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REVIEW ARTICLE

Au nanoparticles in the diagnosis and treatment of ovarian cancer: A new horizon in the personalized medicine

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ABSTRACT

As the world's sixth prevalent malignancy among women, the increased rate of mortality in ovarian cancer (OC) patients is due to late diagnosis that causes a high rate of proliferation within the abdominal cavity. The sensitivity of screening and detection methods for the diagnosis of ovarian cancer in the early stages is insufficient. Considering the high rate of ovarian cancers resistance to most traditional treatments that cause the risk of disease recurrence and death, it is necessary to design new treatments and diagnostic methods. In this regard, nanoparticles and nanotechnology can be viable options for suppressing these limitations. One of the goals of nanotechnology is to improve the approaches of diagnosing, treating, or their combination (theranostics) in a variety of diseases including cancer. Au nanoparticles can simultaneously integrate therapeutic and imaging agents due to their special and extraordinary physicochemical properties and function as theranostic platforms. Next to their numerous distinct features, such as small size, surface impacts, quantum size, and electrical and optical effects, AuNPs proved to be relatively secure, stable, and require a simple preparation. Gold nanoparticles can be exerted as carriers for a more effective and targeted diagnostic and therapeutic agent delivery in the treatment of ovarian cancer. They can limit drug toxicity at tumor site and consequently reduce the toxicity of normal cells and tissues. Gold nanoparticles can be used as nano-theranostics agents and facilitate personalized medicine for a more efficient treatment of ovarian cancer by providing the simultaneous delivering of diagnostic and therapeutic agents.

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INTRODUCTION

Ovarian cancer (OC) is the world's sixth prevalent malignancy in women that leads to the death of more patients than the other malignancies of female reproductive system. [1]. Ovarian cancer cells are a heterogeneous group of cancer cells. Malignant tumour cells primarily disseminate in the peritoneal cavity and tend to multiply rapidly, putting pressure on the visceral organs. Ovarian carcinoma is a particularly dangerous illness with a low cure rate of 30% that only temporarily respond to chemotherapy. Many genetic and epigenetic factors can contribute to the transformation of ovarian cell carcinoma cells. With the ability to quickly grow and proliferate, the delayed diagnosis of these cells can induce ascites, intestinal obstruction, and tumour cachexia. Certain factors can reduce the danger of ovarian cancer in different patients such as increasing the number of alive births, enlarging

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the number of unfinished pregnancies, and using oral contraceptives. Women that suffer from obesity, cervical polyps, and gallbladder illnesses, as well as those with a "immediate" intolerance to contraceptives, are all linked to an elevated chance of developing this disease [2-5]. There are numerous studies with solid proofs on the significant effects of age on the progress of ovarian cancer. According to these researches, women in the age of 65 and above have a higher chance of containing ovarian cancer than the younger individuals . Also, a significant increase was reported in the mortality rate of this cancer in women aged 65 and above [6]. According to the data of *BRCA1 / 2* gene mutations, there are similar biological features among the basal-like breast tumors and ovarian malignancies that include containing a high level of genomic instability and being incapable of repairing DNA. There are factors that can contribute to this cancer including deficient pregnancies, specific surgeries like hysterectomy and tubal ligation, related family history, oophorectomy, oral contraceptive use, and postmenopausal hormone replacement therapy, as well as lifestyle habits such as smoking and consuming alcohol [7, 8]. The majority of ovarian cancer patients are diagnosed when facing the advanced levels of this disease. The combination of surgical debulking and drug treatment, as well as chemotherapy and radiation therapy, are among the list of currently available therapeutic options for front-line therapy . Although a high percentage of advanced ovarian cancer patients respond to the first treatment, yet 70% of the cases relapse to their disease and ultimately face death [9]. The high rate of ovarian cancer resistance to most chemotherapy drugs points out the importance of discovering novel treatments and emphasizes the need for significant advances in therapeutic strategies and early detection. The advances of nanotechnology provided the design of related approaches that can be adapted for the treatment of chemo-resistant OC. Nano-based therapeutics can function as enticing viable alternatives for the conventional therapies of various diseases including malignancies [10]. The outcomes of patients' treatments can be improved by the application of Nanoparticles (NPs) as an applicable platform for delivering cytotoxic agents and facilitating early disease diagnosis. The biological and photothermal therapeutic applications of Au nanoparticles (AuNPs) were extensively investigated in recent years. AuNPs are capable of binding to a variety of organic compounds while containing a simple synthesizing procedure [11]. This article provided a summary on the properties of AuNPs, their contribution to tumor diagnosis, and their potential for treating ovarian cancer. In this regard, we attempted to study gold nanoparticles, which stand as a new horizon in the field of personalized medicine.

