Advancements in the Bio-efficacy of Gold-based Complexes: A Comprehensive Review of Synthetic Approach and Therapeutic Potential

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Abstract. Gold-based compounds have emerged as promising candidates in medicinal chemistry due to their unique physicochemical properties and broad therapeutic potential. This review highlights recent developments in gold (I), gold (III), and gold-nanomaterial systems, emphasizing their anticancer, anti-inflammatory, antimicrobial, antiviral, and neuroprotective activities. Key mechanisms include redox modulation, enzyme inhibition, and targeted biomolecular interactions. Advances in gold–polymer composites and nanoscale architectures have improved stability, selectivity, and controlled drug release, expanding their relevance in precision medicine. Clinically progressing platforms such as gold nanocrystals, nanoshell photothermal agents, and nucleic-acid-functionalized constructs underscore their translational promise. Additionally, diverse synthetic strategies and structure–activity insights demonstrate the advantages of gold over other metals. Conclusively, this review outlines gold's growing impact on therapeutic innovation and biomedical research.

1 Introduction

The alkylating agent mechlorethamine, a nitrogen mustard, was one of the earliest medications used clinically in modern medicine to treat cancer. It was discovered in the 1940s that it was effective in treating lymphomas [1-3]. The first medicine to cure a solid tumor was the antimetabolite methotrexate in 1956. The following year, a new class of chemicals called pyrimidine analogs was produced, the first of which was 5-fluorouracil [4-7]. There have been numerous successful anticancer medication developments since then [8-13]. Modern clinical oncology relies heavily on chemotherapy. It was immediately clear that off-target toxicity and treatment resistance were two of the biggest problems with the possibility for systemic administration of cytotoxic drugs to cancer patients when it was first identified in the middle of the twentieth century. The scientific and medical communities were driven to seek ways to overcome these restrictions, which in turn influenced the development of current research and therapeutic practices in the field [14, 15]. Medication development initiatives shifted their emphasis to targeted therapies and

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anti-cancer medication combinations to address resistance while minimizing off-target adverse effects **(Figure 1)** [16-18].

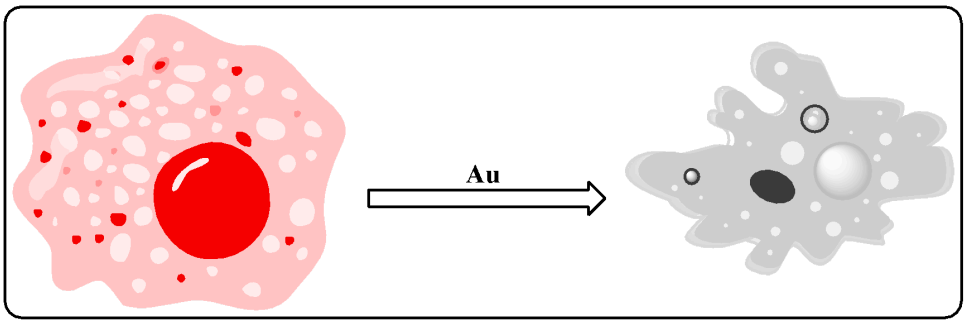


Fig. 1. Au-based Chemotherapy.

Gold, traditionally valued for its aesthetic and financial worth, has emerged as a significant element in the realms of catalysis, complex chemistry, and medicinal applications. Its unique chemical and physical properties, including high resistance to oxidation, excellent conductivity, and strong relativistic effects, have positioned gold as a versatile and impactful material in these fields [19, 20].

In recent years, gold-based polymer composites have emerged as a groundbreaking class of materials in biomedical research, particularly for their applications in anticancer and antiviral therapies. These composites combine the unique physicochemical properties of gold, such as high biocompatibility, resistance to oxidation, and plasmonic behavior, with the versatility of polymers, which offer tunable mechanical properties, biodegradability, and functionality for targeted delivery [21]. This synergy has led to the development of advanced materials capable of addressing some of the most challenging aspects of modern medicine, including selective targeting, controlled drug release, and minimal off-target effects. Cancer and viral infections remain leading global health challenges, with both diseases exhibiting significant resistance to conventional therapies [22]. Gold-based polymer composites offer promising solutions by leveraging their ability to interfere with specific biological pathways, enhance drug solubility and stability, and deliver therapeutics with high precision. For instance, in cancer therapy, these composites are utilized for photothermal therapy, drug delivery, and radiation enhancement [23]. Similarly, in antiviral applications, they demonstrate potent activity against a range of viruses by inhibiting replication, enhancing immune responses, and serving as carriers for antiviral agents. Figure 2 highlights the advancements made over the last decade in the bio-efficacy of gold-based polymer composites, focusing on their mechanisms of action, innovations in design, and applications in anticancer and antiviral therapies [24]. Towards a synthetic part, gold-based catalysts have revolutionized the field of heterogeneous and homogeneous catalysis. Unlike other noble metals, gold exhibits remarkable catalytic activity at the nanoscale. Gold nanoparticles, for example, are highly effective in oxidation reactions, hydrogenation, and carbon-carbon coupling processes [25]. Their unique electronic structure enables them to activate small molecules such as O_2 and CO, making them indispensable in green chemistry and industrial processes [26].

