Targeted gold nanoparticles for ovarian cancer (Review)

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Abstract. Among all malignant gynecological tumors, ovarian cancer (OC) has the highest mortality rate. OC is often diagnosed at advanced and incurable stages; however, early diagnosis can enable the use of optimized and personalized treatments. Intensive research into the synthesis and characterization of gold nanoparticles (AuNPs) has been performed with the aim of developing innovative materials for use in biological and photothermal therapies for OC. AuNPs can be chemically modified and functionalized by binding to a variety of organic compounds and biomolecules, such as peptides, antibodies and therapeutic agents, via simple synthetic processes. They are particularly suitable for use as carriers for drug delivery. In the present review, the synthesis and characteristics of AuNPs are summarized, and their potential in OC therapy are discussed.

Contents

1. Introduction

Cancer is among the most serious ailments endangering human health, ranking second only to cardiovascular disease (1). Ovarian cancer (OC) is a heterogeneous group of malignancies of the fallopian tubes, ovaries and abdominal cavity (2). It is the fifth deadliest and eighth most common cancer affecting females worldwide (3). Conventional cancer treatments for OC include radiation, surgery, traditional chemotherapy and invasive catheters (4). Epithelial OC (EOC) is the most common type of gynecological malignancy (5). Despite great breakthroughs in EOC therapy, patients frequently experience chemotherapeutic resistance and disease relapse within five years, highlighting that improved therapeutic options are necessary (6). Therefore, the accurate targeting of treatment is important for improving patient prognosis.

Nanoparticles (NPs) typically range in diameter from 1 to 100 nm, with small NPs composed of only a few to several hundred atoms (7,8). Nanomaterials (NMs) are widely utilized in material science and nanotechnology due to their unique properties, which differ from those of conventional materials. The appeal of NPs for medical purposes lies in their special and significant features, including a surface-to-mass proportion, quantum nature and the capability of adsorbing and transporting other compounds, including proteins, drugs and probes (9). The morphologies of NPs can be highly varied and are indicative of their distinctive characteristics (10). The nanoscale dimensions of NPs render them suitable for biolabeling by enabling interaction with biomolecules at both the surface and intracellular levels, generating valuable signals and specific targets for diagnostic and therapeutic applications (11). Due to their unique features, NPs are highly valuable in various applications, including tissue engineering, biomarker identification and drug delivery systems (12). The value of NPs for medical purposes may be attributed to various features, including their surface-to-mass proportion, quantum nature and ability to adsorb and transport other compounds, including proteins, drugs and probes. As studies on NMs have become more prevalent, metal NPs have been evaluated for a broad range of uses, including electronics, catalysis and sensing (9,13,14). Functionalized NPs, particularly those derived from metal NPs, have the potential to serve as valuable biological probes for a range of uses, including organic chemistry research tools, bioassays, clinical diagnosis and cancer treatment (15). In addition, the use of NPs for drug encapsulation is viewed as a promising and effective approach for drug delivery (11).

Among different inorganic NPs, gold NPs (AuNPs) are actively studied for their different biomedical applications. This is mainly due to their stability, simple and easy synthesis, low-cost preparation techniques, size-controllable synthesis, biocompatibility, relatively easy surface modification and low toxicity properties (16-18). In the present study, the features of

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AuNPs, their potential in OC therapy and their contributions to tumor treatment are reviewed.

2. AuNPs

Properties of AuNPs. AuNPs are ideal carriers as they can be functionalized or modified with various chemical groups and are inert to biological systems (19,20). Owing to their biocompatibility and ability to be surface modified with biocompatible molecules, AuNPs can be engineered to minimize undesirable immune responses, such as antibody production (21-23). Furthermore, AuNPs are resistant to oxidation and can be synthesized by controlled crystallization methods, which provide AuNPs with precise morphologies and advantageous size distributions (14).

The electronic and optical properties of AuNPs can be modulated by altering their shape, size, aggregation state and surface chemistry (14). When AuNPs are used as nanocarriers in various applications, chemical modification is necessary. It is crucial that the surface functionalization of the AuNPs is appropriate for the intended usage, for example, to improve their stability and biocompatibility while preventing aggregation (24). The primary purposes of the surface modification of AuNPs include: i) Stabilizing the AuNPs by the attachment of ligands to the AuNP surface, ii) enabling additional functionalization reactions through the bonding of linkers to the AuNP surface, and iii) facilitating further functionalization or bioconjugation by directly immobilizing functional ligands and biomolecules on the AuNP surface, thereby expanding their application range (24-29) (Table I).

Synthesis of AuNPs. Approaches for synthesizing AuNPs can be categorized as either 'top-down' or 'bottom-up' methods (30,31) (Fig. 1). Top-down methods typically involve producing NPs by reducing the size of bulk materials. This serves as the basis for most physical approaches, including pulsed laser ablation, plasma arc discharge, evaporation-condensation, spray pyrolysis, ball milling, vapor and gas phase processes, and lithographic techniques (32,33). However, the unfinished surface structure of the resulting NPs represents a disadvantage (34). Another constraint of these top-down methods is their high costs, as a substantial quantity of energy is needed to maintain high-temperature and high-pressure conditions (24). Bottom-up methods are those that generate NPs from smaller components, including atoms and molecules, and include chemical synthesis techniques, including microemulsion, coprecipitation, chemical reduction, microwave-assisted synthesis, electrochemical, sonochemical, solvothermal and thermal decomposition methods. Green biological synthesis methods also fall into this category. Compared with physical and chemical methods, the use of whole organisms or biological molecules to synthesize NPs offers notable advantages. Biological synthesis methods are nontoxic and relatively sustainable, providing a comparatively environmentally friendly approach to NP synthesis (30,35).

The synthesis of AuNPs by biological methods can be a relatively straightforward process that does not require high temperature or pressure. The procedure generally involves the dropwise addition of a biological extract, such as that from bacteria, fungi and/or plants, into a solution of $HAuCl_4$ salt with thorough mixing to initiate AuNP synthesis (36). Subsequent formulation of the AuNPs consists of two primary phases: In the first phase, the gold precursor, typically in the form of an aqueous gold salt solution, is reduced to form AuNPs using a reducing agent, such as citrate. In the second phase, the AuNPs are stabilized by the introduction of a capping agent, which prevents the agglomeration of the metallic NPs (37).