OVARIAN CANCER (OC) SCREENING TEST

The patients of ovarian cancer commonly show a low rate of endurance due to their late-stage detection and diagnosis. On the other hand, public screening is neither cost-effective nor practicable. However, there are specific patient subgroups that volunteer for ovarian cancer screening (mostly those with genetic risk factors). Bimanual pelvic examination, cancer antigen (CA) 125, and transvaginal ultrasonography are among the available screening procedures in current years. Pelvic examination can be an inexpensive treatment for women who are already on regular schedule of taking gynecologic exams and their results can be accountable if performed by a trained examiner; however, this route lacks the required sensitivity and specificity as a screening test [12, 13]. 80 percent of ovarian carcinomas cases report an elevation in the radioimmunoassay of CA 125, which is a tumor-specific antigen, whereas this inducement is observed in only 50 percent of women with ovarian cancer. The elevated state of this factor is also observed in women with benign ovarian illness and those who are generally healthy, which limits its specificity. Transvaginal ultrasound (TVUS) is one of the available screening methods for OC, which implicates transvaginal ultrasonography for identifying the growth and masses throughout the scanned area. Next to being quiet costly, ultrasound is incapable of providing a sufficient sensitivity and specificity for distinguishing the cases of malignant and benign tumors. Therefore, exerting a combination of TVUS and CA125 levels in patients with high CA125 levels may be a better screening strategy for the diagnosis of OC [14-16].

DIAGNOSIS OF OVARIAN CANCER

Ovarian cancer is recognized as the leading cause of gynecological cancer death due to displaying few early symptoms, being noticeable at an advanced stage, and containing poor chances of survival. The related researches of last decade attempted to focus on improving the outcomes of ovarian cancer treatments by utilizing imaging

techniques and serum indicators to screen the early stage of this disease for preclinical purposes. The common EOC symptoms that appear months before diagnosis include abdominal bloating, early satiety, nausea, abdominal distension, alteration in bowel function, urinary symptoms, back pain, fatigue, and weight loss. The measurement of CA125 concentrations and the performance of pelvic ultrasound are included throughout the initial examination. The conduction of further imaging, such as chest, abdomen, or pelvis CTs for staging, as well as pelvic MRI if required, should be considered to correctly characterize the extension of EOC. Furthermore, it is crucial to have a pathological detection on tumor tissue due to the varying histological subgroups of ovarian cancer that implicate different treatment methods. In conformity to the reported observations over the last decade, EOC is known as a collection of disorders with unique precursor lesions, tissues of origin, molecular biology, clinical presentation, chemosensitivity, and patient outcome [17-20]. The increased mortality in OVC patients is due to the high rate of death caused by its late diagnosis, which leads to a massive proliferation throughout the abdominal cavity. The early identification of OVCA can be facilitated through the technological advancements that implicate physical diagnosis, clinical histories, CA-125 serum protein detection, physical evaluation, and ultrasound examination[21-23].

COMMON TREATMENTS OF OVARIAN CANCER

Standard stages of ovarian cancer management:

