characteristics, make them the ideal instrument for drug transport to the brain [26].

The ability of AuNPs to alter neuronal activity has been examined in various neurological systems [27]. In 2008, a study was carried out to investigate the distribution of AuNPs across different organs in mice after receiving intravenously colloidal forms of AuNPs of various sizes. They discovered that the capacity of AuNPs to penetrate the central nervous system is primarily determined by size, with AuNPs of 15 nm having 500 times the ability to enter the brain than AuNPs of 100 nm [28].

The interactions between AuNPs and biomolecules are probably most strongly influenced by the surface chemistry of AuNPs [29]. The capacity of AuNPs to engage complementary DNA fragments with high affinity is an unexpected but now fairly well-recognized characteristic [18].

It is reported that AuNPs improve neurite length, stimulate adhesion and proliferation, modify action potentials, and influence Ca^{2+} influx [27]. Additionally, neurons of the dorsal root ganglion with channels of ion of the P2X3 receptor, Na^{+} channels, and transient receptor potential vanilloid member 1 could bind to manufactured AuNPs, which affected neuron-neuron communication [30].

In an *in vivo* investigation, Zhang., *et al*. (2018) discovered that tiny-sized AuNPs might easily collect in normal cardiac tissue by various delivery routes; however, the tissue distribution of AuNPs in a sick heart can be distinct. The study also shows that AuNPs can circulate in the circulatory system without being eliminated after digestion. Furthermore, when exposed to fluids that include proteins, such as serum or whole blood, AuNPs typically form a protein corona [31].

Furthermore, research has shown that AuNP inhibits the production of cell adhesion molecules (CAMs) caused by tumor necrosis factor-alpha (TNF-α) is inhibited by AuNP in human umbilical vein endothelial cells (ECs) and aortic ECs. Furthermore, AuNPs inhibited TNF-α induced intracellular ROS generation and the nuclear factor kappa B (NF-κB) signaling pathway while increasing CAM protein ubiquitination. However, TNF-α binding to ECs and the mammalian target of rapamycin (mTOR) pathway of protein synthesis were not affected [32].

Although AuNPs offer remarkable features that make them excellent drug delivery scaffolds, studies have shown that high concentrations and prolonged exposures, both *in vitro* and *in vivo*, negatively impact neuronal performance [33,34]. Direct exposure to AuNPs causes abnormal Ca^{2+} transients within neurons [35] and glial cells [36], resulting in action potentials and oxidative damage. AuNP-related interference with cellular exocytosis has also been linked to decreased neurotransmitter synthesis and release [34,37].

Furthermore, cytoskeletal proteins, including actin and tubulin, were shown to be distorted in pheochromocytoma (PC-12) cells [38], and the synaptic activity of hippocampus neurons of the hippocampus changed after exposure to AuNP [39]. Although several studies have documented concentration-dependent adverse effects associated with AuNP exposure in central nervous system (CNS) neurons [40], its function—especially in glial and neuronal cells of the peripheral nervous system (PNS)—is not fully understood. Also, studies have shown that high concentrations of AuNP reduce body mass, spleen index, and red blood cell count [41].

AuNPs: Consumption

AuNP can be safely ingested orally or by injection (intraperitoneal or intravenous route). When injected, it interacts with the principal tissue barriers before entering circulation [42,43]. However, exposure to AuNP can occur during research and production or in applications through dermal exposure, breathing, implantation, and adhesion of airborne and surface materials, which becomes challenging to detect [44].

AuNPs are typically found in the liver and spleen after being consumed or absorbed via the skin. They are absorbed by macrophages and stored inside lysosomes, the cell's "waste recycling center". Although nothing was known about the long-term destiny of nanoparticles, gold's reputation as a "noble" metal, chemically inert, suggested that it would remain unchanged in these cellular components indefinitely [45].

