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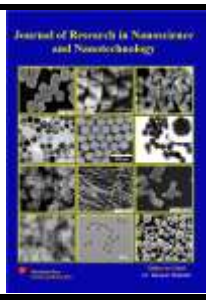

Exploring the Potential of Gold Nanoparticles in Nanomedicine: A Comprehensive Analysis of Benefits and Limitations

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ABSTRACT

This paper delves into the utilization of gold nanoparticles (Au-NPs) in nanomedicine, examining both their advantageous properties and associated drawbacks. Au-NPs have gained significant attention in biomedical applications owing to their unique physicochemical characteristics, such as biocompatibility, tunable optical properties, and facile surface functionalization. These attributes render Au-NPs promising candidates for various therapeutic and diagnostic purposes in nanomedicine. However, their implementation also presents challenges, including concerns regarding toxicity, stability, and scalability. This review offers a critical assessment of the advantages and disadvantages of employing Au-NPs in nanomedicine, aiming to provide insights for researchers and clinicians navigating the complexities of nanoparticle-based therapies.

Keywords:
Gold nanoparticles, Nanomedicine,
Physicochemical characteristics,
Biocompatibility, Toxicity

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1. Introduction

In recent years, the field of nanomedicine has witnessed remarkable advancements, driven by the exploration of nanoscale materials for innovative diagnostic and therapeutic applications [1-5].

Among these materials, gold nanoparticles (Au-NPs) have emerged as particularly promising candidates, owing to their unique physicochemical properties and versatile functionality. This introduction provides an overview of the potential of Au-NPs in nanomedicine, offering insights into their advantageous properties as well as the challenges associated with their implementation. Au-NPs have garnered significant attention in biomedical research due to their exceptional biocompatibility, a crucial attribute for successful integration into biological systems [6, 7]. Unlike many other nanoparticles, Au-NPs exhibit minimal cytotoxicity and immunogenicity, making them well-suited for in vivo applications. This inherent biocompatibility is attributed to the noble metal nature of gold and its inert behavior within biological environments, allowing Au-NPs to interact with cells and tissues without eliciting adverse reactions. Consequently, Au-NPs hold promise for various biomedical applications, including drug delivery, imaging, diagnostics, and therapy. One of the most notable features of Au-NPs is their tunable optical properties, particularly their ability to exhibit surface plasmon resonance (SPR) under specific conditions. SPR is the collective oscillation of conduction electrons in response to incident light, leading to the absorption and scattering of photons at specific wavelengths [8, 9]. The wavelength at which SPR occurs is highly sensitive to the size, shape, and surface chemistry of Au-NPs, offering opportunities for precise control over their optical behavior. This tunability enables the development of Au-NP-based contrast agents for a wide range of imaging modalities, including photoacoustic imaging, computed tomography (CT), and surface-enhanced Raman scattering (SERS). By harnessing the unique optical properties of Au-NPs, researchers can enhance the sensitivity and specificity of disease detection, enabling earlier diagnosis and personalized treatment strategies [10, 11].

Furthermore, Au-NPs exhibit facile surface functionalization, allowing for the conjugation of targeting ligands, therapeutic agents, and imaging molecules. The surface of Au-NPs can be modified with various functional groups, peptides, or antibodies to impart specificity towards disease biomarkers or cellular receptors. This functional versatility enables the precise targeting of Au-NPs to specific tissues or cell types, facilitating targeted drug delivery and reducing off-target effects. Additionally, Au-NPs can serve as carriers for therapeutic payloads, protecting drugs from degradation and improving their pharmacokinetic properties. Despite the numerous advantages offered by Au-NPs, their implementation in nanomedicine is not without challenges. Concerns regarding the potential toxicity of Au-NPs, particularly in terms of long-term exposure and accumulation in vital organs, necessitate thorough evaluation of their safety profile. Additionally, ensuring the stability and scalability of Au-NP synthesis and functionalization processes is critical for their translation from bench to bedside.

In summary, this review highlights the immense potential of Au-NPs in nanomedicine, emphasizing their advantageous properties and discussing the challenges associated with their utilization. By critically evaluating the benefits and limitations of Au-NPs, researchers and clinicians can gain valuable insights into the complexities of nanoparticle-based therapies, ultimately advancing the development of innovative biomedical solutions.

2. Investigation of Au-NPs properties

2.1. Localized Surface Plasmon Resonance (SPR)

i. Imagine electrons on the Au-NP surface as tiny springs. Light excites them, making them collectively oscillate like bouncing springs.
ii. Specific light wavelengths resonate with this oscillation, causing intense absorption or scattering, depending on the NP's size and shape.

iii. Spherical NPs scatter red/orange light, making them visible for bioimaging in cells.
iv. Rod-shaped NPs can be tuned to scatter near-infrared light, useful for deeper tissue penetration and photothermal therapy or heating cancer cells [12].

2.2. High X-ray Absorption

i. Au-NPs readily absorb X-rays, making them excellent contrast agents for medical imaging.
ii. Attached to specific molecules, they can highlight tumors or other abnormalities in X-ray scans.
iii. This property, combined with biocompatibility, makes Au-NPs potential candidates for targeted radiotherapy, delivering focused radiation to cancer cells [13].