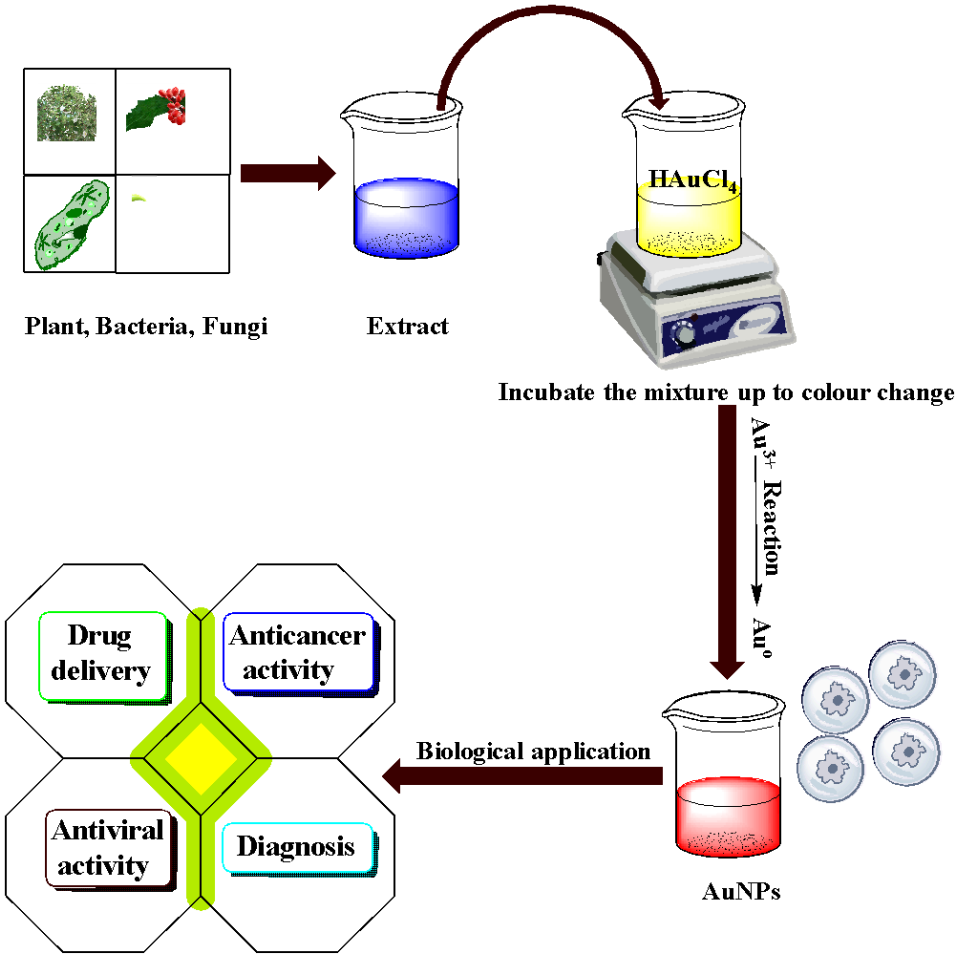


Fig. 2. bio-efficacy of gold-based complexes in most sciences

From a biological perspective, gold compounds have been extensively studied for their therapeutic properties. Auranofin, a gold(I)-based compound, is an FDA-approved drug for the treatment of rheumatoid arthritis. Beyond this, gold compounds are being investigated for their anticancer, antimicrobial, and anti-inflammatory activities. The ability of gold complexes to interact with biomolecules, modulate redox activity, and inhibit specific enzymes underpins their potential in medicinal applications **(Figure 3).** Beyond traditional gold salts such as auranofin, several modern gold-based therapeutics including catalytic gold nanocrystals (CNM-Au8), PEGylated gold-TNF conjugates (CYT-6091/Aurimune), gold-silica nanoshell photothermal agents (AuroShell/AuroLase) and gold-core spherical nucleic acids (NU-0129) have entered early human studies (Phase 0–II), demonstrating feasibility of systemic delivery, target engagement or focal tumour ablation and justifying continued clinical development **(Table 1)** [27].

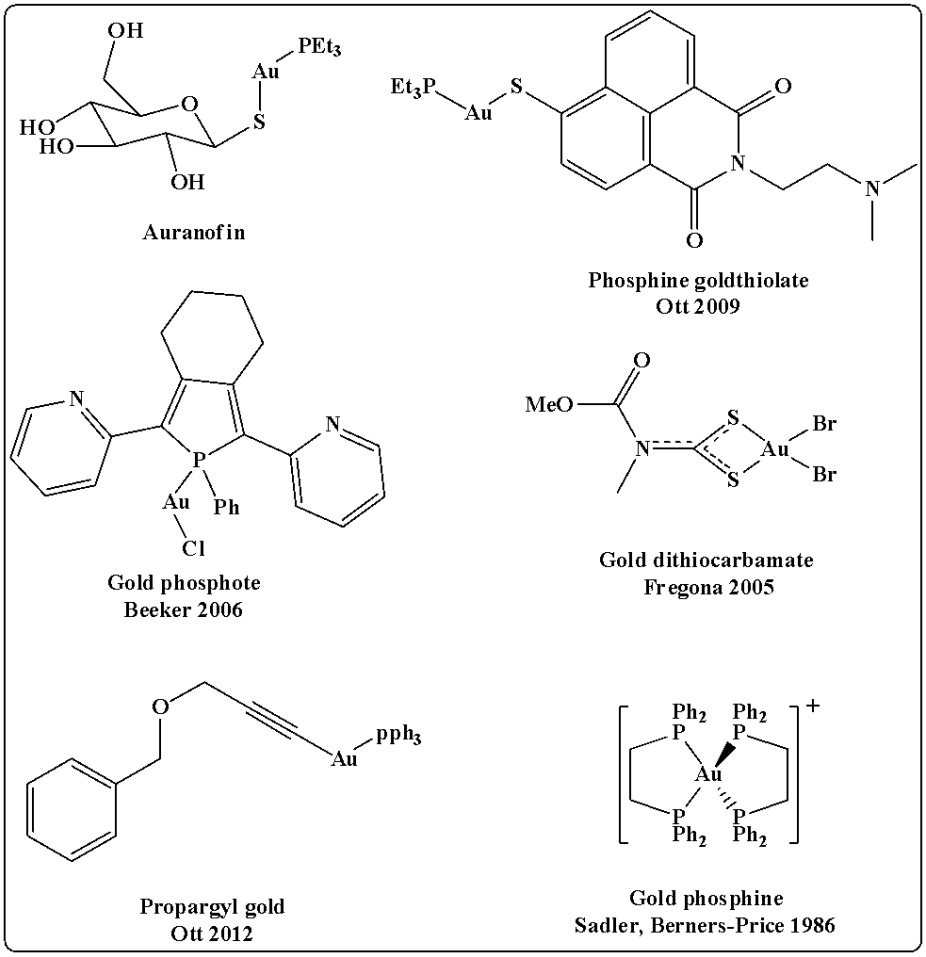


Fig. 3. Reported gold complexes

Table 1 Gold-Based Drugs in Clinical Trials

Sr. No.	Au-based drug	Clinical phases & key trials*
1	CNM-Au8	– Phase 2/3 "Healey ALS Platform Trial" (ALS) – Phase 2 for Parkinson's disease (NCT03815916) – Also studied in MS (Multiple Sclerosis); there is evidence of "brain target engagement" in MS / PD from clinical data.
2	CYT-6091 (Aurimune)	– Cancer (advanced solid tumors) — used to deliver TNF-α more safely / effectively. – Phase I completed.
3	NU-0129	– Phase 0 / early human trial (NCT03020017) in recurrent glioblastoma / gliosarcoma.

*A proposed biological application of clinically trial drugs.

Recent advances have highlighted the utility of gold catalysts in sustainable energy, such as fuel cells and CO_2 reduction. Gold-based materials have also been reported in photothermal therapy and imaging, leveraging their plasmonic properties. Studies continue to expand the understanding of gold's role in biological systems and its potential to address pressing challenges in medicine and environmental sustainability [28]. This article focused on gold transitioning from a symbol of wealth to a cornerstone of innovation across diverse scientific disciplines. Herein, we summarized its multifunctional roles in catalysis, complex chemistry, and medicine underscoring its transformative impact and promise for future applications [29].

2 Significance of gold in various medicinal area

In medicinal chemistry, the design strategy focuses on optimizing the biological activity and selectivity of compounds to target specific disease pathways while minimizing off-target effects. One powerful approach involves incorporating metal-based molecules into drug design, which enhances the potency and efficacy of compounds [30]. Transition metals such as platinum, gold, and copper can significantly influence the pharmacodynamics of a drug by altering the compound's electronic structure, facilitating interactions with biological targets, or improving bioavailability. Metal coordination can also stabilize the drug molecule, increase its stability in vivo, and promote better interaction with cellular machinery. By leveraging the unique properties of metal ions, researchers can develop compounds with enhanced activity against complex diseases, including cancer and neurodegenerative disorders, where traditional organic molecules may fall short. Thus, metal-based compounds provide a promising avenue for advancing the potency and therapeutic potential of medicinal agents [31-33]. The below **Figure 4** illustrates the importance of gold in medicinal chemistry, featuring its applications such as anti-cancer agents, anti-inflammatory drugs, diagnostics, and drug delivery systems [34].