AuNPs: Rating and costing

Manufacturers thoroughly characterize each batch of AuNPs in terms of size, surface charge, and chemical composition. The most commonly used techniques through which manufacturers check AuNP's quality include: transmission electron microscopy (TEM), hydrodynamic diameter (Dh), dynamic light scattering (DLS), zeta potential, UV-vis spectroscopy, atomic spectroscopies, atomic force microscopy, inductively coupled plasma mass spectrometry, electron diffraction, X-ray diffraction, X-ray photoelectron spectroscopy (XPS), and secondary ion mass spectroscopy (SIMS) [20,46].

The expanding medical sector and the increasing need for nanotechnological medical goods are the primary drivers driving market expansion. As a result, AuNPs are increasingly used in the medical field [47]. Currently, a milligram of AuNP costs around $80 (depending on the size of the nanoparticles). AuNPs cost $80,000 per gram, while a gram of pure, raw gold costs only $50 [48]. However, according to an IMARC (a leading market research company) analysis, the global AuNP market is expected to reach $4.4 billion by 2021. The IMARC group projects that the market will grow at a compound annual growth rate (CAGR) of 12.2% between 2022 and 2027, reaching $ 8.9 billion [47].

AuNPs: Cytotoxicity

AuNPs are helpful because of their ease of synthesis, chemical stability, ease of surface modification, and specific optical features. Also, they are considered biocompatible reagents for biological applications, such as drug administration, cancer treatment, diagnostic devices, photodynamic therapy, and imaging techniques [42]. However, there are still several concerns about its human use (such as immunogenicity and cytotoxicity) [2].

Several *in vivo* studies have been carried out to assess the possible toxicity of AuNPs; however, the results have been ambiguous and variable [41,49]. The nature of AuNPs and a biological system, as well as interactions between AuNPs and live cells, cannot be consistently predicted [50].

The form, stabilizing coatings, concentration, cell line type, animal usage, and administration (dosage, time, and mode of administration) were determined to contribute to the various harmful effects *in vivo* of AuNP (Figure 4) [26,49]. *In vitro* investigations have shown that the size and surface chemistry of AuNPs play an essential role in determining their toxicity.

Chen., *et al*. (2010) studied the toxicity of citrate-capped AuNP of various sizes (spheres with diameters of 3, 5, 8, 12, 17, 37, 50, and 100 nm) in mice. They discovered that the intermediate size range of 8 - 37 nm had deadly consequences on mice, including loss of weight, severe illness, change in fur color, decreased appetence, and reduced average lifespan.