2.3. Catalysis

i. Due to their large surface area and unique electronic structure, Au-NPs can act as catalysts, speeding up chemical reactions.
ii. Imagine the NP surface as a platform where reactant molecules interact efficiently, lowering the energy barrier for the reaction.
iii. This property finds applications in various fields, from pollution control to fuel cells [14].

2.4. Biocompatibility

i. Unlike many other nanomaterials, Au-NPs generally exhibit low toxicity and good compatibility with biological systems.
ii. This makes them attractive for biomedical applications, where interacting with living cells is crucial.
iii. However, research is ongoing to understand the factors affecting their biocompatibility and potential long-term effects [15].

2.5. Surface Functionalization

i. The gold surface readily binds to various molecules, allowing researchers to "decorate" Au-NPs with specific functionalities.
ii. This is like attaching tools to the NPs for specific tasks:
    a. Attaching antibodies allows targeting diseased cells for drug delivery.
    b. Attaching fluorescent molecules enables them to light up for bioimaging.
    c. Attaching specific biomolecules can create biosensors for detecting diseases [16].

2.6. Drug Delivery

i. Au-NPs can be loaded with drugs and delivered directly to diseased cells or tissues.
ii. This targeted approach minimizes side effects compared to traditional therapies.
iii. For example, Au-NPs loaded with cancer drugs can be guided to tumor sites using specific targeting molecules [17].

2. 7. Biosensing

i. Due to their LSPR properties, Au-NPs can interact with light in very specific ways when they bind to biomolecules.
ii. This allows researchers to design ultrasensitive biosensors that detect the presence of specific molecules, such as disease markers or toxins.
iii. The binding event changes the NP's LSPR, indicating the presence of the target molecule [18].

The investigation of Au-NPs properties has garnered significant attention in various scientific disciplines, ranging from materials science to biomedical engineering. Au-NPs possess unique physicochemical characteristics that make them highly attractive for a wide range of applications, including catalysis, sensing, imaging, drug delivery, and therapy. This introduction provides an overview of the importance and scope of studying Au-NP properties, elucidating their diverse applications and the underlying principles governing their behavior. Au-NPs exhibit distinctive optical properties, primarily attributed to their size-dependent surface plasmon resonance (SPR) phenomenon. The localized surface plasmons of Au-NPs result in strong absorption and scattering of light, making them valuable components in optical devices, sensors, and imaging agents. Moreover, the tunability of SPR through size, shape, and surface modifications enables precise control over the optical response of Au-NPs, facilitating tailored applications in various fields.

Beyond their optical properties, Au-NPs possess remarkable biocompatibility, rendering them suitable for biomedical applications. Their inert nature and low cytotoxicity make them ideal candidates for targeted drug delivery, bioimaging, and theragnostic. Additionally, the facile surface functionalization of Au-NPs allows for the conjugation of biomolecules, drugs, and targeting ligands, further expanding their utility in nanomedicine. Furthermore, the investigation of Au-NP properties extends to their chemical and physical characteristics, including stability, dispersibility, and surface chemistry. Understanding these properties is crucial for optimizing Au-NP synthesis methods, enhancing their stability in various environments, and tailoring their interactions with biological systems. The investigation of Au-NP properties plays a pivotal role in advancing scientific knowledge and technological innovations across multiple disciplines. By elucidating the fundamental principles governing their behavior, researchers can unlock new opportunities for the development of advanced materials, devices, and therapies with enhanced performance and functionality.

3. Types of Au-NPs

The Au-NPs come in various types, each distinguished by their size, shape, and structure (Figure 1). Some common types of Au-NPs include [19]:

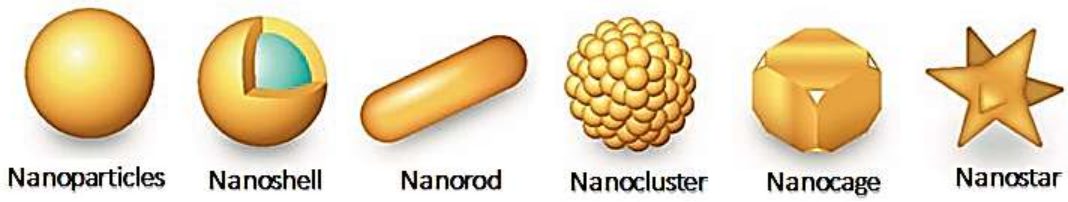

Fig. 1. Unveiling the magic of gold! These nanoparticles don't just glitter, they synthesis into spherical, shells, rods, clusters, cages, and star with unique properties

3.1. Spherical Au-NPs

These nanoparticles have a spherical shape and are among the most common types. They are typically synthesized through chemical reduction methods and have a wide range of applications in biosensing, imaging, drug delivery, and catalysis.

3.2. Gold Nanoshells

Gold nanoshells consist of a dielectric core surrounded by a thin gold shell. Their optical properties can be finely tuned by adjusting the core size and shell thickness, making them useful for applications in cancer therapy, biosensing, and imaging.

3.3. Gold Nanorods

These nanoparticles have an elongated shape resembling rods. Their optical properties depend on the aspect ratio, allowing for tunability of the surface plasmon resonance across the visible and near-infrared spectrum. Gold nanorods are used in photothermal therapy, imaging, and sensing applications.