The use of toxic reducing agents and the gases produced by the process of producing NPs are harmful to humans and the environment. Therefore, safer, nontoxic and environmentally friendly methods for the generation of NPs have been devised, with the use of reducing agents obtained from plant materials, including leaves, roots, flowers and seeds (38). Modification of the reaction time, pH, reaction temperature and fungal biomass can improve the efficiency of the fungal synthesis of AuNPs (39). Commonly employed methods for the characterization of AuNPs include atomic force microscopy, X-ray powder diffraction, scanning electron microscopy, dynamic light scattering, high-resolution transmission electron microscopy, zeta potential, energy dispersive spectroscopy, Fourier transform infrared spectroscopy and ultraviolet (UV)-visible spectroscopy (40). Fig. 2 schematically illustrates various methods for the synthesis, optimization, characterization and conjugation of therapeutic agents with AuNPs. The existing synthesis approaches often involve costly and low-yield purification processes, such as differential centrifugation, to obtain NPs (41). Therefore, the development of nonpoisonous, eco-friendly and clean sustainable synthesis procedures with high yields and low cost is critical (42).

Synthesis and stabilization procedures for precious metal-based NPs using plant extracts are regarded to be safe, economical, eco-friendly and green (43). In one study, AuNP formation was realized at ambient temperature by mixing thyme extract with gold salts. The reaction could be scaled by the adjustment of various reaction conditions, particularly temperature (44). A number of other studies have also synthesized AuNPs by methods using plant extracts or other biological materials, such as fungi and bacteria, to reduce metal salts and obtain bio-friendly, stable metal-based NPs (45,46). For example, the microbial synthesis of AuNPs was first reported in 1980, with the use of *Bacillus subtilis* (47).

Table II presents some other examples of AuNPs that have been synthesized (6,48-63).

Application of AuNPs. The utilization of nanosized materials has facilitated a number of advances in biological applications such as biomedicine. These advances include antitumor activity and drug delivery (64), fluorescent biological labeling, gene delivery, tissue engineering, protein detection, contrast enhancement magnetic resonance imaging, DNA probing, hyperthermia treatment, phagokinetic research and cell or molecular filtration leveraging biological interactions (11).

AuNPs are among the most commonly used materials for diagnostics, bioimaging and cancer therapy due to their inherent stability and low cytotoxicity (65,66). AuNPs of various shapes, such as nanoshells, nanorods, nanocages, nanostars, nanospheres and branched AuNPs, have been manufactured and investigated (67,68) (Fig. 3). For example, the hollow structure of gold nanocages provides a high capacity for loading various types of payloads, while the payload can be rapidly loaded and released

Table I. Surface modification of AuNPs.

First author, year	Surface modification method	Mechanism	Function	(Refs.)
Ielo *et al*, 2021	Secondary modification	'Place exchange' of a thiol ligand	Introduces various functionalities that may react via condensation	(24)
Xiao *et al*, 2018	Physical sorption	Physical sorption of ligands or biomolecules on AuNP surfaces driven by electrostatic and hydrophobic interactions	Modifies the AuNP charge state and the degree of immobilization of functional molecules	(26)
De Luca *et al*, 2018	Dative bonding and formation of self-assembled monolayers	Thiolated ligands densely bond to AuNP surfaces to produce self-assembled monolayers	Stable capping of the AuNPs prevents the coupling of other ligands and biomolecules	(27)
Boyer *et al*, 2010	Polymer coating	Neutral polymers or charged polymers are used to coat the AuNP surfaces	Steric repulsion or repulsive electrostatic interactions, respectively, improve the colloidal stability of the AuNPs	(28)
Presnova *et al*, 2014	Bioaffinity immobilization of ligands	Synthesis of chemically stable protein-@AuNP conjugates by immobilization of affinity-bound biomolecules and ligands	Allows biotinylated nucleic acids, antibodies and aptamers to be immobilized	(29)

AuNP, gold nanoparticles.

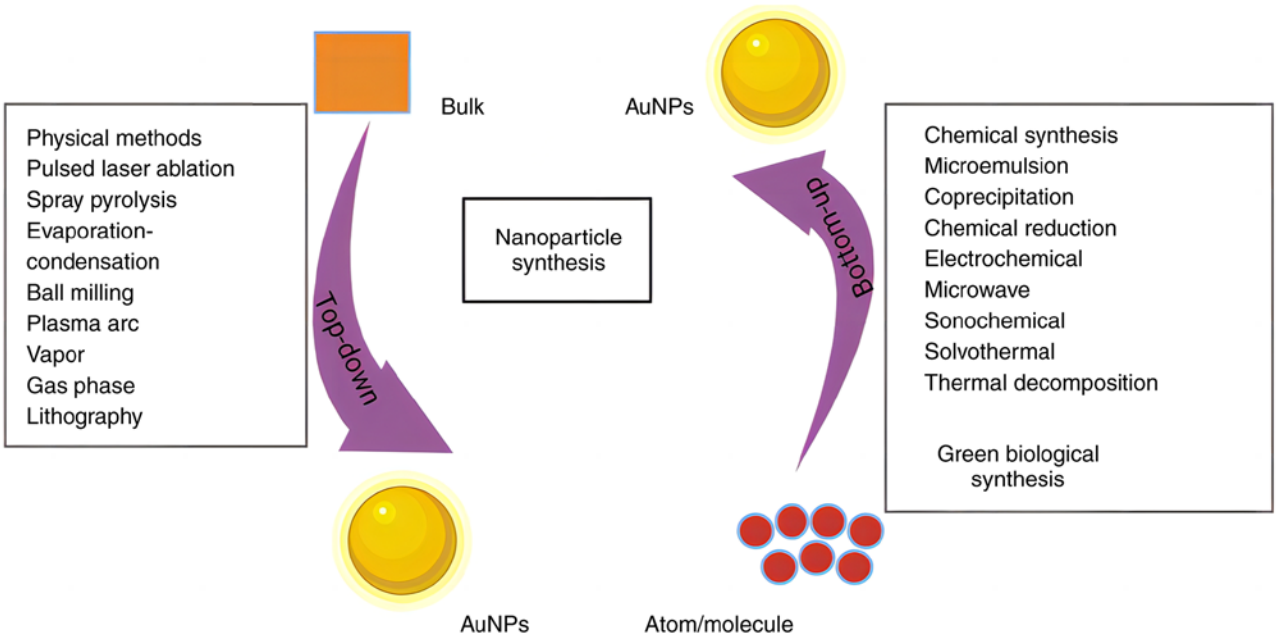

Figure 1. Top-down and bottom-up approaches for AuNP synthesis. Figure created with BioRender software (BioRender.com). AuNP, gold nanoparticle.

through pores in the walls. These features are particularly attractive for drug delivery and controlled release (69,70). Specific applications of AuNPs include their use as contrast agents in medical imaging and as drug carriers for gene delivery (71). AuNPs have been extensively adopted in drug delivery due to their chemical inertness, biocompatibility and ease of functionalization (72,73). In nanomedicine, AuNPs are non-toxic at the doses utilized for drug delivery (74). The high affinity of AuNPs

Table II. Examples of AuNP synthesis and characterization.