The typical treatment of advanced ovarian cancer involves a primary cytoreductive surgery that is followed by performing platinum-based chemotherapy. There are two types of ovarian cancer surgeries that include simple surgery and radical surgery, both of which are parts of primary cytoreductive surgery. Achieving a better comprehension of this disease and its natural history has also enlightened the concept of staging surgery in the beginning levels. Cytoreductive surgery is performed to accurately establish a diagnosis, remove poor perfusion, and reduce the tumor size for the purpose of improving the adjuvant chemotherapy[24, 25]. The majority of patients are subjected to simple surgery that is comprised of hysterectomy and bilateral salpingooophorectomy, infracolic omentectomy, limited retroperitoneal node excision, and segmental resection of small intestine, while involving the minimum risk of complications. The more elaborated treatments of radical surgery implicate a higher risk of bleeding and complications, as well as a longer surgery time and hospital stay, which can be reduced by proper preoperative and postoperative care [26, 27]. The data of tomographic findings from related studies helped in predicting the inability of adequate cytoreduction due to certain factors such as massive ascites, hepatic parenchyma metastases, severe diaphragmatic illness, and other abnormalities. On the other hand, the performance of laparoscopy provides a direct line of sight into the disease's progression. Nevertheless, the patient must consider many parameters before choosing between surgery and neoadjuvant chemotherapy [28, 29]. The probability of metastasis in various areas of peritoneal cavity was estimated to reach up to 11 percent. In addition, the possible occurrence of metastasis throughout the omentum was estimated to be 35 percent, while the chance of having malignant cells in peritoneal lavage was predicted to be 33 percent. Other possible sites of metastasis include lymph node, specifically in the aortic node, with a 2–24 percent probable chance of occurrence throughout the beginning stages of the disease, while the inducement of metastases in pelvic iliac nodes were observed in up to 8–15 percent of the cases [27, 30, 31]. The most common drugs used for the chemotherapy of ovarian cancer include carboplatin, paclitaxel, cisplatin, platinum, doxorubicin (DOX), decitabine (DB), and gemcitabine. According to outcomes, surgery can be a desirable method for tumors that are sized in less than 1 cm. Nevertheless, 75% of patients notice their disease at its advanced (stage III or IV) levels and despite benefiting from first-line therapy, their tumor recurrence occurs in about 15 months from diagnosis [8, 32-35]. Many trials attempted to increase clinical responses (CR) and reduce the induced toxicity in advanced ovarian cancer patients through different chemotherapeutic drugs and combinations [36]. Table 1 provides an overview of the exerted chemotherapy regimens in the treatment of advanced ovarian cancer.

The most important disadvantages of chemotherapy

In general, the overall survival and progression - free survival of patients with advanced ovarian cancer can be increased through chemotherapy [52-54]. The exerted drugs in chemotherapy,

Table 1. displays the first-line chemotherapy regimens used in advanced ovarian cancer patients

Chemotherapy compounds	Reference
Melphalan	[37]
Melphalan hexamethylmelamine	[38]
Cyclophosphamide doxorubicin	[39]
Carboplatin Etoposide	[40]
Cisplatin Cyclophosphamid	[41]
Cisplatin Paclitaxel	[42]
Cisplatin Ifosfamide	[43]
Cisplatin Docetaxel	[44]
Carboplatin Paclitaxil Epirubicin	[45]
Cisplatin Paclitaxel Ifosfamide	[46]
Carboplatin Paclitaxel Gemcitabine	[47]
Cisplatin Gemcitabine	[48]
Cisplatin Irinotecan	[49]
Carboplatin Paclitaxel Epidoxorubicin	[50]
Carboplatin Docetaxel	[42]
Carboplatin Paclitaxel Topotecan	[51]

including alopecia, gastrointestinal effects ,infection myelosuppression and neuropathy, are associated with unwanted side effects [53, 55] and may also implicate the risk of causing drug resistance. Drug resistance can occur for a variety of reasons, including pharmacokinetic, micro-environmental tumor, and cancer-cell-specific abnormalities, which may lead to death in some cases [56]. Multidrug resistance (MDR) stands as a critical barriers to an effective and comprehensive ovarian cancer treatment. The proposed hypotheses for determining the actual underlying causes of MDR and disease relapse are listed in the following [57]. Changes in drug efflux: As an eminent cause of MDR advancement, the direct efflux of chemotherapeutic drugs into the extracellular environment of cells is mediated by the ATP-binding cassette (ABC) family and ATP hydrolysis. The ABC family of transporters with 49 members is responsible for maintaining the intracellular drug concentrations [58, 59].

DNA damage repair dysfunction: A damaged DNA structure by physical, chemical, or biological factors results in triggering the functionality of DNA repair pathway and repair genes to preserve the genome's integrity and stability. On the other hand, the ectopic activation of DNA repair mechanism leads to the frequent progression of tumors. Since the mechanism of chemotherapeutics implicates direct or indirect processes to induce DNA damage and consequently annihilate the tumor cells, the repair abilities of tumor cells' DNA are intensified and eventually lead to the development of MDR[60, 61].

Apoptosis: There are two principal apoptotic processes that include extrinsic or death receptor pathway that is balanced by tumor necrosis factor (TNF) receptors, and the intrinsic or mitochondrial pathway that is accorded by chondriosomes. This balance can be disrupted by the Bcl-2 protein family, which is consisted of pro-apoptotic proteins such as Bax, Bad, and Bid along with anti-apoptotic proteins such as Bcl-2 and Bcl-xl.Any. This inducement can be considered as a major

factor in extending chemotherapeutic resistance and even lead to apoptotic inhibition during carcinogenesis[62, 63].