3.4. Gold Nanocluster

Gold nanoclusters are composed of a small number of gold atoms (typically less than 100) and exhibit unique electronic and optical properties due to their size. They find applications in catalysis, sensing, and biomedical imaging.

3.5. Gold Nanocages

Gold nanocages are hollow structures with porous walls made of interconnected Au-NPs. They have unique optical properties and are used in drug delivery, photothermal therapy, and biomedical imaging.

3.6. Gold Nanostars

These nanoparticles have multiple branches extending from a central core, giving them a star-like morphology. The hierarchical structure results in highly enhanced electromagnetic fields at the tips of the branches, making gold nanostars efficient for applications in surface-enhanced Raman scattering (SERS), photothermal therapy, and imaging [18, 19].

3.7. Chiral Au-NPs

Chiral Au-NPs are a unique class of nanomaterials exhibiting both the inherent properties of Au-NPs and the fascinating world of chirality. They possess specific characteristics such as chirality, size and shape, surface chemistry, biomedical and theranostic applications. These NPs exhibit a non-superimposable mirror image like our left and right hands. This unique structure allows them to interact with other chiral molecules in a specific way. Chiral Au-NPs can be precisely controlled in size and shape, ranging from nanometer to micrometer scales. Their morphology can be tailored to specific applications, like twisted ribbons, spirals, or even intricate helicoid structures. The surface of

these NPs can be functionalized with various molecules, allowing for targeted delivery, biocompatibility, and specific interactions with biological systems. The unique properties of chiral Au-NPs hold immense potential in the field of biomedicine and theranostics, which combines therapeutic and diagnostic capabilities [20].

Chiral nanoparticles can be designed to specifically target and deliver drugs to diseased cells, minimizing side effects and improving treatment efficacy. Their controlled release properties allow for sustained drug delivery over time. The interaction of chiral nanoparticles with specific biomolecules can be used to develop highly sensitive and selective biosensors for disease diagnosis and monitoring. They can detect biomarkers associated with various diseases like cancer or Alzheimer's. Chiral Au-NPs can be used as contrast agents for various imaging techniques like CT scans or photoacoustic imaging, enabling better visualization of tumors or other pathologies. By absorbing light, chiral Au-NPs can generate heat, allowing for targeted destruction of diseased cells through a process called photothermal therapy [21].

In Figure 2, a seed-mediated synthesis of enantiomorphic Au nanooctopods and the chiral morphology dependence of cellular uptake is reported. The chiral Au nanooctopods synthesized with L- or D-glutathione have opposite handedness, resulting in opposite circular dichroism signals, which is consistent with finite difference time domain simulations. D-glutathione Au nanooctopods demonstrate greater than 30% enhanced cellular uptakein GL261 and bEnd.3 cells compared with L-glutathione Au nanooctopods (racemic Au nanooctopods).