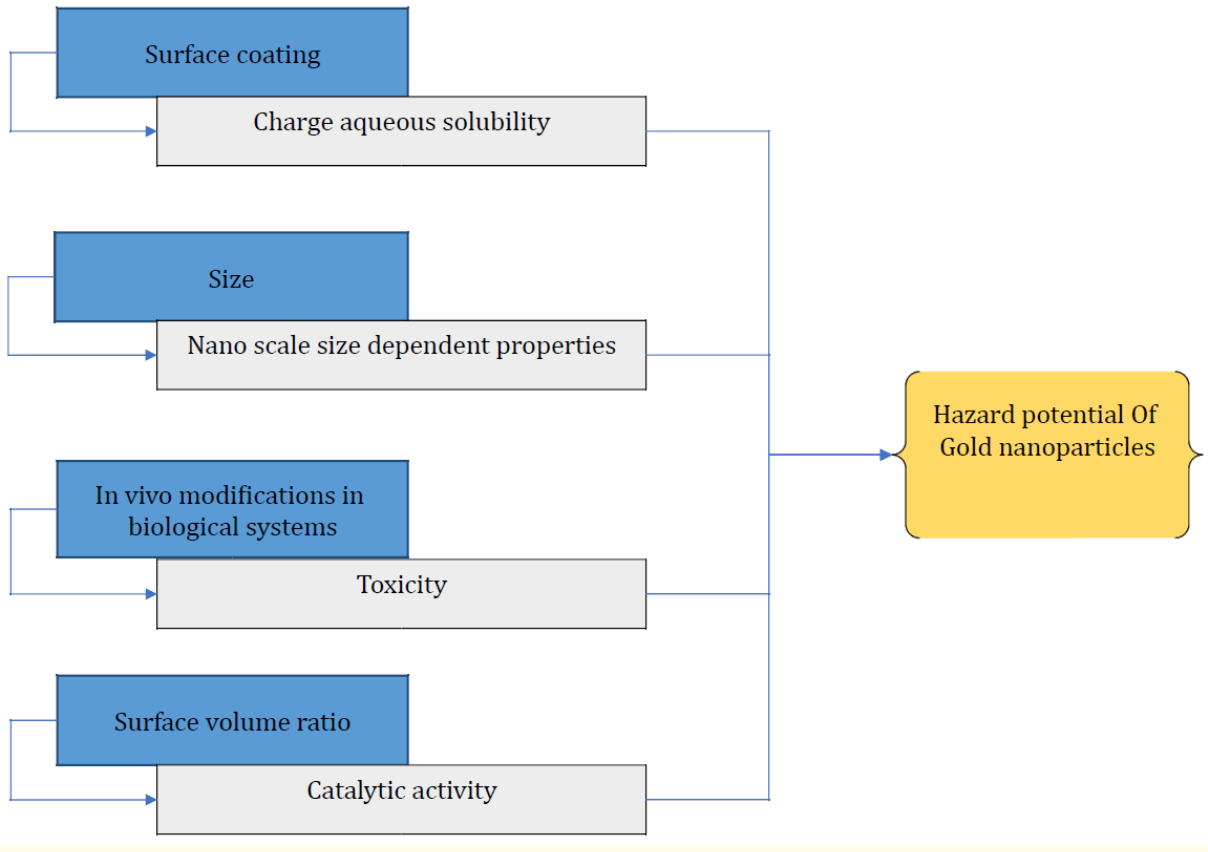


Figure 4: *Aspects of AuNPs that contribute to their exposure potential. Adapted from [50].*

The toxicity of the intermediate size range (18 - 37 nm) has been associated with severe organ failure (liver, spleen, and lungs) [40]. Recently, Kim., *et al*. (2013) used an embryonic zebrafish model to explore the effects of surface charge and size on AuNP *in vivo* toxicity and discovered that surface functionalization determined the toxicity results with embryos (abnormally small and under-pigmented eyes) [51].

Zhang., *et al*. (2010) studied the subchronic toxicity of 13.5-nm AuNPs in mice using 3 different injection strategies (oral, intraperitoneal, and IV). They discovered that oral delivery produces the most significant toxicity compared to intraperitoneal and intravenous injections, as demonstrated by considerably lower body weight, increased spleen weight, and a drop in RBC.

The significant toxicity of oral AuNP may be attributable to intestinal injury [41]. Similarly, Rathore., *et al*. (2014) observed that oral delivery of 10 - 25 nm AuNPs for 21 days causes alveolar inflammation and hepatic and renal damage [52]. Several other experimental investigations showed that the toxicity of AuNPs is dose-dependent, with a safety concentration limit of 1012 particles/mL [4].

Alkilany., *et al*. (2010) investigated the cytotoxicity of colloidal AuNPs. It was discovered that the dispersing medium might also cause cytotoxicity; therefore, the cytotoxicity of AuNP and the dispersing medium should be studied independently [53]. Chronic exposure to AuNPs can cause physiological alterations. Sengupta., *et al*. (2013) observed the *in vivo* interaction of AuNP in experimental animal models after acute and chronic exposures for 90 days.

Acute exposure resulted in a considerable increase in WBC count, RBC count, and hemoglobin percentage. On the other hand, prolonged exposure at a dosage level of 2 mg/kg resulted in significant toxicity and organ damage [54].

The toxicity of AuNPs also depends on the surface ligands' chemical composition. It is often the surface group itself that leads to toxicity [18]. Goodman., *et al*. (2004) have shown how nanoconjugate surface ligands' chemical functionality and charge influence toxicity. These researchers found that while amine-functionalized particles were only mildly toxic, those functionalized with carboxylic acids were nontoxic under all the conditions examined [55].