Drug target mutation: Molecular targeted treatment is recognized as a progressive therapeutic strategy for the cases of cancer. Numerous studies were conducted on this topic due to its lower adverse impacts and higher efficacy than traditional chemotherapy agents., Among the other chemicals and proteins, this technique can implicate the members of signaling pathway in the role of potential targets; nevertheless, other studies reported the possible development of MDR upon the occurrence of a signaling system alteration[58, 64].

Epigenetic alterations: As the principal cause of carcinogenesis, Epigenetic alterations is a unique and crucial method in the development of MDR. The two basic types of epigenetic alterations include DNA methylation, which facilitates the binding of methyl groups to cytosines in CpG islands, and histone modification induced by acetylation or methylation. Several studies confirmed the role of epigenetic alterations, including histone methylation and acetylation and DNA methylation, in the occurrence of cancer cell resistance to different chemotherapeutic drugs [65, 66]. Up to this date, all of the conducted therapies ended in a significant rate of relapse and unsatisfying treatment outcomes, which point out the necessity of performing further researches to discover new therapeutic regimens for ovarian cancer (OVCA) patients [67].

NANOTECHNOLOGY-BASED TECHNIQUES: A POTENT SOLUTION TO SURPASS THE LIMITS OF TRADITIONAL METHODS IN THE DIAGNOSIS AND TREATMENT OF OVARIAN CANCER

Ovarian carcinoma stands as the leading reason of death by gynecologic malignancy, which is caused by delayed initial detection and the recurrence of ovarian cancer (OVCA) due to therapeutic resistance. Many patients experience OVCA recurrence, which makes them resistant to treatment and incurable. According to updated reports, recent observations on ovarian cancer stem cells (CSCs) indicated their high resistance towards conventional cytotoxic chemotherapeutic drugs and confirmed their potent contribution to treatment resistance and OVCA recurrence. The current diagnostic and therapy methods lack the sufficient sensitivity or efficacy for diagnosing OVCA in its early stages, while the high expenditures and absence of a specified detection point results in a late diagnosis. Nanotechnology has proven its strong applicability in the diagnosis and treatment of OVCA while facing an increasing rate of application in this field. [68-70]. The goal of this technology is to enhance the available methods of diagnosing, treating, or their combination (theranostics) for a variety of diseases such as cancer. The exertion of nanocarriers can facilitate the targeted delivery of hydrophobic chemicals, delivery of carrier stabilization, and reduce the systemic toxicity of antineoplastic agent, as well as API biodistribution and pharmacokinetics. The usage of physical adsorption or chemical conjugations can provide the loading of nanocariers with drugs, imaging agents, targeting moieties such as ligands or antibodies, and polyethylene glycol (PEG) in order to extend the half-life of therapeutic agents and improve passive and active tumor targeting [10, 71, 72]. Liposomes, self-assembled polymers, micelles, hydrogels, dendrimers, quantum dots, magnetic nanoparticles, carbon-based nanocarriers (bucky balls and carbon nanotubes), and metal or oxide based nanoparticles (colloidal Au, silica, and titanium dioxide) are some of exerted nanocarriers for the diagnosis and treatment of various types of cancers, especially ovarian cancer. Due to their exceptional physicochemical and optical features, Au nanoparticles were designated in the form of cutting-edge platforms to combine diagnostic and therapeutic strategies. These products may provide significant benefits in cancer settings by taking the role of targeted vehicles to control the drug release, photothermal therapy, and gene therapy, as well as functioning in the form of contrast imaging agents to monitor the disease and therapeutic progress in real time. These image-guided therapeutic platforms can be an effective treatment with an adjustable design for maximizing the personal benefits of patients while minimizing the hazardous side effects[73, 74].

Au nanoparticles

Au is a material with high thermal and electrical conductivity, which can act as an excellent reflector of IR infrared waves. Some of the most important properties of AuNPs at nanoscale include the increased cross section of materials due to their smaller particle size, intensified reactivity[75, 76] and low toxicity[77], as well as being eco-