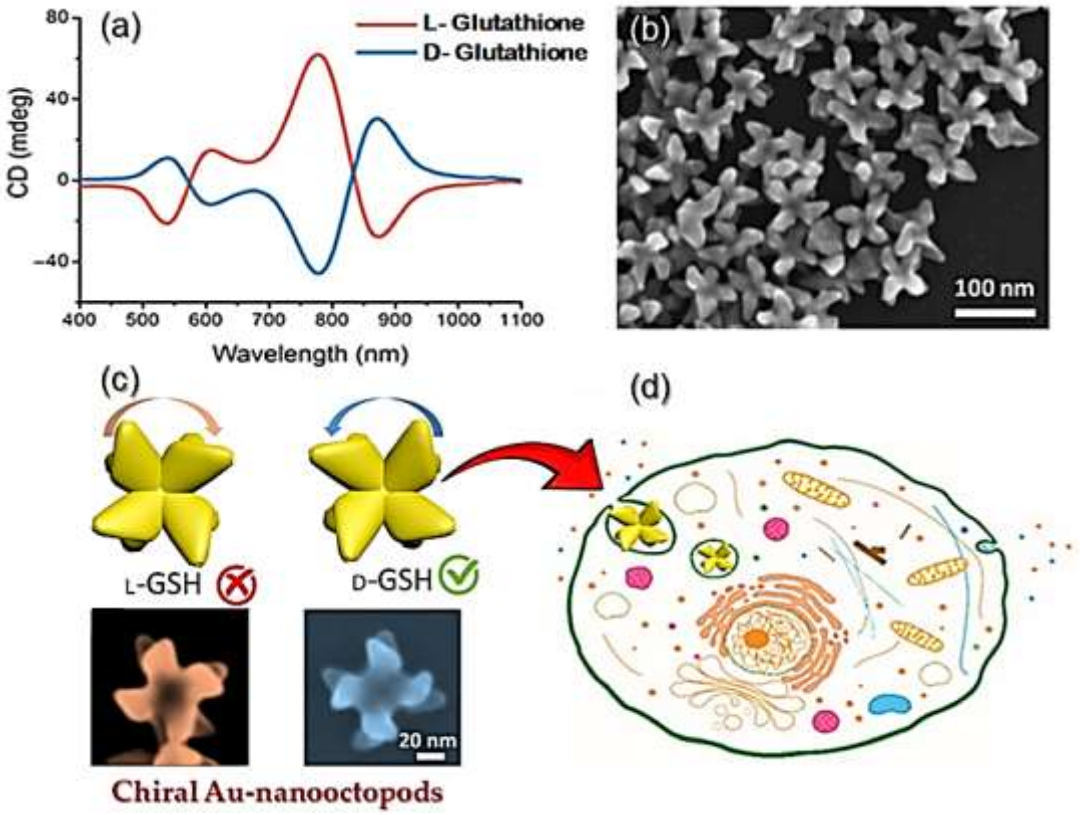

Fig. 2. Characterization of chiral Au nanooctopods (NOPs). (a) Circular dichroism (CD) spectra of chiral Au NOPs in the vis–NIR region. (b) SEM images of L-Glutathione (GSH) NOPs. (d) Models and corresponding SEM images of L- and D-GSH NOPs. (d) Schematic illustration of the chiral morphology-dependent cellular uptake which showed positive response for D-GSH NOPs

This offers a minimally invasive approach for cancer treatment. The exploration of chiral Au-NPs is still in its early stages, but their potential for advancing healthcare and developing innovative theranostic techniques is highly promising. Those mentioned are just a few examples of the diverse types of Au-NPs that existed, each with its unique properties and potential applications. As research progresses, we can expect to see these fascinating nanomaterials play a significant role in future medical advancements. In this review, the focus is on the advantages and disadvantages of the spherical shape of Au-NPs in the delivery of organic substances, and it has been tried to be investigated from different aspects of medical treatment.

4. Advantages of Au-NPs in Nanomedicine

Electrostatic interactions are a crucial factor in how biomolecules, like DNA, proteins, lipids, and carbohydrates, bind to the surface of Au-NPs. Here's a breakdown of how each type interacts. Regarding the possibility of connection in DNA, it can be said that, due to its negatively charged phosphate backbone, DNA readily adsorbs onto positively charged Au-NPs through electrostatic attraction. This makes DNA a popular choice for functionalizing Au-NPs for biosensing applications, where specific DNA sequences can be attached to detect complementary targets. Protein adsorption is more complex than DNA due to their diverse structures and charges. Negatively charged protein regions will bind to positively charged Au-NPs, while positively charged regions might be repelled.

Additionally, hydrophobic interactions and hydrogen bonding can play a role. Protein size and shape also influence how they interact with the Au-NP surface. Lipid as an amphiphilic molecule, with both polar and nonpolar regions, can adsorb onto Au-NPs through various mechanisms. Polar head groups might interact electrostatically with charged Au-NPs, while nonpolar tails can embed themselves into the surface, forming self-assembled monolayers. Lipid size and charge distribution influence their adsorption behaviours. Similar to lipids, carbohydrates display complex interactions with Au-NPs. Charged sugar groups can exhibit electrostatic interactions, while hydroxyl groups might form hydrogen bonds with the gold surface. The specific carbohydrate structure and charge distribution determine its adsorption affinity [22].

Au-NPs have become prominent players in the field of targeted drug delivery due to their unique properties such as biocompatibility, tunable size and surface chemistry, and the ability to form strong bonds with various biomolecules. Monolayer coatings, particularly those formed through covalent bonding, offer a robust and precise way to attach drugs, DNA, proteins, or targeting moieties to the AuNP surface (Figure 3). The chosen molecule is incubated with the prepared Au-NPs under controlled conditions (pH, temperature, time) to promote covalent bonding. Factors like molecule concentration, incubation time, and linker length influence the density and orientation of the coating, impacting efficiency and targeting ability [23].