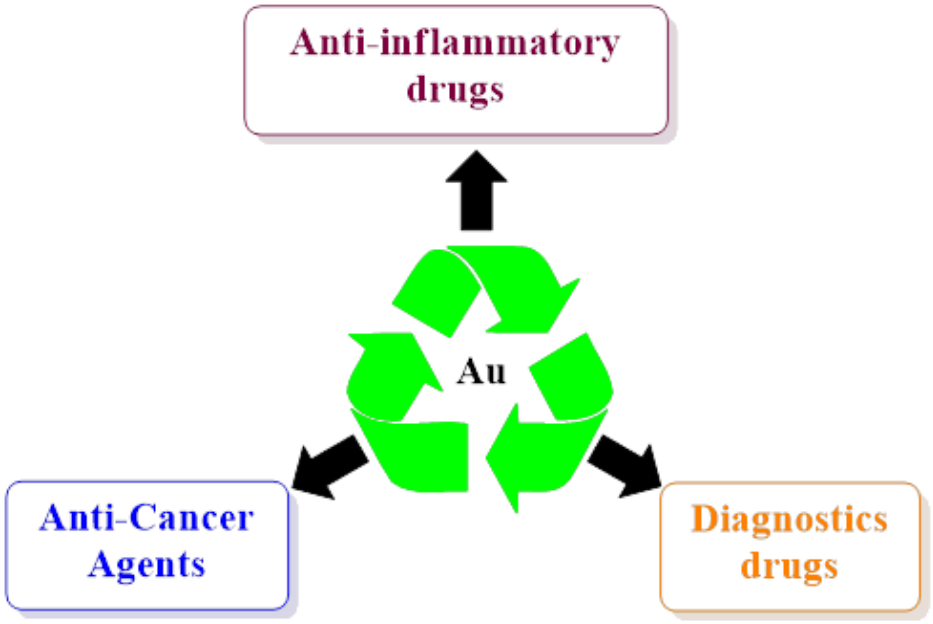


Fig. 4. Significance of gold-based drugs in medicinal chemistry

2.1. Au in anticancer study

Gold complexes, particularly those of gold(I) and gold(III), have attracted significant interest in medicinal chemistry due to their potential as anticancer agents. Gold(I) complexes, such as auranofin, have been shown to exhibit cytotoxicity against various

cancer cell lines [35]. These compounds primarily exert their effects by interacting with cellular thiol groups, disrupting redox homeostasis, and impairing the function of proteins involved in cell growth and survival. Gold complexes can also interfere with critical enzymes like topoisomerases, which play a role in DNA replication and repair, leading to DNA damage and cell cycle arrest [36]. Gold(III) complexes, being more electrophilic, have demonstrated stronger interactions with biological molecules, potentially leading to the activation of apoptotic pathways. By inducing cell cycle arrest at different phases and promoting apoptosis, gold complexes can effectively limit the proliferation of cancer cells. Ongoing research aims to refine these properties, improving the therapeutic potential of gold-based compounds in oncology [37].

2.2. Au in anti-inflammatory properties

Gold complexes have long been studied for their anti-inflammatory effects, with auranofin being one of the most well-known examples. Auranofin was initially developed for the treatment of rheumatoid arthritis (RA) and remains a clinically approved drug for this purpose. The mechanism of action of gold complexes in inflammation primarily involves the inhibition of nuclear factor kappa B (NF-κB), a transcription factor that regulates the expression of pro-inflammatory cytokines [38]. By modulating the immune response and reducing the activation of NF-κB, gold complexes can suppress inflammation and tissue damage associated with autoimmune diseases. In addition, gold complexes can influence immune cell function by inhibiting enzymes involved in inflammatory signalling pathways. Their ability to reduce inflammatory mediators makes them valuable not only for RA but also for other chronic inflammatory conditions, such as inflammatory bowel disease, asthma, and psoriasis [39].

2.3. Au in antimicrobial activity

The antimicrobial potential of gold complexes has become an area of considerable interest, particularly given the growing problem of antibiotic resistance. Gold(I) and gold(III) compounds have demonstrated activity against a range of bacterial, fungal, and parasitic pathogens. Their antimicrobial effects are thought to stem from their ability to bind to and disrupt microbial thiol groups, which are essential for the function of many enzymes and proteins [40]. Additionally, gold complexes can destabilize microbial membranes, leading to cell death. In particular, gold nanoparticles (AuNPs) have been investigated for their ability to target bacterial and fungal cells, acting as novel agents against resistant strains [41]. Gold complexes have shown promise in the treatment of infections caused by both Gram-positive and Gram-negative bacteria, as well as fungal infections. However, further research is required to optimize their effectiveness, safety, and therapeutic applications in the context of antimicrobial resistance [42].

2.4. Potential of Au in the neurodegenerative diseases

Researchers are also looking at the possibility of using gold complexes to treat neurological illnesses including Parkinson's and Alzheimer's. The antioxidant capabilities of gold complexes are one of the main ways in which they may provide neuroprotective effects. Because of their roles in cellular damage and neuroinflammation, reactive oxygen species (ROS) are thought to play a role in the development of numerous neurodegenerative disorders. Antioxidants in the form of gold complexes, especially gold(I) complexes, have been demonstrated to reduce oxidative stress and scavenge reactive oxygen species (ROS) [43]. Metal ions such as copper and iron contribute to reactive oxygen species (ROS) production and pathogenic protein aggregation; however, gold complexes can chelate these ions. As an example, gold complexes have the potential to prevent the damaging beta-amyloid plaques from aggregating in Alzheimer's disease. To validate the therapeutic utility of gold-based compounds for the treatment of neurodegenerative diseases, more research is required, despite encouraging first results [44].

2.5. Au as targeted drug delivery systems

Gold nanoparticles (AuNPs) have been extensively studied for their ability to serve as vehicles for targeted drug delivery. These nanoparticles can be functionalized with various ligands, antibodies, or other molecules to target specific receptors on disease cells, such as those found on cancer cells. The use of gold nanoparticles in drug delivery offers several advantages, including enhanced stability of therapeutic agents, improved solubility, and the potential for controlled release [45]. Gold nanoparticles can protect drugs from premature degradation and can be engineered to release their payload at a specific site within the body, such as within a tumor. Moreover, their ability to be easily modified and functionalized makes them highly versatile in terms of targeting different diseases. This targeted approach not only enhances the efficacy of the therapeutic agents but also minimizes systemic side effects, offering a promising strategy for precision medicine [46].