First author/s, year	Name	Morphology	Size, nm	Ingredients	Characterization	(Refs.)
Lee *et al*, 2022	HA-AuDEN-Dox	Spherical	<2	$HAuCl_4$, G6-NH_2 dendrimer solution, $NaBH_4$, HA, Dox	UV-vis, fluorescence spectroscopy, TEM, DLS and zeta potential	(49)
Lee *et al*, 2020	Dox-DNA-AuNP	-	13	$HAuCl_4$, sodium citrate, DNA, sodium chloride, sodium phosphate buffer, Dox	UV-vis, zeta potential, DLS and fluorescence spectroscopy	(48)
Kotcherlakota *et al*, 2017	Au-TR-DX-si	Spherical	105	$HAuCl_4$, $NaBH_4$, Dox, erbB2 siRNA, TR	UV-vis	(50)
Kotcherlakota *et al*, 2019	Au-C225-p53DNA	Spherical	52.3±2.6	$HAuCl_4$, C225, polyethylene imine, p53 DNA	UV-vis	(51)
Piktel *et al*, 2021	Peanut-shaped AuNPs	Peanut-like	60.00±4.24x30±3.49	Cetrimonium bromide, $HAuCl_4$, $AgNO_3$, $NaBH_4$, ascorbic acid	UV-vis	(6)
Piktel *et al*, 2021	AuP@CSA-131	Peanut-like	60±5x30±3.5	CTAB, $HAuCl_4$, $NaBH_4$, $AgNO_3$, MHDA	HAADF-STEM, Fourier-transform Raman spectroscopy and TGA	(52)
Jabir *et al*, 2020	LG/LGC	-	11/13	$HAuCl_4$, $NaBH_4$, GSH, linalool/CALNN	UV spectrophotometry, SEM and TEM	(53)
Asl *et al*, 2023	AuNPs	Spherical	15.1±3.7	$HAuCl_4$, NaOH, dimethyl sulfoxide, *Satureja rechingeri* Jamzad aqueous leaf extract	XRD, FTIR, UV-vis, TEM, SEM, EDX, DLS and zeta potential	(54)
Xiong *et al*, 2014	AuNPs	-	20	$HAuCl_4$ trihydrate, trisodium citrate, $NaBH_4$	DLS and zeta potential	(55)
Kip *et al*, 2022	AuNCs	Cone-shaped	100	$HAuCl_4$, *o*-phenetidine, hexane	UV-vis, DLS and STEM	(56)
Patra *et al*, 2010	Au-PSH-CP-FA	-	5	$HAuCl_4$, $NaBH_4$, CP, FA, tritiated FA, [^{3}H]thymidine	UV-vis, TEM and ICP	(57)
Borghei and Hosseinkhani, 2022	Wh@AuNPs	-	-	$HAuCl_4$, whey, 3,3',5,5'-tetramethylbenzidine	UV-vis	(58)
Wang *et al*, 2014	15P-PPy-NPs	-	-	AuNPs, pyrrole aqueous solution, SDS, acidic $(NH_4)_2S_2O_8$ solution, EDC	UV-vis and TEM	(59)
Shen *et al*, 2022	RHMH18@AuDNPs	-	Varies with reaction time and $HAuCl_4$ concentration	$RHMH_{18}$ protein, $HAuCl_4$, NaOH, phosphate-buffered saline, DTX	TEM	(60)
Van de Broek *et al*, 2011	Branched AuNPs	Branched	60.4±9.7	$HAuCl_4$, sodium citrate, BSPP, H_2O_2, NaOH, HCl, HNO_3, anti-HER2	UV-vis	(61)

Table II. Continued.

First author/s, year	Name	Morphology	Size, nm	Ingredients	Characterization	(Refs.)
Geng *et al*, 2011	Glu-AuNPs	-	14.37±2.49	$HAuCl_4$, $NaBH_4$, sodium citrate, PEG, Glu	TEM and XPS	(62)
Cui *et al*, 2017	GNP-NHN=Dox-mPEG	-	179.0±7.5	$HAuCl_4$, hydrazine hydrate, DCC, DMAP, TFA, NPC, mPEG, Dox HCl, $NaBH_4$	FTIR and NMR	(63)

AuNP/GNP, gold nanoparticle; HA, hyaluronic acid; AuDEN, dendrimer encapsulated AuNPs; Dox/DX, doxorubicin; G6-NH2, amine-terminated poly(amidoamine); UV-vis, ultraviolet-visible spectrophotometry; TEM, transmission electron microscopy; DLS, dynamic light scattering; TR, bifunctional recombinant fusion protein TRAF(C); si/siRNA, small interfering RNA; C225, cetuximab; CSA-131, cationic steroid antibiotic 131; CTAB, cetyl trimethylammonium bromide; MHDA, 16-mercaptohexadecanoic acid; HAADF, high-angle annular dark-field; STEM, scanning TEM; TGA, thermogravimetric analysis; LG, linalool-AuNP; LGC, linalool-AuNP-CALNN peptide; GSH, glutathione; SEM, scanning electron microscopy; XRD, X-ray diffraction; FTIR, Fourier-transform infrared; EDX, energy-dispersive X-ray spectroscopy; PSH, mercapto-PEG of molecular weight 2,000; CP, cisplatin; FA, folic acid; ICP, inductively coupled plasma; Wh, whey; 15P, SHSWHWLPNLRHYAS protein; PPy, polypyrrole; NPs, nanoparticles; SDS, sodium dodecyl sulfate; EDC, 1-ethyl-3-[(3-dimethylamino) propyl]carbodiimide; AuDNPs, DTX-loaded AuNPs; DTX, docetaxel; BSPP, bis(*p*-sulfonatophenyl)phenylphosphine dihydrate dipotassium salt; Glu, 1-thio-β-glucose; PEG, polyethylene glycol; XPS, X-ray photoelectron spectroscopy; mPEG, modified PEG; DCC, dicyclohexylcarbodiimide; DMAP, 4-dimethylaminopyridine; TFA, trifluoroacetic acid; NPC, N-hydroxysuccinimide propionate; NMR, nuclear magnetic resonance.