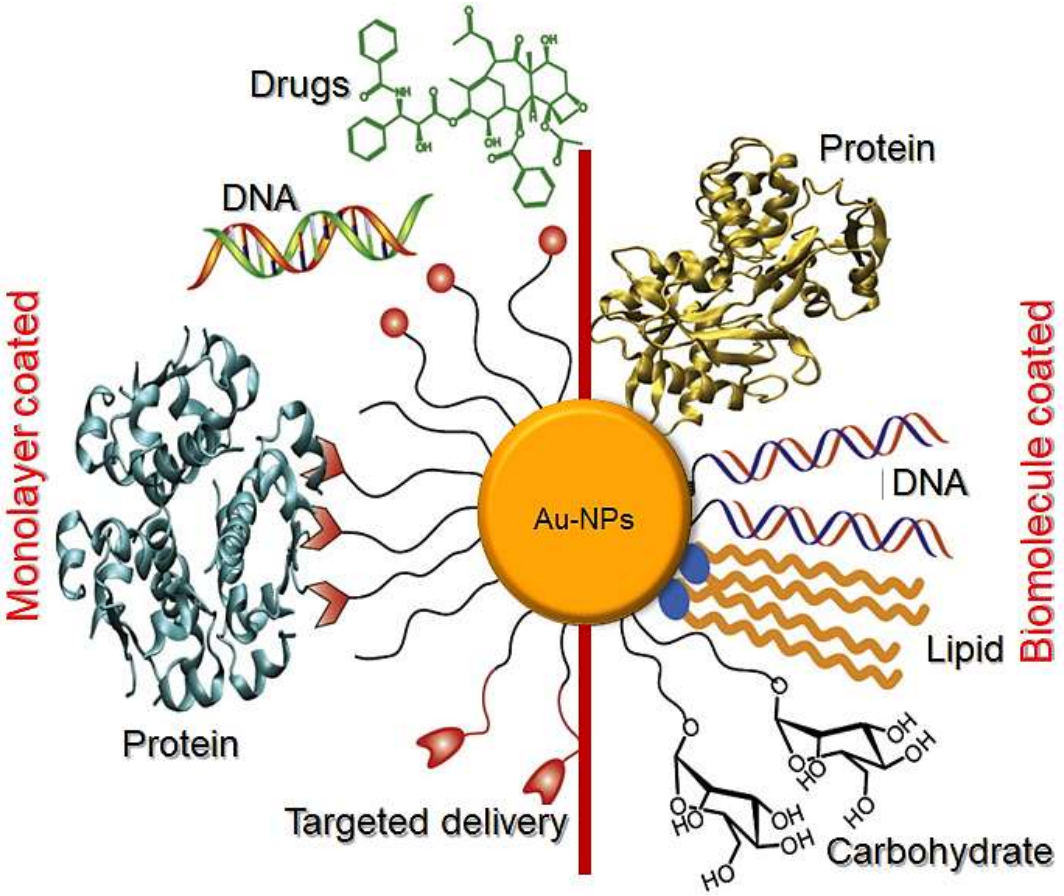

Fig. 3. Schematic illustration of biomolecular and monolayer coating of bio-organic compounds with Au-NPs

Here's a detailed breakdown of the monolayer coating process.

4.1. Surface Preparation

The first step involves cleaning and activating the Au-NPs surface to create reactive sites for bonding. This often involves removing organic contaminants and creating thiol (R-SH) groups on the gold surface. Common methods include treatment with piranha solution (H_2SO_4/H_2O_2) or citrate-capped AuNPs [24].

4.2. Molecule Selection and Modification

The molecule you want to attach (drug, DNA, protein, targeting agent) needs specific modifications to enable covalent bonding with the AuNP surface. This typically involves adding functional groups like thiols (R-SH), di-sulfides (R-S-S-R'), or amines ($R-NH_2$) to the molecule, depending on the chosen linker and bonding strategy.

4.3. Covalent Bonding Strategies
4.3.1. Thiol-gold bond

This is the most common strategy due to the strong affinity of sulfur to gold. Thiolated molecules spontaneously bind to the activated gold surface, forming a chemisorption bond.

4.3.2. Disulfide bond

This involves creating a disulfide bridge between a thiol on the molecule and two nearby thiols on the AuNP surface, offering higher stability.

4.3.3. Carboxyl-amine coupling

This method uses carbodiimide reagents to activate carboxylic acid groups on the molecule and form amide bonds with amine groups on the AuNP surface.

4.3.4. Click chemistry

This versatile approach utilizes Huisgen cycloaddition between azide and alkyne groups for efficient and specific coupling.

4.4. *Advantages of Covalent Monolayer Coating*
4.4.1. Stability

Covalent bonds provide strong and stable attachment, preventing premature release of the payload. Specificity: Tailored molecules attached via covalent bonds enable targeted delivery to specific cells or tissues, minimizing off-target effects.

4.4.2. Controlled release

Triggers like enzymes, pH changes, or light can be incorporated into the design to control the release of the payload at the target site.

4.4.3. Synthesis complexity

Covalent modification of molecules and linker design can be intricate.

4.4.4. Potential immunogenicity

Foreign molecules attached to the Au-NPs surface might trigger immune responses. Overall, monolayer coating with covalent bonding offers a powerful approach for fabricating functionalized AuNPs for targeted drug delivery, DNA transfection, protein delivery, and various other biomedical applications. Careful selection of molecules, linker strategies, and optimization techniques are crucial for achieving the desired performance and maximizing therapeutic impact.

4.5. Brilliant to Reveal the Benefits of Au-NPs in Nanomedicine

Au-NPs have emerged as captivating stars in the nanomedicine horizon, not just for their literal gleam, but for their unique properties that offer ground-breaking opportunities in diagnosis, therapy, and drug delivery. Unlike many other nanomaterials, Au-NPs exhibit low toxicity and compatibility with biological systems, minimizing risks and side effects for patients. This biocompatibility opens the door to their diverse applications within the human body. Au-NPs possess a fascinating property called SPR. When light interacts with these nanoparticles, it excites electrons on their surface, causing

them to collectively oscillate. This unique interaction allows scientists to manipulate the optical properties of Au-NPs, tailoring them for specific purposes. For instance, their light scattering capability makes them excellent contrast agents in various imaging techniques like X-ray and CT scans, highlighting tumors or other abnormalities with high precision. Additionally, by harnessing the heat generated during SPR, Au-NPs can be used in photothermal therapy, selectively killing cancer cells while sparing healthy tissue (Figure 4) [24].