2.6. Au- complexes in diagnostic imaging

Gold-based compounds, particularly gold nanoparticles (AuNPs), have shown promise in various diagnostic imaging techniques due to their unique optical properties. The high atomic number of gold makes gold nanoparticles particularly effective in enhancing contrast in imaging modalities such as X-ray and computed tomography (CT) imaging [47]. This property is leveraged to improve the visualization of tissues or abnormalities, such as tumours. Additionally, gold nanoparticles can be used in surface-enhanced Raman scattering (SERS), a technique that significantly amplifies Raman signals, allowing for the detection of small quantities of biomolecules [48]. This makes gold nanoparticles useful in early disease detection, as they can bind to specific biomarkers associated with diseases like cancer. By enhancing the sensitivity and resolution of imaging, gold complexes hold significant promise for non-invasive diagnostic applications, paving the way for earlier and more accurate disease detection [49].

3 Gold(I) vs. Gold(III) complexes in medicinal chemistry

In the context of medicinal chemistry, gold(I) and gold(III) complexes differ significantly in their chemical properties and therapeutic applications. Gold(I) complexes, such as auranofin, are more stable and often interact with biomolecules through the formation of covalent bonds with thiol groups, which play a critical role in the regulation of cellular functions [50]. These complexes tend to have lower toxicity and are commonly used in treatments for autoimmune and inflammatory diseases, as well as cancer. On the other hand, gold(III) complexes are more reactive due to their higher oxidation state and tend to form stronger covalent bonds with nucleophilic centers, such as nitrogen and oxygen in DNA and proteins [51]. This reactivity makes gold(III) complexes potent anticancer agents, as they can disrupt DNA replication and induce apoptosis in cancer cells. However, the higher reactivity of gold(III) compounds also poses challenges related to stability and selectivity, making them more difficult to develop for clinical use compared to gold(I) complexes [52].

In short, gold complexes hold significant promise in medicinal chemistry, offering a diverse range of therapeutic applications from cancer treatment to antimicrobial and anti-inflammatory therapies. Their ability to interact with biomolecules, particularly through sulphur coordination and redox modulation, gives them a unique mechanism of action that distinguishes them from other classes of drugs. While gold(I) complexes have seen success in treating conditions like rheumatoid arthritis and cancer, gold(III) complexes are being explored for their more potent anticancer effects. Additionally, gold nanoparticles offer exciting potential in drug delivery and diagnostic imaging, allowing for more targeted and personalized treatment approaches. However, while preclinical results are encouraging, further research is necessary to optimize the safety, efficacy, and clinical utility of gold-based compounds in medicine [53].

4 Diversity in au-based synthetic approaches

Many researchers and experts see gold nanoparticles as having great potential for use in the future, particularly in healthcare. As opposed to other building methods, biosynthesis using plants, bacteria, and fungi achieves the goal with less harm. Gold nanoparticles have made it into cancer treatment [54].

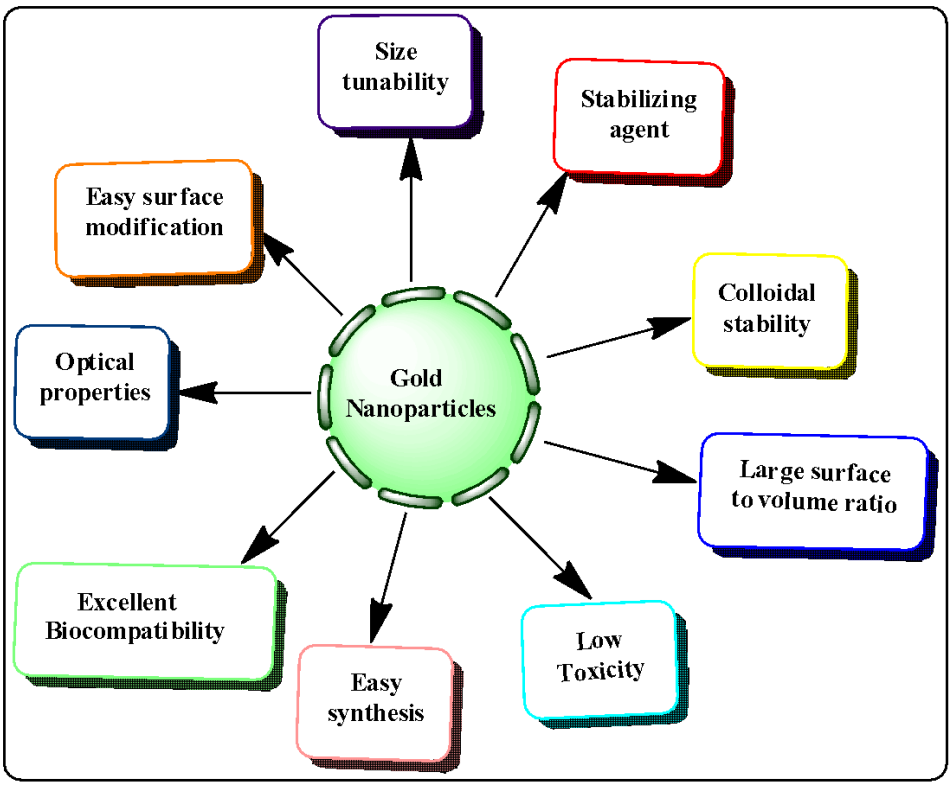
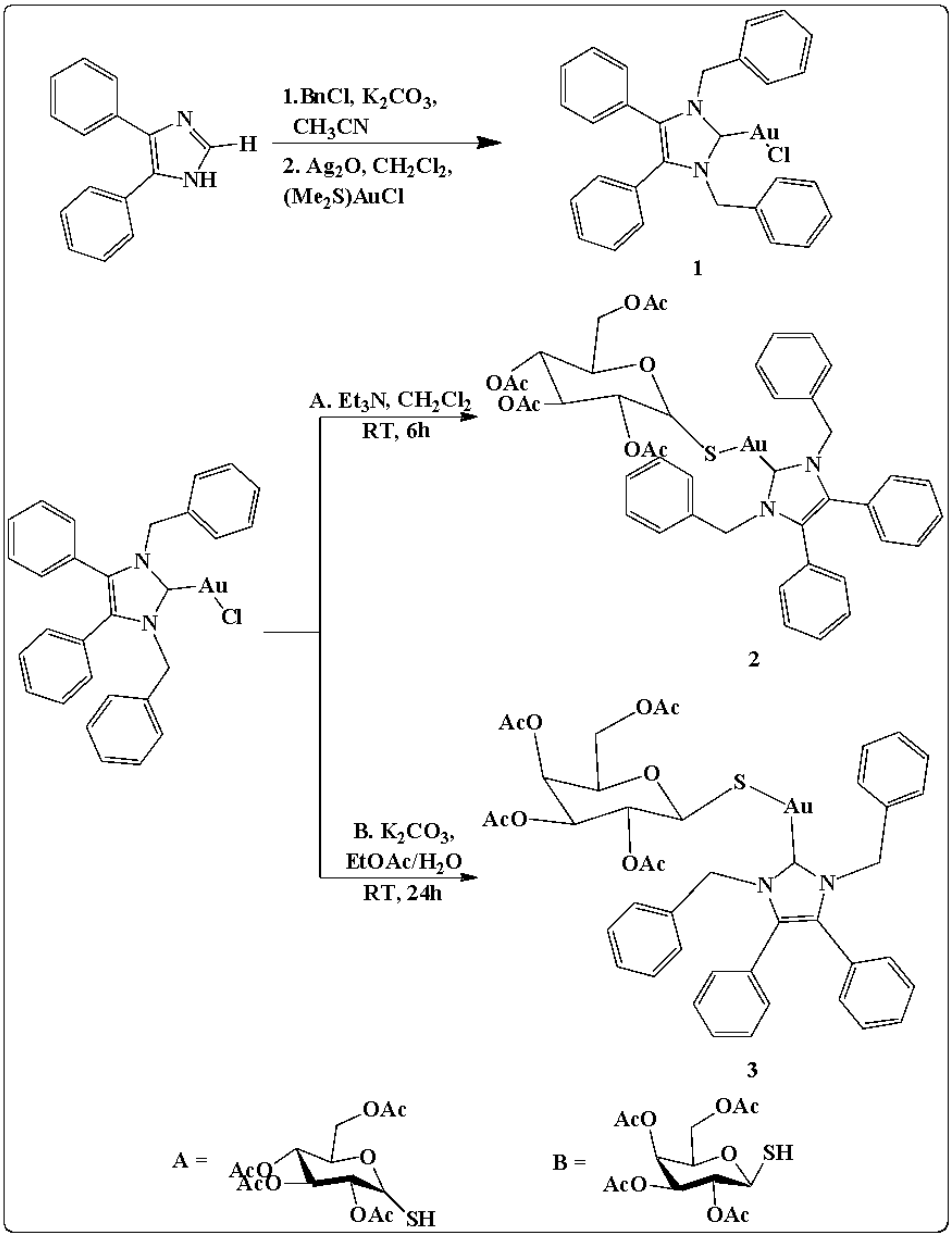