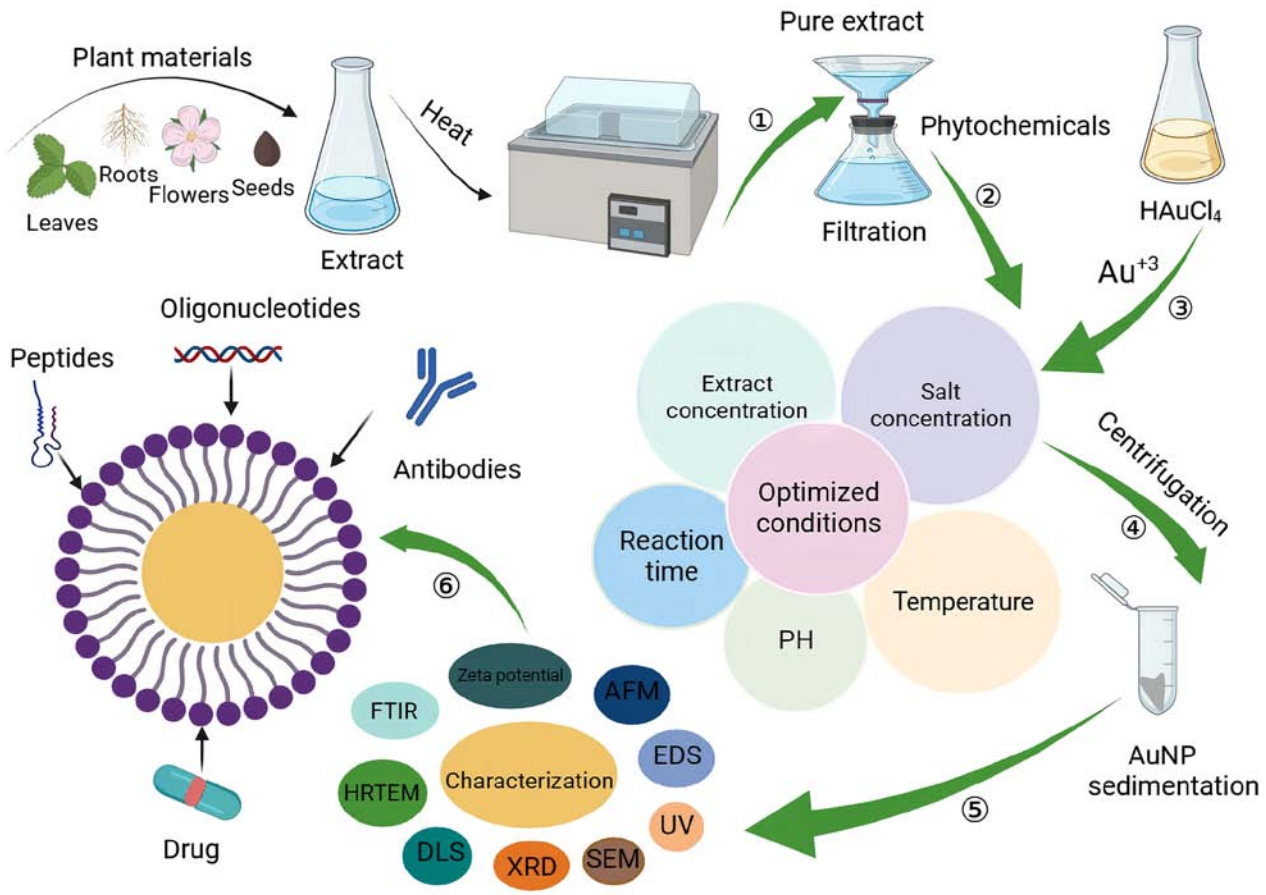

Figure 2. Schematic illustration of the synthesis, optimization and characterization of AuNPs and their conjugation with therapeutic agents. In step 1, an extract of plant material is obtained. Steps 2 and 3 involve optimizing the synthesis of AuNPs by adjusting various reaction parameters. In step 4, the reaction mixture is centrifuged to obtain AuNPs in the form of a pellet. In step 5, thorough characterization and elucidation of AuNP properties, including morphology and size, is performed. In step 6, functional groups are attached. AuNPs with appropriate characteristics and high stability can then be conjugated with therapeutic agents, such as peptides, drugs, antibodies and oligonucleotides. Figure created with BioRender software (BioRender.com). AuNPs, gold nanoparticles; AFM, atomic force microscopy; EDS, energy-dispersive X-ray spectroscopy; UV, ultraviolet; SEM, scanning electron microscopy; XRD, X-ray diffraction; DLS, dynamic light scattering; HRTEM, high-resolution transmission electron microscopy; FTIR, Fourier-transform infrared spectroscopy.

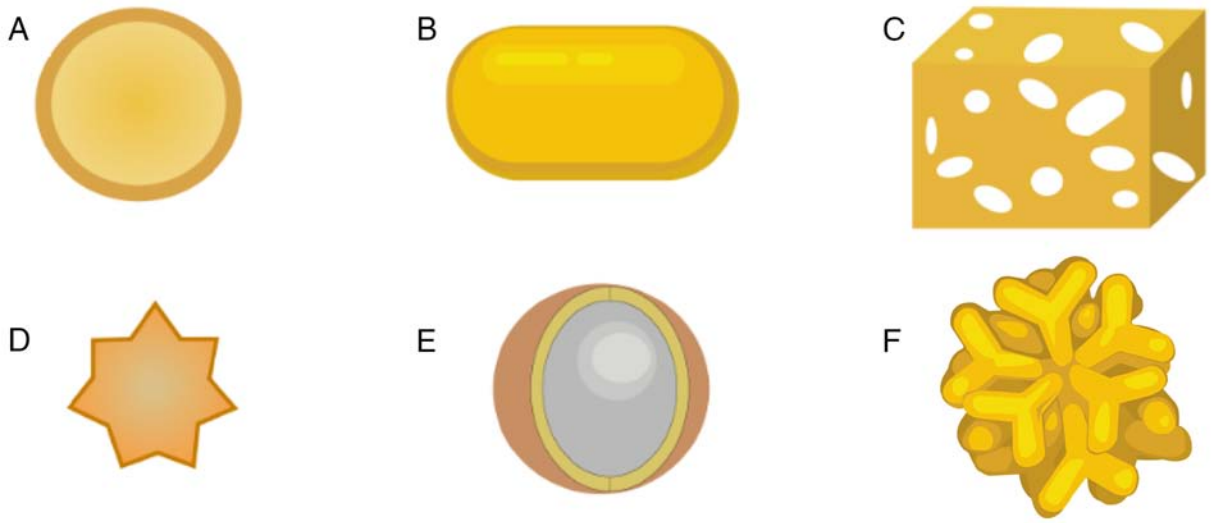

Figure 3. AuNPs of different morphologies. (A) Nanoshells, (B) nanorods, (C) nanocages, (D) nanostars, (E) nanospheres and (F) branched AuNPs. Figure created with BioRender software (BioRender.com). AuNPs, gold nanoparticles.

for thiols, polymers and amines allows the introduction of reactive molecules that can be employed for targeting, including peptides, antibodies, carbohydrates and aptamers, and for the conjugation of therapeutic agents, including radionuclides, drugs, photosensitizers, genes and small interfering RNAs (75).