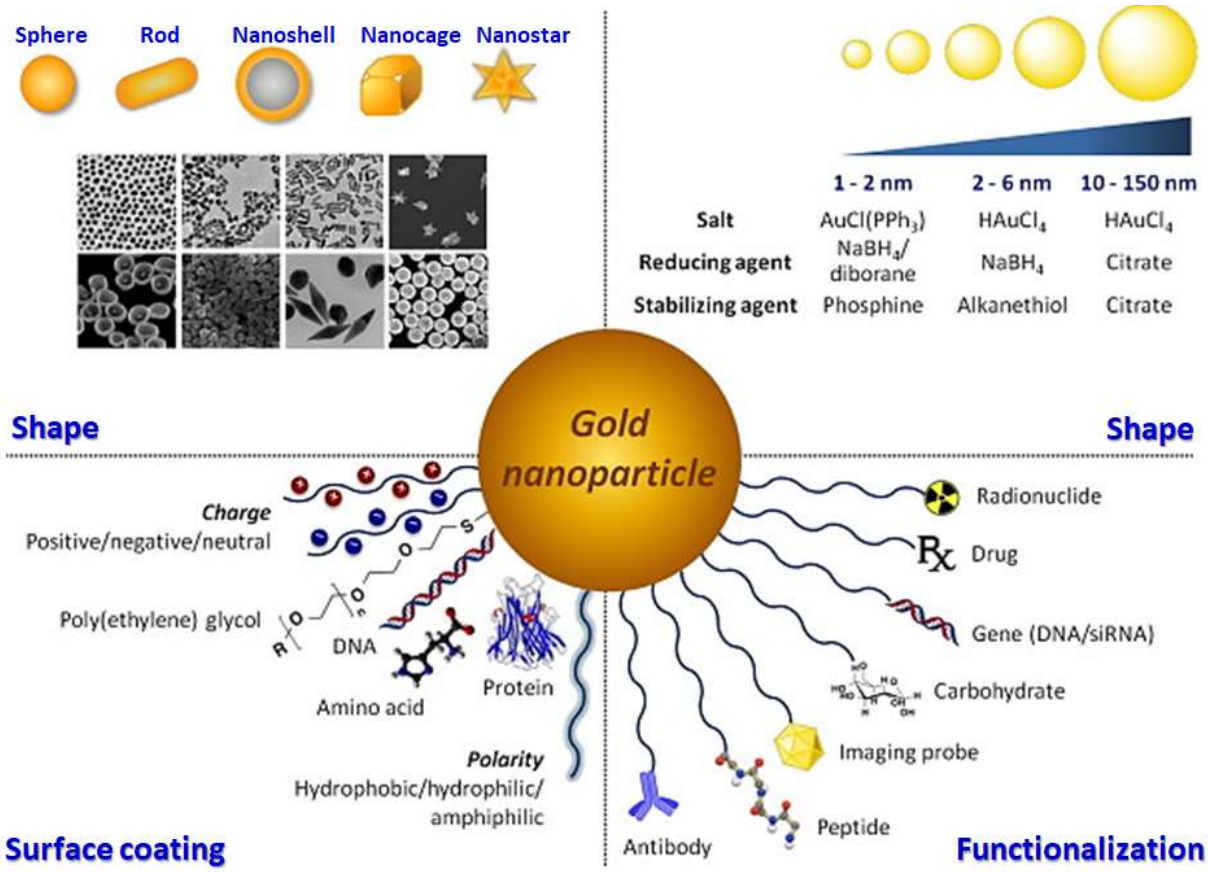

Fig. 4. Advantages of Au-NPs in terms of size and shape for use in nanomedicine applications

One of the most exciting advantages of Au-NPs lies in their ability to serve as efficient drug delivery vehicles. Their surfaces can be readily modified with various molecules, including drugs and targeting molecules. This "functionalization" allows scientists to create smart Au-NPs that seek out specific diseased cells in the body, delivering their payload directly to the target site. This targeted approach minimizes side effects on healthy tissues, often a major concern with traditional therapies. Additionally, the small size and tunable shape of Au-NPs allow them to easily navigate biological barriers, reaching even hard-to-access areas within the body. Tumors present a unique opportunity for Au-NP-based therapies. These rapidly growing masses often have leaky blood vessels and impaired lymphatic drainage, leading to the Enhanced Permeability and Retention (EPR) effect. This natural phenomenon works in our favor, as Au-NPs injected into the bloodstream tend to accumulate within tumors due to their size and the EPR effect. This targeted accumulation allows for high concentrations of therapeutic agents to be delivered directly to the tumor site, maximizing their effectiveness while minimizing systemic exposure. The size and shape of Au-NPs are not simply aesthetic choices; they play a crucial role in their functionality [25].

By meticulously controlling these parameters, scientists can optimize Au-NPs for specific applications. Smaller nanoparticles, for example, exhibit better penetration into tissues, while larger

ones offer larger surface areas for drug loading. Similarly, rod-shaped nanoparticles have unique optical properties ideal for photothermal therapy, while spherical nanoparticles excel in drug delivery. This meticulous control over size and shape allows researchers to craft Au-NPs with tailor-made properties for diverse nanomedicine applications. The advantages of Au-NPs extend beyond therapy and drug delivery. Their unique properties make them valuable tools for diagnostic purposes. As mentioned earlier, their SPR-based light scattering makes them excellent contrast agents, enhancing the detail and accuracy of medical scans. Additionally, Au-NPs can be functionalized with specific biomolecules, allowing them to act as biosensors, detecting the presence of disease markers or pathogens in biological samples with high sensitivity. The advantages of Au-NPs in nanomedicine paint a truly golden picture. Their biocompatibility, tunable properties, and ability to be functionalized offer unprecedented opportunities for targeted therapy, efficient drug delivery, and accurate diagnostics. While challenges remain, ongoing research and development are continuously refining these versatile tools. As we unlock the full potential of Au-NPs, we can expect a brighter future for personalized medicine, where treatment strategies become as unique and precise as the patients themselves.