AuNPs' toxicity is also affected by their manufacturing technique. AuNPs derived from plant extracts, seaweed, and microorganisms, for example, are less or nontoxic and are regarded as appropriate for biomedical applications. Furthermore, in certain circumstances, cell-killing abilities (for malignant cells) have been conferred on AuNPs by bioconjugation with relevant molecules [2].

However, a particular size (5 nm) of AuNP caused DNA damage in HepG2 hepatoma cells in a comet assay and chromosomal damage in a mammalian *in vivo* micronucleus test, primarily due to increased ROS generation, according to Xia., *et al*. (2017) [56].

AuNPs may damage testicular functioning by altering histology, sperm quality, fertility, and testosterone levels. Oxidative stress is believed to be a common mechanism of AuNP-induced toxicity, activating NF- κB signaling by up-regulating the transcription of pro-inflammatory genes such as IL-1, IL-6, IL-8, and TNF-a, culminating in DNA damage and death. In mouse Leydig cells, AuNPs were taken up and shown to be poisonous and impede testosterone synthesis.

Liu., *et al*. (2020) also looked at how much AuNP accumulated in the male mice's testes and how this affected the male reproductive system's function. The findings demonstrated that AuNPs could concentrate in the testes and inhibit testosterone synthesis in Leydig cells by downregulating the expression of 17-hydroxylase, thus decreasing the quality of epididymal spermatozoa [57].

AuNPs: Potentially positive effects on humans

AuNPs are FDA-approved metallic nanoparticles that have shown significant potential in several medical applications. Figure 5 shows the pharmacological and physiological roles of AuNPs in various organ systems and disorders [32,58].

Future investigations on AuNPs

AuNPs are viewed as having a bright future by scientists and researchers, particularly in the medical area [59]. The multifunctionality of AuNP is its primary advantage over conventional therapeutic drug delivery and biological techniques. Targeted delivery, molecular imaging, and molecular treatment for different diseases are all made possible by the conjugation of targeting ligands or biomaterials, imaging labels, medicinal medicines, and many other functional groups into the AuNP.

The AuNP is unusual in specific ways due to its fascinating optical features, which can be used for both imaging (to identify disease) and therapeutic (to treat disease) purposes [60]. Some vaccine-conjugated AuNPs have been studied in animal models with promising results against *S. pneumoniae* and *L. monocytogenes*.

Diseases	Potential Applications or Possible Action Mechanisms
Cancers: pancreatic, breast, prostate, colon, melanoma, sarcoma, and lung cancers	Anti-cancer activity; diagnosis; imaging applications; photothermal and photodynamic therapies; anti-cancer drug and gene delivery
Retinopathy: age-related macular degeneration (AMD); diabetic retinopathy (DR)	Anti-angiogenesis; anti-inflammation; reduced the VEGF activation and induced cell proliferation and migration
Neurological diseases: Alzheimer's disease; Parkinson's disease	Inhibited the aggregation of Aβ peptides and the degradation of Aβ aggregates; inhibition of acetylcholinesterase and butyrylcholinesterase; anti-inflammation
Skin disorders	Wound healing; acne; synergistic effect with natural products
Bowel diseases	Against inflammatory bowel diseases (IBD); alleviates the lipopolysaccharide-induced intestinal epithelial barrier dysfunction
Bone cartilage disorders	Rheumatoid arthritis treatment; Promotion and regulation of the differentiation; protection for bone and cartilage tissue; the inhibition of osteoclast; inhibit angiogenic activities, suppress inflammation or serve as antioxidant
Cardiovascular diseases	CT imaging as CT contrast agents; anti-inflammatory biological activity; reduce arterial neointimal hyperplasia
Infections	Antimicrobial effects; overcome microbial drug resistance; detect specific DNA fragments of *Mycobacterium tuberculosis*; antiviral activity, coronavirus vaccines and the detection. The antibacterial activity shown might be due to the presence of co-existing toxic chemicals which were not completely removed after AuNPs synthesis.
Metabolic syndrome	Type 2 diabetes and obesity treatment; improvement in glucose intolerance and hyperlipidemia; lipolysis; more effects during liposuction
Food safety evaluation	AuNPs-conjugated DNA, enzymes, or antibodies are used in biosensors for the detection of foodborne pathogens