It has been suggested that AuNPs are redox active and noncytotoxic, as they can reduce reactive oxygen and nitrite species without inducing the secretion of tumor necrosis factor (TNF)-α, interleukin (IL)-1β and other inflammatory factors, which makes then ideal nanomedicine candidates (76). Ben Haddada *et al* (77) demonstrated that AuNPs prepared using *Hubertia ambavilla* are nonpoisonous to human skin fibroblasts and can scavenge free radicals and protect fibroblasts and dermal cells against UV-A radiation-induced damage. In addition, Taratummarat *et al* (78) reported that spherical AuNPs of diameter 20-30 nm are nontoxic to mice, and exhibit anti-inflammatory properties. It has been reported that positively charged particles are more toxic to bacteria than are negatively charged or neutral particles, indicating that surface charge affects the toxicity of AuNPs (79). However, other studies have reported conflicting findings, with one reporting that positively charged AuNPs exhibited no toxicity to human epithelial cells (80), while another reported that both positively and negatively charged AuNPs were toxic to human keratinocytes (81). The reason for such differences may be the various physicochemical features of different NPs, and the lack of a standardized method to verify toxicity (82). Moreover, Shukla *et al* (76) suggested that AuNPs do not elicit an initial immunological response or induce the production of the proinflammatory cytokines IL-1β and TNF-α until a high concentration of 100 μM is reached. In addition, Ghosh *et al* (83) reported that AuNPs do not trigger complement activation. Due to their lack of toxicity and immunogenicity, AuNPs are an ideal choice for drug delivery scaffolds. Moreover, the ability to functionalize AuNPs renders them highly promising vehicles for drug delivery applications (84-87). Currently, nanomedicine is advancing the development of novel therapeutic and diagnostic tools, including biosensors for biomolecule detection, tumor chemotherapeutics, and gene or drug delivery. Owing to their good biocompatibility and small particle size, AuNPs are promising candidates for biological applications (88).

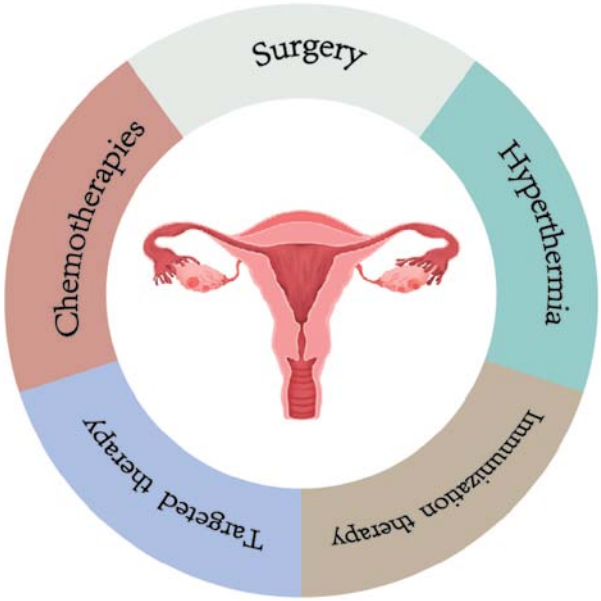

Figure 4. Different treatment methods for ovarian cancer. Figure created with BioRender software (BioRender.com).

There are many methods for the treatment of OC, which vary in their advantages and disadvantages (Fig. 4). Importantly, AuNPs can be used for OC treatment. In one study, *in vitro* experiments demonstrated that AuNPs successfully induced autophagy and apoptosis in SK-OV-3 cells via reactive oxygen species (ROS)-mediated pathways, indicating their potential as new nanotherapeutics (6). AuNPs hold great promise in diagnostic and therapeutic medicinal applications.

3. Drug delivery systems targeting OC

The large surface-to-volume ratio and good biocompatibility of AuNPs, together with the ability to synthesize AuNPs

with varied morphological characteristics and surface chemistries, render AuNPs very suitable for use as drug delivery vehicles (89). AuNPs coupled with targeted molecules can precisely deliver tumor-targeting drugs via both passive and active targeting mechanisms (90,91).

Passive targeting involves the nonspecific accumulation of NPs in tumors due to the specific characteristics of the tumor microenvironment (92,93). In passive targeting, AuNPs primarily exploit the enhanced permeability and retention effect. Drugs attached to AuNPs can selectively accumulate in tumor tissues and persist for an extended period due to vascular leakage and compromised lymphatic drainage, respectively (94,95). Although a meta-analysis of 117 studies (96) on nanodrug delivery found that only 0.7% of NPs successfully reached the tumor site, indicating that although passive targeting often results in low delivery efficacy, AuNPs have an improved ability to target tumor tissue. In addition, AuNPs can be attached to a variety of ligands, including drugs, peptides, antibodies and oligonucleotides, to enhance their targeted delivery properties (97-99). AuNP carriers can protect peptides, antibodies and oligonucleotides from enzymatic degradation, thereby improving their effectiveness in transporting drugs into solid tumors (100). Table III presents some examples of targeted AuNPs and their properties.

Drugs. Drug-conjugated AuNPs are considered to be highly promising and efficient nanoprodrugs. Such a conjugate may be constructed, for example, by the attachment of multiple thiol-terminated polyethylene glycol (PEG)-drug conjugates onto the surface of AuNPs via thiol-Au covalent bonds (63). The attachment of drugs to the surfaces of AuNPs offers several advantages while minimizing the risk of severe systemic toxicity (101). For instance, due to their small size, they can efficiently travel through capillaries to reach target cells. Chemotherapeutic agents can be loaded or attached to the AuNPs and can be passively or actively targeted to the tumor site (82). In addition, the incorporation of modifiers that are responsive to external stimuli, including pH or enzymes, into the linking molecules facilitates drug release (37).