Fig. 5. Synthetic and biological adaptation of gold and its complex forms.

Figure 5 illustrates the key advantages of gold nanoparticles (GNPs), emphasizing their versatility and utility across various scientific fields. Gold nanoparticles are easy to synthesize with precise control over size, enabling tunable properties. Their excellent colloidal stability and large surface-to-volume ratio make them highly effective for catalytic and biological applications [55]. GNPs exhibit remarkable optical properties, such as surface plasmon resonance, useful in imaging and sensing. Their low toxicity and excellent biocompatibility make them safe for biomedical applications, including drug delivery and diagnostics. Additionally, their surface can be easily modified to tailor functionality, enhancing their adaptability for specific uses [56].

4.1. Synthesis of NHC-Au(I)-SR complexes

Nitrogen heterocyclic compounds are cyclic organic molecules that contain at least one nitrogen atom in the ring. They are crucial in biochemistry and medicine, forming the structural basis for many essential molecules like nucleic acid bases (guanine, cytosine, adenine, and thymine) and numerous pharmaceuticals, agrochemicals, and dyes [57-59]. To create the target compounds, the thiols were linked to NHC-Au(I) chloride **1 (Scheme 1)**. The acetyl-protecting groups were kept in target molecules **2** and **3**, because they could be easily hydrolysed to create the active form of the NHC-Au (I) complexes under physiological conditions, and they might be labile.

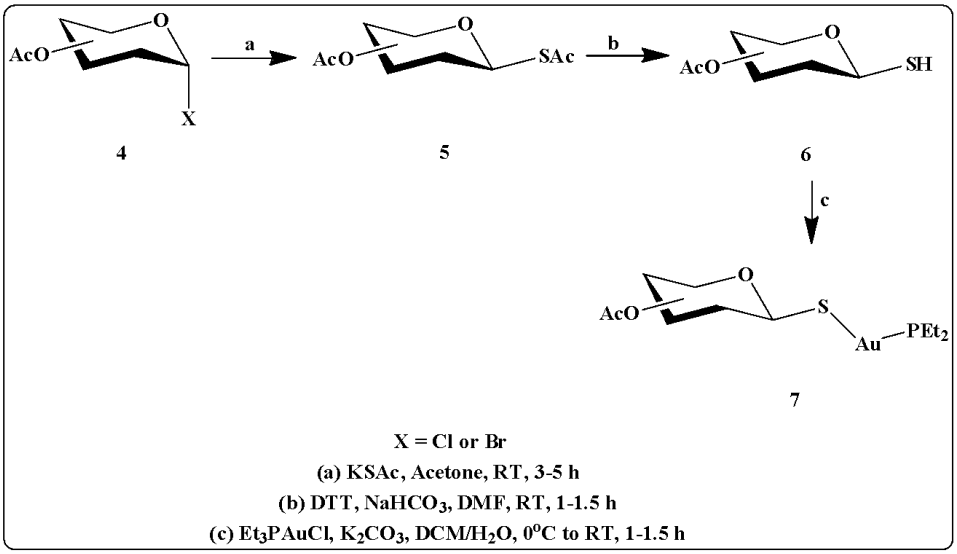


Scheme 1

Compound **2** was successfully produced by first coupling α-thioglucose **A** with chloride **1** in CH_2Cl_2 while Et_3N was present. Interestingly, the α-anomeric thiol showed strong reactivity towards the NHC-Au(I) chloride, while being less nucleophilic than its ß-counterpart [60]. Under identical circumstances, ß-thiol **B** and chloride **1** were coupled, but unexpectedly, no matter how long the reaction was allowed to run, it still did not produce the expected result. It was therefore decided to use biphasic conditions, which have been effectively used to synthesize lanthionine derivatives and S-glycopeptides. High yields of complex **3** were achieved when an aqueous solution of K_2CO_3 was applied to a combination of **B** and **1** in EtOAc [61].