5. Disadvantages of Au-NPs in Nanomedicine

The utilization of Au-NPs in nanomedicine, while promising, is not without its drawbacks. One significant limitation is the cost associated with their production, which can be prohibitively expensive, hindering their widespread use in certain medical applications. Additionally, Au-NPs may pose concerns regarding clearance from the body, as they have been found to accumulate in certain organs over time, potentially leading to long-term toxicity or adverse effects. Another challenge is the biodistribution of Au-NPs within the body, which can be challenging to predict due to factors such as size, shape, and surface chemistry. This unpredictability raises concerns about their safety and efficacy in targeted drug delivery and imaging applications. Furthermore, Au-NPs may elicit immune responses in some individuals, causing allergic reactions or inflammation, thereby limiting their clinical utility. Moreover, navigating regulatory challenges presents a significant barrier to the clinical translation of Au-NP-based medical products. The lengthy and complex regulatory approval process for such products delays their introduction into clinical practice, impeding the development of innovative nanoparticle-based therapies. Overall, while Au-NPs hold immense potential in nanomedicine, addressing these disadvantages is essential to maximize their benefits and facilitate their safe and effective integration into clinical practice (Figure 5) [22, 26].

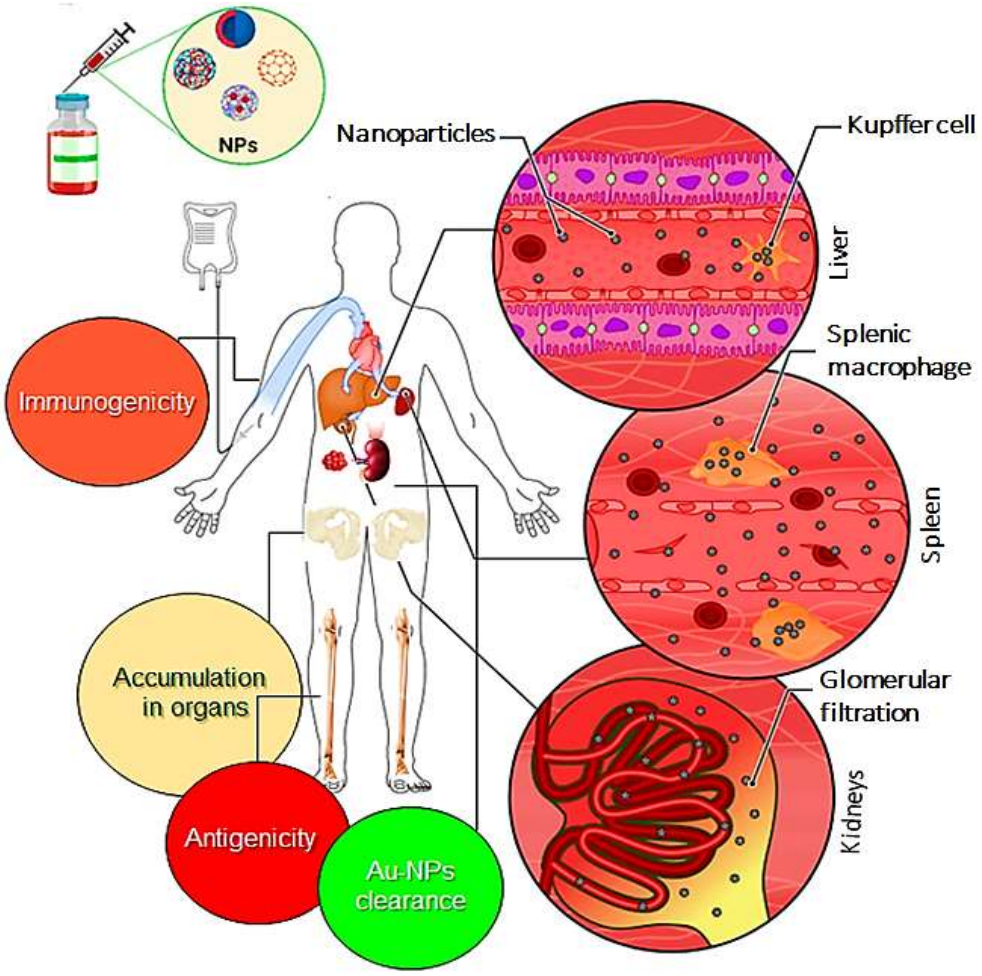

Fig. 5. Au-NPs small enough to pass through the glomerular membrane (below 5 nm) are able to be excreted through the urine. Also, the remaining nanoparticles have the opportunity to accumulate in tumor tissues