The utilization of NP-based carriers for the delivery of anticancer agents is a promising strategy for reducing the dosages of antineoplastic compounds, as it minimizes their systemic toxicity while simultaneously enhancing their therapeutic efficacy (102). Piktel *et al* (52) used nanotechnology to manufacture a new nanosystem composed of AuNPs functionalized with a shell comprising cationic steroid antibiotic-131. This nanosystem exhibited marked activity against OC cells *in vitro* and prevented the development of ovarian tumors in animals with minimal toxicity. In another study, Dox-DNA-AuNPs exhibited an excellent anticancer effect in an *in vitro* propagation test, and efficacy in the prevention of tumor development in a xenograft mouse model over a 16-day treatment period. Compared with free Dox, Dox-DNA-AuNPs exhibited an ~2.5-fold greater inhibition of tumor development, demonstrating their strong ability to inhibit cancer development (48).

Cisplatin (CP) is a first-line chemotherapeutic drug for OC. Although CP is very useful as a cancer treatment, it has numerous side effects (103,104). Patra *et al* (57). described the manufacture and functional characterization of an AuNP-based drug delivery system for the potential treatment of OC. The system was fabricated by the reaction of AuNPs with folic acid (FA), mercapto-PEG of molecular weight 2,000 (PSH) and CP, to form an Au-PSH-CP-FA-based drug delivery system. *In vitro* proliferation assays revealed that the CP retained its cytotoxicity in this system, while normal cells were protected against cytotoxicity. Asl *et al* (54) successfully synthesized AuNPs using an extract derived from *Satureja rechingeri* Jamzad. The obtained spherical AuNPs displayed potent anticancer activity against CP-resistant OC cells, and low cytotoxicity to normal cells, indicating their biocompatibility. These findings indicate that AuNPs have strong potential for the treatment of OC.

By focusing on cancer cell markers that are more highly expressed in tumor tissues than in normal cells and tissues, active targeting agents can improve the precision of tumor tissue targeting (105-107). Lee *et al* (49) created a targeted drug delivery system for the treatment of OC that was responsive to changes in pH and glutathione (GSH) levels. This was created by the attachment of hyaluronic acid molecules to the surface of dendrimer-encapsulated AuNPs via 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide and N-hydroxysuccinimide chemistry, and then loading Dox onto the Au surface. This nanodrug demonstrated high biocompatibility, excellent stability and effective targeting through the CD44 receptor. In addition, it effectively penetrated cancer cells, where the release of Dox was induced in response to the acidic pH and high GSH levels of the tumor microenvironment. This inhibited tumor growth while causing fewer toxic side effects in mice. Certain AuNPs have the ability to undergo photothermal transformation, which generates heat, thereby promoting *in situ* drug release and tumor ablation (108,109). For example, in one study, ultrasmall NPs were incorporated into RHMH8 fusion protein via biomimetic mineralization to form RHMH18@Au complexes which were further loaded with docetaxel (DTX). The resulting RHMH18@AuDTX NPs contained AuNPs clustered in the human serum albumin (HSA) portion of the fusion protein and histidine-encapsulated DTX. These RHMH18@AuD NPs formed a uniform dispersion in saline and exhibited chemo-photothermal therapeutic effects in ovarian tumor tissue. In addition, *in vitro* experiments demonstrated that under the influence of MMP-2, the RHMH18@AuDTX NPs decomposed into arginine-glycine-aspartic acid (RGD)-HSA@Au and His@DTX NPs. It is likely that these two components function in different areas of the tumor tissue, with RGD-HSA@Au playing a photothermal role in the extracellular matrix, and His@DTX NPs entering tumor cells due to their nanoscale size and charge interactions with the cell surface. This dual-targeting approach was demonstrated have good biocompatibility and a favorable anti-OC effect *in vivo*, and presents a promising novel strategy for tumor treatment (60).

Peptides. Various peptides have been employed for the specific delivery of therapeutic AuNPs (110).

A previous study demonstrated that SK-OV-3 cells are efficiently targeted by 15P (sequence, SHSWHWLPNLRHYAS) conjugated to AuNPs via polypyrrole (PPy) linkers. These conjugates demonstrated hyperthermic effects on the SK-OV-3 human OC cell line when exposed to near-infrared

Table III. Properties of selected AuNPs targeting OC.

First author, year	Name	Properties	Passive/ active targeting	Drug/targeting agent	Receptor	Drug release system	(Refs.)
Lee *et al*, 2022	HA-AuDEN-Dox	Multivalent terminals of dendrimers can be functionalized with targeted ligands for active targeting, inhibiting ovary tumor growth	Active	HA, Dox	CD44	pH and GSH stimuli-responsiveness	(49)
Lee *et al*, 2020	Dox-DNA-AuNP	Excellent anticancer activity for OC cells	Active	Dox	-	pH-dependent	(48)
Kotcherlakota *et al*, 2017	Au-TR-DX-si	Non-toxic, target-specific uptake and significant OC tumor suppression	Active	Dox, TR, erbB2 siRNA	HER2	-	(50)
Kotcherlakota *et al*, 2019	Au-C225-p53DNA	Delivers p53 DNA and C225 specifically to OC cells that overexpress EGFR	Active	C225, p53 DNA	EGFR	-	(51)
Piktel *et al*, 2021	Peanut-shaped AuNPs	Reduce the viability and proliferation of OC cells by triggering ROS-mediated apoptosis and autophagy	Passive	-	-	-	(6)
Piktel *et al*, 2021	AuP@CSA-131	Improved anticancer compared with CSA-131, enabling the effective dose to be reduced	Active	CSA-131	-	-	(52)
Jabir *et al*, 2020	LG/LGC	Significant antiproliferative effect on SK-OV-3 cells	Active	Linalool	-	-	(53)
Asl *et al*, 2023	AuNPs	Potent anticancer activity against CP-resistant OC cells	Passive	-	-	-	(54)
Xiong *et al*, 2014	AuNPs	Sensitize OC cells to CP by depleting stem cell pools and inhibiting key molecular pathways	Active	CP	-	-	(55)

Table III. Continued.