4.2. Synthesis of Auranofin

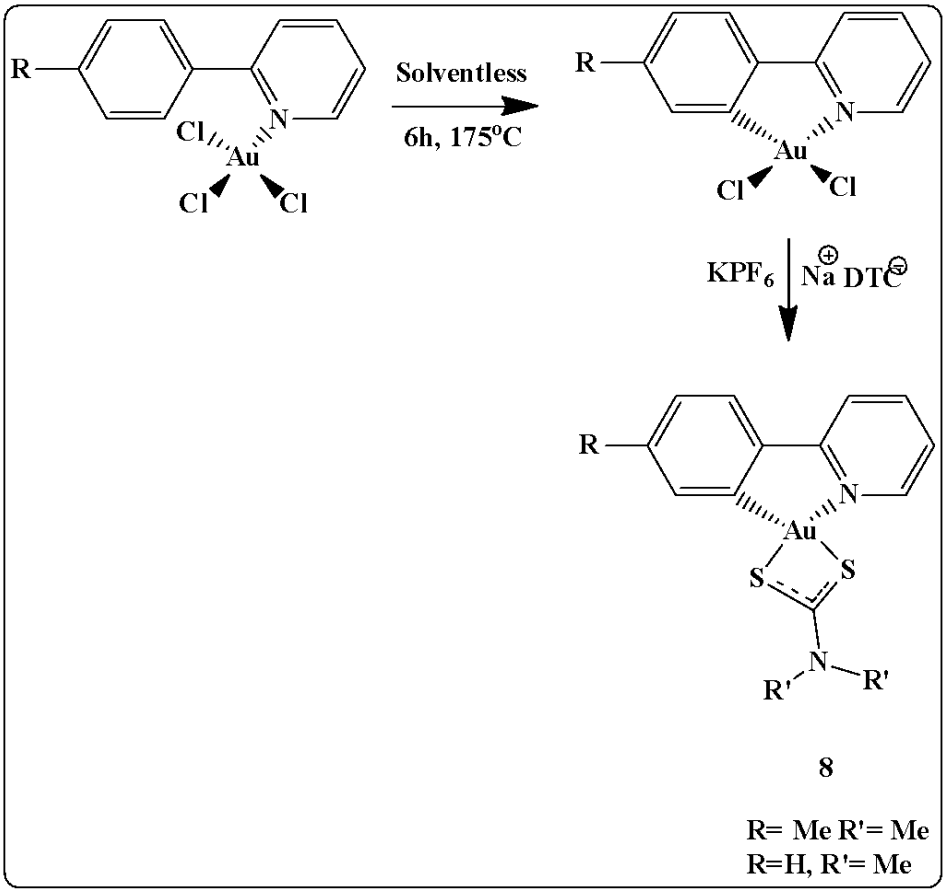
Few research has examined auranofin's structure-activity relationship (SAR). Earlier studies found no need for the thioglucose ligand, suggesting that the target-bound pharmacophore is most likely AuI or $[(PEt_3)\ Au]^+$. According to the procedures described in **Scheme 2**, the auranofin analogues were created by changing the thiol structures. Compound **7** was synthesized using β-glycosyl thiol **6** and Et_3PAuCl [62-64]. To summarize, authors reacted α-glycosyl halide and was subjected to a simple SN^2 reaction with KSAc to produce acetylated thioglycoside **5**. The glycosyl thiol **6**, which was obtained by S-deacetylation of the anomeric thioacetate **5** through trans-thio-esterification with dithiothreitol (DTT), was subsequently treated with Et_3PAuCl under mild basic conditions for 1−1.5 hours to yield auranofin [65].



Scheme 2

4.3. Selective Anticancer Metallodrugs Based on Gold(III) Dithiocarbamate Complexes

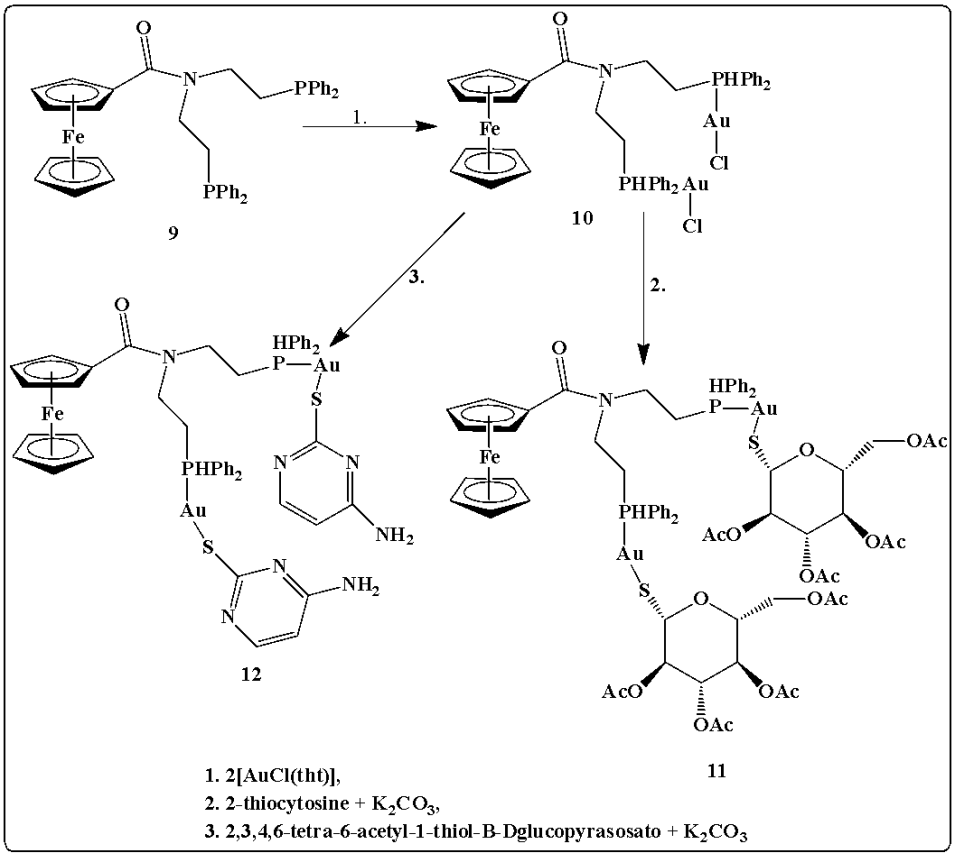
The development of new and direct synthetic pathways devoid of mercurial compounds was an effort to overcome the current method of generating cyclo-metalated molecules with biphenyl ligands, which entails transmetalation procedures with organomercurial complexes. For cyclometallation ligands that necessitate large levels of C-H bond activation, the most prolonged method-reverse refluxing in MeCN while watering the precursor $[AuCl_3]$ [66–68]—is useless. To get the cyclo-metalated precursor we need from a simple solventless thermal cyclometallation, we used the technique devised by Grant *et al.* A one-pot reaction was used to create the dithiocarbonate derivatives from the parent dichloro complex and the sodium salt of the DTC ligand that was chosen. The cationic chelated complex was formed and the chloride ligands were substituted as a result of this reaction. The target compound was precipitated after 30 minutes by adding potassium hexafluorophosphate **(Scheme 3)**. Isolation of complex **8** produces good results [69].