6. Bibliometric Study of Au-NPs for Delivery Application

Figure 6, showed the number of publications and citations in Web of Science. A total of 564 publications and 28,101 number of citations have been listed since 2002 in Web of Science related to Au-NPs based drug delivery applications, the sum of citations also increased significantly over years (2021). There is a reduced bibliometric study on the number of publications and citations of Au-NPs from 2022 until the end of February 2024, which may be due to the high cost of their production, which has hindered their widespread use in medical applications. The next reason may be due to concern about the possibility of cleansing from the body. On the other hand, the biodistribution of Au-NPs in the body has been challenging and has raised concerns about their safety and efficacy in targeted drug delivery and imaging applications. Also, Au-NPs may trigger immune responses in some individuals, causing allergic or inflammatory reactions. In addition to all this, the lengthy and complex regulatory approval process for such products delays their introduction into clinical practice, prevents the promotion of published research, and hinders its practical development [27]. So, all the mentioned cases could be a reason for the reduction of publication and citation in research related to the production and usage of Au-NPs. Hence, investigating distinctive Au-NPs architectures, such as those with chiral configurations, becomes imperative to achieve targeted cellular penetration for drug delivery and the eradication of cancerous cells.

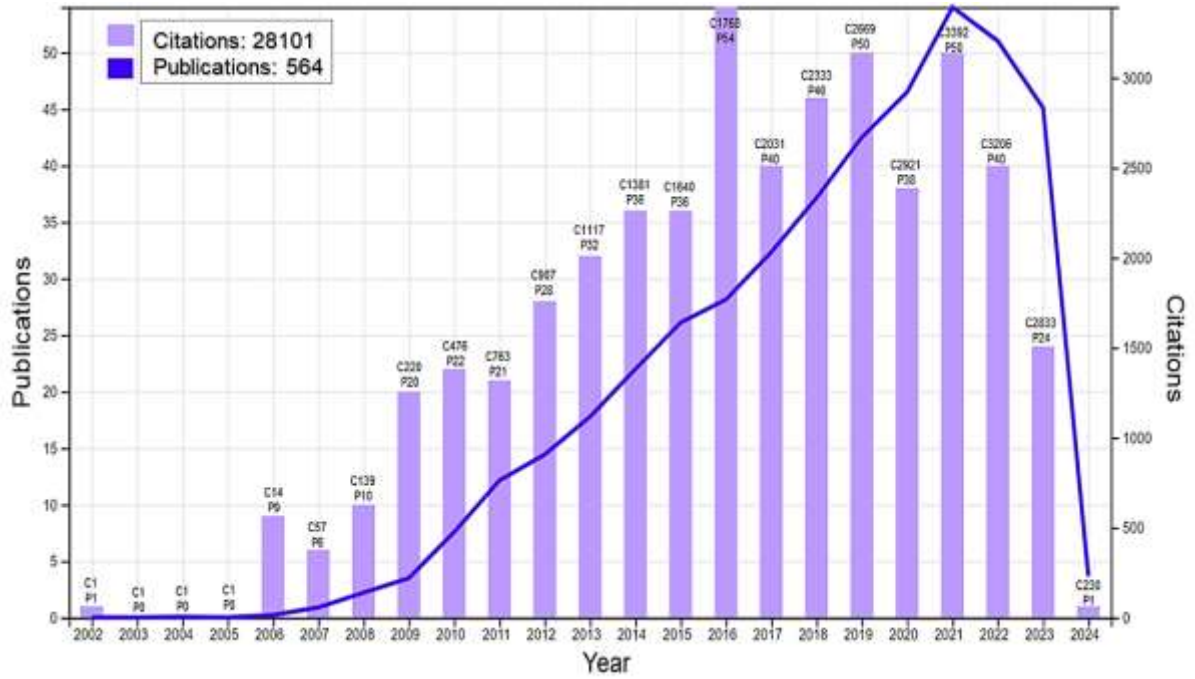

Fig. 6. Number of published articles and their citation for Au-NPs and its delivery application in Web of Science. (2002-February 2024)

7. Conclusion

In conclusion, this review has comprehensively explored the vast potential of Au-NPs in the field of nanomedicine. We have discussed their advantageous properties, including exceptional biocompatibility, tunable optical properties, and facile surface functionalization, which render them highly promising for a wide array of biomedical applications such as drug delivery, imaging, diagnostics, and therapy. The tunable optical properties of Au-NPs, particularly their ability to exhibit surface plasmon resonance (SPR), offer opportunities for precise control over their optical behavior, enabling the development of contrast agents for various imaging modalities. Furthermore, their facile surface functionalization allows for targeted delivery of therapeutic payloads and enhances specificity towards disease biomarkers or cellular receptors. However, the review also acknowledges the challenges associated with the implementation of Au-NPs, such as concerns regarding their potential toxicity and the need for thorough evaluation of their safety profile. Additionally, ensuring the stability and scalability of Au-NP synthesis and functionalization processes is crucial for their translation from bench to bedside. By critically evaluating both the benefits and limitations of Au-NPs, this review provides valuable insights for researchers and clinicians, ultimately contributing to the advancement of innovative biomedical solutions in nanomedicine. In conclusion, the challenges ahead in not removing the obstacles ahead in the use of Au-NPs in recent years have reduced the published research and number of citations in this area. Therefore, it is suggested to investigate special structures, including gold chiral structures, in order to provide an effective and selective answer in cell permeability for the application of drug delivery to inhibit or prevent the proliferation of malignant cells.

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