First author, year	Name	Properties	Passive/ active targeting	Drug/targeting agent	Receptor	Drug release system	(Refs.)
Patra *et al*, 2010	Au-PSH-CP-FA	Enhanced cytotoxic effect on OC cells and protective against cytotoxic damage in normal cells	Active	CP, FA	Folate receptor	pH and GSH stimuli-responsiveness	(57)
Wang *et al*, 2014	15P-PPy-NPs	Target SK-OV-3 cells *in vitro*	Active	15P	VEGFR3	-	(59)
Shen *et al*, 2022	RHMH18@AuDNPs	Good biocompatibility and active chemotherapeutic photothermal synergistic effect on human ovarian tumors	Active	DTX	-	pH-dependent	(60)
Van de Broek *et al*, 2011	Branched AuNPs	Actively target HER2-expressing SK-OV-3 cells	Active	Anti-HER2	HER2	-	(61)
Geng *et al*, 2011	Glu-AuNPs	Enhance the effectiveness of radiotherapy on OC cells	Active	Glu	-	-	(62)

AuNP, gold nanoparticle; OC, ovarian cancer; HA, hyaluronic acid; AuDEN, dendrimer encapsulated AuNPs; Dox/DX, doxorubicin; GSH, glutathione; TR, bifunctional recombinant fusion protein TRAF(C); si/siRNA, small interfering RNA; C225, cetuximab; EGFR, epidermal growth factor receptor; ROS, reactive oxygen species; CSA-131, cationic steroid antibiotic 131; LG, linalool-AuNP; LGC, linalool-AuNP-CALNN peptide; CP, cisplatin; PSH, mercapto-PEG of molecular weight 2,000; FA, folic acid; 15P, SHSWHWLPNLRHYAS protein; PPy, polypyrrole; NPs, nanoparticles; VEGFR3, vascular endothelial growth factor receptor 3; AuDNPs, DTX-loaded AuNPs; DTX, docetaxel; Glu, 1-thio-β-glucose.

laser irradiation, with high tumor specificity. The hyperthermic effect of the PPy-conjugated AuNPs or 15P conjugates on tumor cells *in vivo* was investigated in nude mice bearing subcutaneous SK-OV-3 tumors. Significant inhibition of tumor growth was observed following near-infrared laser-mediated treatment with both types of conjugates. These findings indicate that 15P-PPy-AuNPs have excellent biocompatibility, and the ability to effectively induce the photothermal ablation of tumor cells in a tumor-targeted manner. The study also found that while 15P-PPy-NPs effectively bind to and ablate SK-OV-3 cells, they have no effect on HL-7702 or HepG2 cells (59).

Linalool is a monoterpene compound that is active against numerous cancer cell lines, but limited in its application by its high toxicity. A novel peptide conjugate of AuNPs and linalool was synthesized and characterized by Jabir *et al* (53), with the aim of reducing the general toxicity of linalool and improving its targeting ability. Linalool was loaded onto AuNPs by reaction with GSH and linalool, followed by the loading of CALNN peptide onto the surface of the linalool-loaded AuNPs via a chemical reaction. The peptide conjugate demonstrated strong antiproliferative effects on SK-OV-3 OC cells.

Antibodies. Drug-loaded AuNPs are able to actively target tumors by strategies using antibody-modified ligands (110-112). Immunoglobulins and antibody fragments are the most frequently employed molecules for antibody targeting (104). HER2-positive OC is recognized as being aggressive in nature, resistant to chemotherapy and being associated with a high mortality rate (113). Therefore, targeting HER2 receptors is considered as a potential approach for improving the effectiveness of treatment and survival rates in patients with OC. Van de Broek *et al* (61) linked anti-HER2 nanobodies to branched AuNPs and demonstrated their specific effect on HER2-positive SK-OV-3 cells. These authors reported that the anti-HER2 conjugated AuNPs specifically bound to the cells, indicating that the nanobodies retained their specificity following conjugation to the AuNPs. In addition, targeted photothermal damage of the tumor cells was achieved *in vitro* by near-infrared laser irradiation of the branched AuNPs,

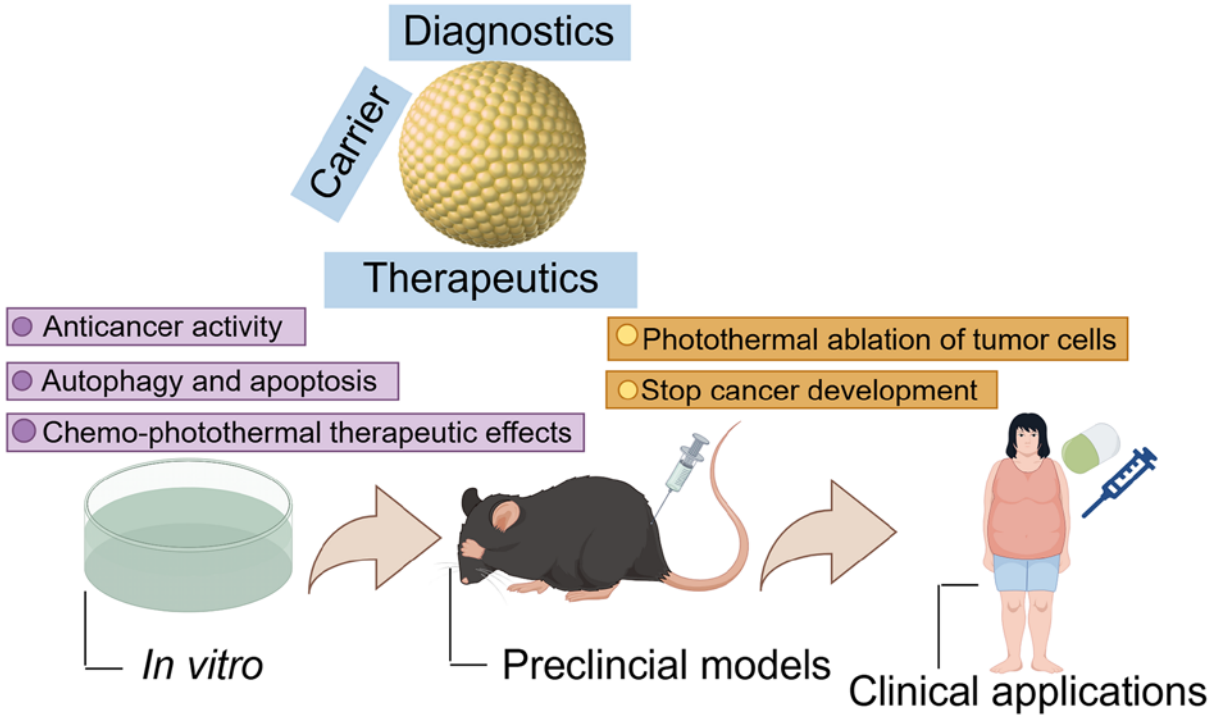

Figure 5. Potential applications of gold nanoparticles in ovarian cancer. Figure created with BioRender software (BioRender.com).

while exposure of the cells to either near-infrared light or AuNPs alone did not affect cell viability; notably, when the two components were combined, cell death was limited to the area of laser/NP cotreatment. By contrast, AuNPs conjugated with anti-PSA nanobodies did not induce cell death upon laser exposure, underscoring the high specificity of these anti-HER2 AuNPs.