Scheme 3

4.4. Synthesis of Gold Complexes with the Ligand

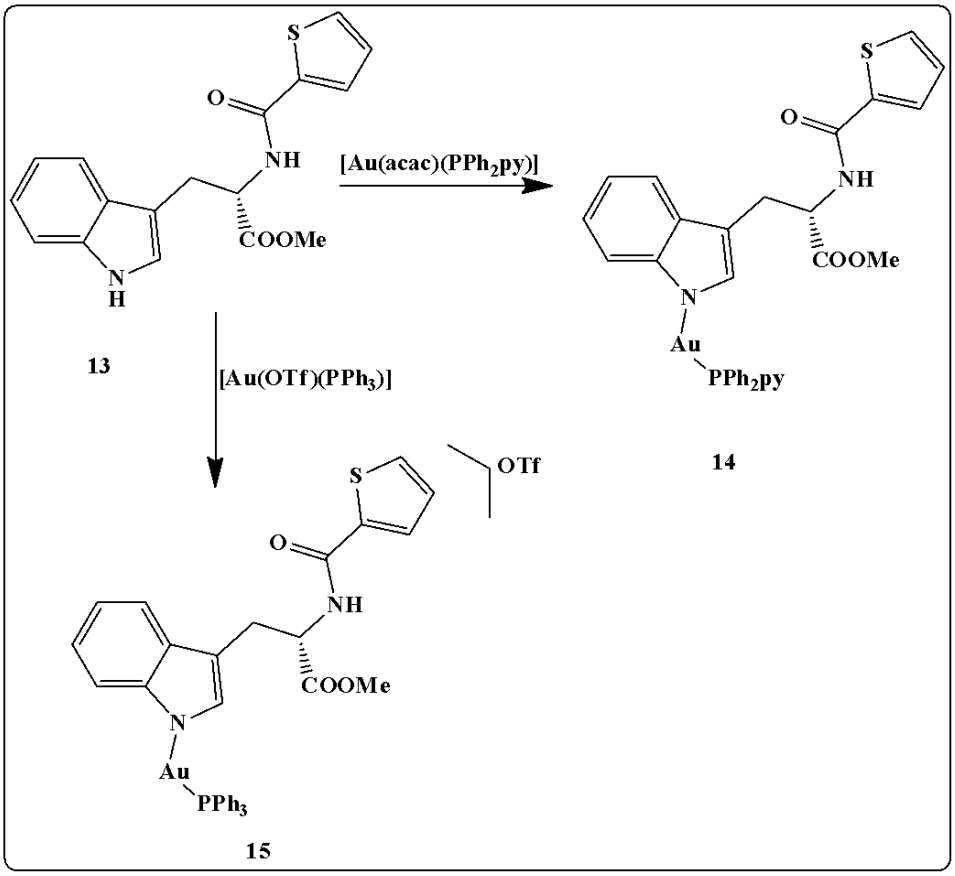
When the gold species that contains di-phosphine **9** reacts with $[Au_2Cl_2\{(PPh_2CH_2CH_2)2\text{-}NCOFc\}]$. Complexes **11** or **12 (Scheme 4)** were obtained by combining thiols such 2-thiocytosine or 2,3,4,6-tetra-6-acetyl-1-thiol-β-D-glucopyranoside with **10**, in the presence of K_2CO_3 [70].



Scheme 4

4.5. Synthesis of Metal Complexes

The thiophene bioconjugate complexes **14, 15** of Au(I) and Au (III) with tryptophan methyl ester **13** were produced more recently using the method outlined in **Scheme 5**. Research on the cytotoxicity of tryptophan derivatives **14, 15** has been conducted on a number of cancer lines, including A549, Hep-G2, and NIH-3T3. In two of the cell lines, the gold complexes (**14** and **15**) demonstrate moderate to good activities, with IC_{50} values ranging from 16 ± 0.97 to 56 ± 3.5 μM, while the thiophene bioconjugate **13** demonstrates no activity at all [71].



Scheme 5

4.6 Advantages of gold in np-based complex compounds: a touch of physical science

In physiologically relevant chemistry, gold compounds may play multiple roles. Drugs made with gold are safe for humans to consume because of the element's lability and low toxicity. The extremely fundamental nature of the gold centers in trinuclear and tetranuclear clusters makes them quite intriguing. We anticipate that future research may yield intriguing new bio-related findings [72]. **Figure 6** shows the spectroscopic characteristics of gold compounds that are sensitive to volatile organic compounds (VOCs) and other molecular interactions. These qualities are a result of the compounds' aurophilic interactions with themselves and other heavy element ions [73].

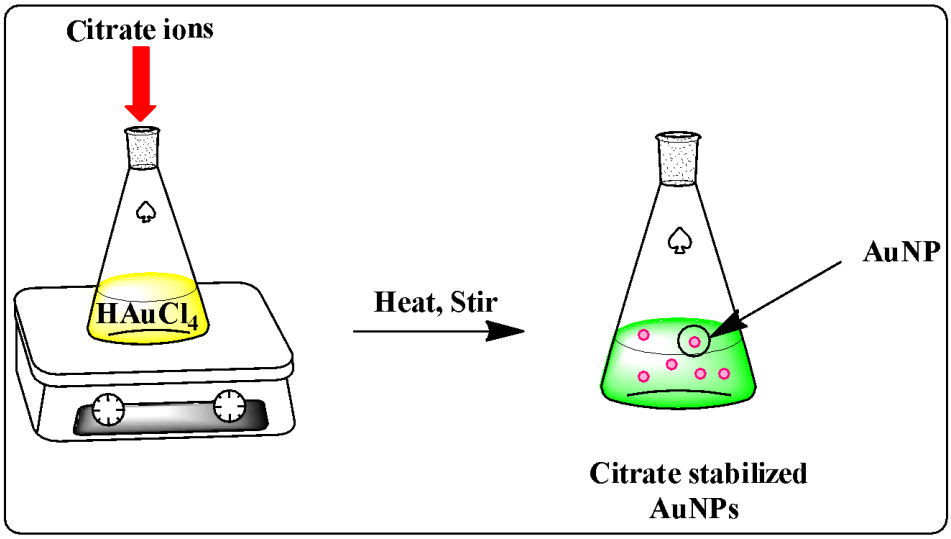


Fig. 6. The unique ability of gold compounds to generate NPs.

5 Beneficially site of gold over other metals

Gold has several advantages over other metals, making it highly valuable in various applications. One of the key benefits of gold is its exceptional chemical stability. Unlike many other metals, gold is highly resistant to oxidation and corrosion, which ensures its longevity in harsh environments. This stability is crucial in fields such as electronics, where gold is used to create reliable and durable conductive connections. Additionally, gold's unique electronic configuration allows it to form strong bonds with ligands, making it an ideal choice for catalytic applications, including organic synthesis and fuel cell technology. Its resistance to tarnishing also enhances its utility in nanotechnology and biomedicine, where consistent performance is critical [74].

Another significant advantage of gold is its biocompatibility, which distinguishes it from many other metals. Gold is non-toxic and non-reactive with biological systems, making it suitable for applications in drug delivery, imaging, and cancer therapy. Unlike metals such as nickel or copper, which may cause allergic reactions or toxic effects, gold is safe for use in medical devices and treatments [75]. Furthermore, its excellent optical properties, such as surface plasmon resonance, enable gold nanoparticles to be used in advanced imaging techniques and biosensors. This combination of stability, biocompatibility, and functional versatility makes gold a superior choice over other metals for applications that require precision, durability, and safety **(Table 2)**.

Table 2 Comparison of Au to other metals.

Property	Gold	Other Metals
Oxidation Resistance	High (does not corrode)	Moderate to Low (e.g., iron rusts)
Biocompatibility	Excellent	Varies (e.g., nickel is allergenic)
Toxicity	Low	High for many (e.g., mercury, lead)
Conductivity (Electrical)	High	Lower (e.g., titanium, aluminium)
Catalysis (Selective)	Excellent for nanoscale	Moderate (e.g., platinum, palladium)

Gold's combination of stability, biocompatibility, and unique physical properties makes it irreplaceable in many specialized applications [76].

6 Gold in polymer chemistry

Gold plays a pivotal role in polymer chemistry due to its unique catalytic and physicochemical properties. Gold catalysts are particularly effective in polymerization reactions, such as ring-opening polymerization and living polymerization, allowing precise control over polymer architecture, molecular weight, and distribution. Additionally, gold nanoparticles (AuNPs) can be embedded into polymer matrices to enhance their optical, thermal, and electrical properties [77]. For instance, gold-functionalized polymers exhibit improved conductivity and stability, making them valuable for applications in flexible electronics, sensors, and imaging technologies. Gold's inert nature and high affinity for unsaturated bonds further facilitate its use in modifying and functionalizing polymers through efficient click chemistry reactions [78].