Figure 5: *Aspects of AuNPs that contribute to their exposure potential. Adapted from [50].*

Several studies on functionalized AuNPs have revealed that AuNPs could be employed as an efficient drug delivery technique to treat infections caused by *S. pneumoniae and L. monocytogenes.* Nonetheless, more research is needed to transfer these preclinical findings into practical applications [26].

Because of their unique, essential characteristics, AuNPs have been extensively researched and used in cancer diagnostics and therapy. However, despite the promising data acquired from laboratory investigations, relatively few cancer therapeutic options based on AuNPs are now being used in clinical studies or are about to enter clinical trials.

The reason is that these techniques must overcome several obstacles to transition from laboratory research to clinical practice. These challenges include overcoming NPs' clearance or renal excretion to reach tumor tissue effectively, overcoming multiple physiological barriers to exert a therapeutic impact, and figuring out how to metabolize nanoparticles after treatment. The most promising option is to rationalize using the physical and chemical features of AuNPs [61].

Although there are several ideas in the scientific literature for different potential medicinal uses of AuNP for treatment, they have yet to be approved by health organizations [14].

The physiological fate of AuNPs *in vivo* has yet to be well known. Little is known about the absorption process of negatively charged AuNPs, which may require a distinct set of proteins that are difficult to identify. Nevertheless, ongoing efforts to produce AuNP have addressed the critical difficulty of targeting specific cells and, eventually, organs and tissues. Adding targeted moieties such as aptamers, antibodies, peptides, and small compounds can be beneficial.

However, inserting the solely targeted moiety without impairing the monolayer's functioning is efficient. AuNPs design and synthesis can further develop to achieve the objective of them functioning as effective delivery vehicles [60].

Since surface modification of functionalized AuNPs with genuine surface components can significantly alter the outcome, it is necessary to examine these compounds' cytotoxic effects, pharmacokinetics, and pharmacodynamics [53]. Recently, studies have been conducted to put biocompatible molecules on the surface of gold and to create a new and improved method for the preparation, such as using green chemistry to manufacture biogenic NPs.

All of these advances could expand the use of AuNPs in nanomedicine [5]. In the described *in vivo* investigations, intravenous injection is the most common delivery method. Nevertheless, more studies are needed to explore the cytotoxicity of AuNP delivered through various pathways, such as inhalation, oral uptake, and dermatological absorption of AuNP [53].

Conclusion

AuNP is unique, as its intriguing properties can be used for imaging and therapeutic applications. Many studies have shown that AuNPs are helpful to humans because of their functional pharmacological qualities in various disorders. Furthermore, considering their high surface loading of medication and genes and regulated release of payloads, AuNP-based delivery vectors have shown promise in therapeutics. Although there are several recommendations for potential AuNP-based systems for drug administration, treatment, imaging, or imaging in the scientific literature, only some of these systems have been evaluated in human trials, and regulatory bodies have formally authorized none. Many questions about the fate of AuNPs after medicinal use and their possible toxicity still need to be answered. Some researchers have found that AuNPs are not harmful; however, many other investigations have found the opposite.

The toxicity of gold nanoparticles may be directly related to the size of the particles, shape, surface potential, dosage, and production technique. As a result, more extensive toxicological experiments are required to demonstrate the safety of AuNPs in therapeutic settings. Most AuNP-related preparations are now in clinical trials. Increasingly, nano-related formulations will enter clinical therapy and diagnostics of diseases in the future, making AuNPs more significant in biomedicine.

Conflict of Interest Statement

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

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