Genes. Kotcherlakota *et al* (51) developed stable AuNPs, designated Au-C225-p53DNA, for the specific delivery of p53 DNA to OC cells with upregulated epidermal growth factor receptor (EGFR) expression. The authors demonstrated that the targeted delivery of the wild-type p53 gene using these NPs effectively inhibited the growth of ovarian tumors in mice with SK-OV-3 xenografts by the restoration of gene function. The C225 component of these NPs, also known as the EGFR-targeting antibody cetuximab, served as a targeted delivery system for the efficient administration of the p53 gene and the treatment of OC.

In another study, Kotcherlakota *et al* (50) combined AuNPs with the engineered bifunctional recombinant fusion protein TRAF(C) to fabricate a drug delivery system. This system facilitated the target-specific delivery of Dox and an erbB2-targeting small-interfering RNA into SK-OV-3 cells, which have upregulated expression levels of the HER2 receptor. These findings collectively suggest that AuNP-mediated gene therapy is a promising therapeutic approach for OC.

Others. In one study, thioglucose was used to modify the surface of AuNPs. The rationale behind this approach was that cancer cells have a greater metabolic rate and, therefore, a much higher glucose uptake rate than normal cells. The selective glucose uptake by cancer cells facilitated the specific internalization of the thioglucose-coated AuNPs (Glu-AuNPs) (114). *In vivo* data demonstrated that the accumulation of the Glu-GNPs in cancerous tissue was 10-fold greater than that in normal ovarian and uterine tissues. In another study, Geng *et al* demonstrated the potential of thioglucose-bound AuNPs as a sensitizer for the radiotherapy of OC. When SK-OV-3 cells were treated with the AuNPs alone, irradiation alone or the AuNPs in conjunction with irradiation, the intracellular accumulation of AuNPs resulted in greater antiproliferative activity compared with irradiation alone. The interaction between X-ray radiation and AuNPs was shown to lead to an increase in the production of ROS (62).

Combination therapies have garnered attention as a strategy to overcome the limitations associated with traditional cancer treatments. There has been an increasing interest in the use of ultrasound (US) to increase the intracellular concentration of chemotherapeutic agents, particularly in preclinical research. In addition, research has shown that NPs can enhance the efficacy of US therapy (115-117). Kip *et al* (56) exploited the US-active property of nanocone-shaped AuNPs in a combined US and CP treatment strategy. Triple-combination therapy comprising US, AuNPs and a low dose of CP was found to effectively overcome drug resistance in OC cells *in vitro*, indicating its potential for the reduction of chemotherapy-induced side effects.

An economical, facile and eco-friendly method has been devised for the fabrication of anisotropic AuNPs utilizing whey proteins (Wh@AuNPs) (58). These Wh@AuNPs were found to exhibit potent catalytic activity and the ability to emit strong red fluorescence upon complexation by trypan blue, indicating their potential use in optical sensors and live/dead cell imaging. In addition, the Wh@AuNPs exhibited cytotoxic activity against breast cancer and OC cells but no toxicity

toward normal cells, indicating that Wh@AuNPs may be novel theranostic agents that do not harm normal cells. However, further research is necessary to confirm the theranostic effectiveness of these Wh@AuNPs *in vivo*.

4. Therapeutic potential of AuNPs in OC

The poor biodegradability of AuNPs *in vivo* poses a significant challenge for clinical applications. Experiments in mice revealed that only 9% of 40-nm AuNPs administered by intravenous injection were excreted from the liver over 6 months (118). Other preclinical experiments demonstrated that a year postinjection, there was no detectible reduction in the quantity of 155-nm AuNPs retained *in vivo* (119). Higbee-Dempsey *et al* (120) synthesized biodegradable AuNPs modified with thiolated dextran, and introduced hydrophobic acetal groups onto the surface by the covalent modification of dextran. The acetal groups cleaved when exposed to an acidic environment, rendering the AuNPs highly soluble and susceptible to degradation. This carrier system was shown to facilitate the clearance of >85% of the AuNPs from the livers of mice within a span of 3 months. Therefore, this study resolves a key issue hindering the clinical translation of AuNPs and their use as nanocarrier systems.

Conjugated AuNPs have garnered widespread application as biomarkers and biodelivery vehicles within the medical sphere, with potential utility in early and advanced cancer diagnostics and therapeutics. This approach has demonstrated promise in the early identification of cancer stem cells within salivary gland tumors, as evidenced by a clinical trial using a nanocomposite of AuNPs conjugated to CD24 (NCT04907422) (121). Therefore, it is anticipated that clinical trials utilizing AuNP therapy for OC are likely to be underway in the future (Fig. 5).

5. Conclusions and prospects

NPs are widely used for targeted drug delivery, therapeutic purposes, catalysis, imaging and hyperthermia. AuNPs are used for various medical purposes, for example, as targeted therapeutic agents or drug delivery carriers, as well as in electronics and sensing applications. In the treatment of OC, AuNPs have been shown inhibit tumor growth, overcome drug resistance, reduce the toxicity of anticancer drugs, and prevent cancer cell invasion and migration. They can be combined with other therapies, including chemotherapy and radiotherapy, to provide an improved therapeutic effect. Despite these advances, certain constraints are associated with the development of AuNPs. First, AuNPs may exhibit toxicity at certain concentrations, particularly with long-term exposure (122). Therefore, further research is necessary to understand their toxicity and ensure biocompatibility. Second, the methods for synthesizing AuNPs are varied and often require strict experimental conditions and technical expertise. Thus, the development of simpler and more efficient preparation methods would be advantageous. Third, AuNPs often exhibit nonuniform particle size distributions, which affects their properties and application effectiveness (123). Therefore, improvements in their preparation methods are required to achieve more uniform particle size distributions. Fourth, AuNPs can aggregate and lose their activity during storage and use, which impacts their stability and long-term storage capability (124). Further research to develop more stable AuNP materials is essential. Finally, the cost of preparing AuNPs is high, limiting their potential for large-scale manufacture and use. Therefore, it is important to focus on reducing synthesis costs and improving scalability to enable the commercialization of AuNPs.

In summary, the development of AuNPs faces challenges and limitations that require further research and improvement. By addressing these issues, the application prospects of AuNPs can be further expanded.

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Authors' contributions

WH was responsible for writing the original draft of the manuscript, and for visualization. FY reviewed and edited the manuscript. QZ contributed to conceptualization of the study, supervision, editing and manuscript revision. KC conceived the idea of the study. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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