Beyond material science, gold-polymer composites have significant applications in biomedicine and environmental sustainability. Gold's biocompatibility and low toxicity make it ideal for drug delivery systems, tissue engineering scaffolds, and diagnostic tools. Moreover, gold-polymer systems are widely utilized in developing smart materials that respond to stimuli like light or heat, enabling innovations in soft robotics and photothermal therapies [79]. On the environmental front, gold-catalyzed polymers contribute to sustainable solutions, such as pollutant degradation and recyclable materials. These advancements underscore gold's versatility and its transformative impact on polymer chemistry, bridging industrial, biomedical, and environmental applications [80].

With an eye on their potential use as sensing materials, the authors detail gold nanoparticles coupled with functional polymers. We will go over the analytical uses of gold nanoparticles, their optical characteristics, and how to synthesize them with polymer functionalization. There are two types of polymer-functionalized gold nanoparticles: those that are conjugated with biopolymers and those that are conjugated with artificial polymers. Our main focus is on colorimetric and fluorometric sensing with gold nanoparticles. Specifically, we are able to put sensitive tests to practical use through fluorometric detection. Additionally, sensitivity probing using chemical amplification with gold nanoparticles is also covered [81].

7 Gold as polymer composite

Worries regarding human safety are on the rise alongside the interest in using gold nanoparticles in biomedicine. Knowing the negative consequences of exposure to these new materials, as well as the nano-bio interactions that cause nanomaterials to be hazardous, is now of the utmost importance**. Figure 7** shows that the size and mode of administration of NPs are two of the most important parameters influencing their toxicity [82].

The image highlights key factors affecting the toxicity of gold nanoparticles (AuNPs), including size, shape, surface charge, dose, exposure time, functionalization, and route of administration. These factors influence how AuNPs interact with biological systems, affecting cellular uptake, distribution, and potential toxicity. For instance, surface charge and coatings modify their interactions with cells, while size and shape determine penetration and biodistribution. Proper consideration of these variables is essential for ensuring the safe and effective use of AuNPs in various applications [83].

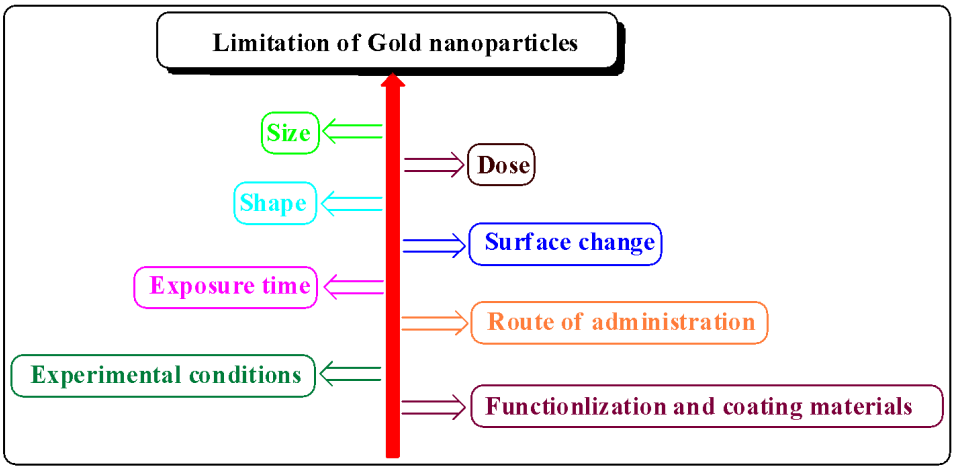


Fig. 7. Factors influencing the non-adaptabilities of AuNPs.

8 Pharmacological Stability and Safety

Advances in the design of gold-based therapeutics have focused on improving both pharmacological stability and *in-vivo* safety, addressing the well-recognized limitations of early gold(I) salts.

Stability is enhanced primarily through rational ligand and coordination-sphere engineering, where strong σ-donor ligands such as thiolates, *N*-heterocyclic carbenes, phosphines, and cyclometalated frameworks protect the Au(I)/Au(III) centre from hydrolysis, ligand exchange, and redox degradation in biological environments. Parallel developments in gold nanotechnology further contribute to stability: nanoparticle, nanocluster, and core shell architectures physically shield the gold core, while PEGylation or lipid coatings prevent aggregation, prolong circulation, and reduce non-specific protein adsorption. Safety is improved by incorporating targeting elements such as antibodies, peptides, folate, or nucleic-acid ligands which concentrate gold formulations at diseased tissues and limit systemic exposure.

Trigger-responsive designs, including Au(III) prodrugs activated by tumour-associated conditions (low pH, high glutathione) or externally triggered nanoshells used in photothermal therapy, ensure spatially and temporally controlled release of the active species. Newer approaches also minimize systemic gold burden through catalytic mechanisms, as seen in gold nanocrystals, which operate at sub-stoichiometric doses and reduce long-term tissue accumulation. Together, these complementary strategies markedly improve the chemical integrity, biocompatibility, and therapeutic index of next-generation gold-based agents, supporting their progress toward clinical translation [35-39].

9 Conclusion

Gold-based compounds have emerged as versatile and powerful tools in medicinal chemistry, offering unique advantages in stability, biocompatibility, and mechanistic diversity compared to traditional organic therapeutics and other metal-based agents. Their broad spectrum of activity ranging from anticancer and anti-inflammatory effects to antimicrobial, antiviral, and neuroprotective actions highlights gold's potential to address complex and treatment-resistant diseases. Advances in nanotechnology, ligand engineering, and polymer gold hybrid materials have further expanded their biomedical relevance, enabling targeted delivery, improved pharmacological stability, and controlled therapeutic activation.

Looking ahead, the successful clinical translation of gold-based therapeutics will require coordinated progress in toxicity assessment, long-term biodistribution studies, and

regulatory standardization for nanostructured materials. Several promising candidates have already progressed into early-phase clinical trials, demonstrating feasibility and motivating continued investment in translational research. Regulatory frameworks must also adapt to address the unique behavior of nanoscale gold constructs, ensuring reproducible manufacturing, safety, and quality control.

Overall, gold continues to evolve from a classical noble metal into a transformative platform for next-generation therapeutics. With ongoing advances in synthetic design, mechanistic understanding, and regulatory alignment, gold-based systems hold strong promise to transition from laboratory innovation to clinically impactful medicines.

HIGHLIGHTS

- Gold-based complexes and nanostructures exhibit broad therapeutic potential, including anticancer, anti-inflammatory, antimicrobial, and neuroprotective activities.
- Advances in ligand design, nanotechnology, and polymer-gold hybrids enhance stability, selectivity, and targeted drug delivery.
- Clinically progressing gold systems such as nanocrystals, nanoshells, and nucleic acid-functionalized constructs demonstrate growing translational promise.
- Diversified synthetic approaches and structure-activity insights clarify the unique advantages of gold over other therapeutic metals.
- Key challenges and future directions in clinical translation, toxicity evaluation, and regulatory alignment are highlighted.

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