friendly[78] and stable[79] next to containing surface plasma resonance[80], the option of surface modification and functionalization[81], and high thermal[82] and electrical conductivity[83]. Furthermore, these nanoparticles have a wide range of applications and medical implementations due to their identical biocompatibility qualities. They also contain an electronic-optical structure that led to the rise of several applications in the fields of sensors and biosensors. AuNPs can be used as an antibacterial agent[84], the release of drugs and therapeutic agents[85] in nanowires and catalytic applications[86], Hyperthermia[87], and sensors[88], as well as for the fabrication of electronic chips[89], Raman spectroscope[90] and Diagnosis of diseases [91]. The unique factors of these products has characterized them in a different class from conventional cancer treatments. Their simple synthesis in various sizes and shapes provided a variety of optical properties including intense light absorption and scattering, a high rate of photothermal conversion, photostability, and colloidal stability, as well as being biocompatible, contain a simple ligand conjugation chemistry, and facilitate extended molecule loading per particle. Due to their reduced particle size and surface chemistry, Au nanoparticles can be coated with small molecules, aptamers, polymers, and biomarkers in order to expand their range of applications [92-94]. Next to their ability to carry active chemicals, AuNPs stand as potent theranostic platforms since they can exhibit a high affinity and specificity for cancer cells as a result of containing various targeting moieties, while simultaneously holding therapeutic and imaging agents [92-95].

AuNPs in the diagnosis of ovarian cancer: imaging-based detection

Although there is a lack of any available routine screening of OVCA for healthy women, yet there are some screening options for at-risk patients that implicate a routine pelvic examination, transvaginal sonography, and a blood serum biomarker test known as CA125. However, the current screening and detection methods lack the sufficient sensitivity for identifying OVCA in its early stages in order to improve the patient's prognosis by treatment interference. In addition, exorbitant expenditures and a lack of point-of-care screening procedures lead to a delayed diagnosis and inadequate care for the patients. Biomarker screening provides the best results upon being performed on blood, urine, or saliva samples in people at the risk of developing OVCA [96, 97]. The accommodation of considerably improved radiative features, electromagnetic field improvement, and the ability to conjugate with contrast agents proves the effectiveness of AuNPs in the role of imaging agents for the in vitro and in vivo imaging-based diagnostics of cancer cells (Table 2). Light scattering imaging, two-photon fluorescence (TPF) imaging, photoacoustic imaging / tomography (PAT), x-ray computed tomography (CT), surface-enhanced Raman spectroscopy (SERS), and magnetic resonance imaging (MRI) can be exerted in the course of this procedure[98-100].

AuNPs in the treatment of ovarian cancer

Although studies have confirmed the effects of performing treatment with conventional chemotherapy and surgery in improving the statues of advanced ovarian cancer patients, however, most of the cases end with death due to drug-resistant subsequent to 5 years. Therefore, the enhancement of molecular targeted therapies may lead to the design of more effective treatments [119]. The ineffectiveness of traditional therapies in treating ovarian cancer is undeniable, which highlights the necessity of designing novel approaches to improve the obtained efficacy [120]. In fact, the exertion of various chemotherapy agents can enhance the survival rate of patients with ovarian cancer, but their application is limited by their distribution through the whole body, which leads to high normal organ toxicity. The small sizes (10-100 nm) of particles in nanotechnology can improve blood circulation and enhance the status of accumulated therapeutic drugs at the tumor sites [121, 122]. In addition, another fundamental barrier in the treatment of ovarian cancer is drug resistance, which can be most probably surpassed through the provided approaches by nanotechnology. The formulations that are based upon nanotechnology involve encapsulated, conjugated, or entrapped / loaded forms in nanocarriers or drug delivery vehicle / vectors [123, 124]. The controlled delivery of chemotherapeutic drug (s) in a targeted attempt can lead to the achievement of nanotechnology-based therapies that would directly affect the cancer site for extended time intervals while causing a minimal or zero normal organ toxicity[125]. The administration of numerous traditional chemotherapeutic agents are conducted through oral or intravenous routes, which contain weak

Table 2. Methods based on AuNPs s in the diagnosis of ovarian cancer

Nanostructure	Method of diagnosis	Application	Reference
gelatin-coated AuNPs	two-photon excited (TPE) fluorescence	- as an accountable label-free contrast agents for the non-invasive NIR imaging of NIH:OVCAR-3 ovary cancer cells	[101]
Au nanoparticle	dynamic light scattering and fluorescence dual-signal	- sensing of cancer antigen-125	[101]
Au–silver core–shell nanoparticles	SERS	-evaluation of cancer diagnosis, the in vitro antiproliferative impacts of SERS-nanotags against human ovarian adenocarcinoma cells (NIH: OVCAR-3)	[102]
AuNPs	Surface-enhanced Raman spectroscopy (SERS)	- as a sensor platform for monitoring CA125 antibody-antigen probe molecules	[103]
AuNPs@g-C3N4 nanoprobe	electrochemiluminescence biosensor	- distinguishing phosphatidylserine (PS)-positive exosomes,a potent biomarker for early diagnosis of ovarian malignancy	[104]
nanospheres (Ru@AuNPs)	two-photon luminescence (PTL)	-the coupling of inert Ru(II) polypyridyl complexes to Au nanospheres facilitates the progress of two-photon luminescence for effective photothermal impact	[105]
Au Nanoparticle Coated Reduced Graphene Oxide	photoacoustic Imaging	-potent photothermal agent and capable of facilitating the diagnosis and therapy of ovarian cancer	[106]
chitosan oligosaccharide-stabilized Au nanoparticles	photoacoustic Imaging	- as a novel type of optical contrast agents for photoacoustic imaging (PAI)	[107]
Au nanoparticles	Ultrasound	- AuNPs notably improved the ultrasound contrast and were efficiently bound and taken up by HeLa cells without any alteration in their viability	[108]
PEGylated Au nanoparticles	Computed Tomography	- nanoparticle can be exerted as computed tomography contrast agent - it can facilitate the identification of tumor cells with a higher expression of CD24 at the early stages with more efficiency when compared to the other routine methods	[109]
folic acid-modified diatrizoic acid-linked dendrimer-entrapped Au nanoparticles	Computed Tomography	- AuNPs displayed a noticeable potentials as imaging probes for targeted CT imaging of human cervical cancer	[110]
AuNPs	surface enhanced Raman spectroscopy (SERS)	- As a clinical diagnostic tool for the detection of other MMP proteinases in fluid biomass samples, increasing the number of biomarkers needed to better describe diseases such as cancers, including ovarian cancer	[111]

Continued Table 2. Methods based on AuNPs s in the diagnosis of ovarian cancer

Nanostructure	Method of diagnosis	Application	Reference
galactoxyloglucan endowed Au nanoparticles	Surface-Enhanced Raman Scattering	- AuNPs (PST-GNPs) with cancer-cell-selective toxic nature and satisfying biocompatibility for tracing the in vivo NP dissemination in a label-free fashion to obtain important biochemical details on a molecular level	[112]
CuBTC@MoS2-AuNPs	electrochemical biosensors	-as an Ultrasensitive Layer for the Electrochemical Detection of the Ovarian Cancer Biomarker CA125	[113]
PAMAM/AuNPs	electrochemical biosensors	-the detection of cancer antigen 125 (CA125) oncomarker	[114]
Au nanoparticles	electrochemical biosensors	-Sensor for Sensitive BRCA1 Detection	[115]
Au nanoparticles	electrochemical biosensors	-a sensitive label-free impedimetric immunosensor for the detection of cancer biomarker epidermal growth factor receptor (EGFR) for clinical screening and prognosis of tumors such as ovarian tumors	[116]
Au nanoparticles	electrochemical biosensors	-Ultrasensitive immunoassay of carcinoma antigen 125 in untreated human plasma	[117]
human serum albumin conjugated Au nanoparticles (HSA–AuNPs)	electrochemical biosensors	-Impedimetric Sensor for Sensitive Detection of miRNA-200c In various cancers such as ovarian cancer	[118]

pharmacokinetics along with a narrow therapeutic window. Next to their quick rate of reaching the maximum tolerated concentration in the blood, these drugs leave the bloodstream afterwards due to their low blood circulation half-life[126, 127]. The side effects of anti-cancer drug, similar to the impacts of radiotherapy, remain a major limitation in the advancement of cancer treatment. As a result, it is needed to improve drug bioavailability in the tumor region while being restricted to the appointed target and cause a reduction in the amount of prescribed drug, which decreases the number and severity of side effects and leads to the delivery of proper and sufficient dosage of combined drugs to the designated target through a controlled manner. Due to a variety of unique physiochemical properties, numerous studies were performed on Au nanoparticles (Au NPs) for the objectives of drug delivery, radiosensitizers, and photothermal and photodynamic therapy agents. It is also notable that the controllable production of nanomaterials can provide products with controlled sizes and shapes. There are a variety of clinical applications for the unique optical, chemical, and biological features of Au nanoparticles that involve drug and gene delivery. Among the other appealing qualities of these nanoparticles, one can point out the intensification of their surface plasmon, the ease of surface modification, accommodation of a controlled method that provides their interaction with thiol groups, and their non-toxic nature. These properties can be utilized to develop a platform for achieving an effective and selective design for performing the targeted intracellular release of particular drugs [128-130]. The recent progresses of Au nanoparticles exertion in drug and Therapeutic agents delivery systems is presented in Table 3.

Theranostics based on Au nanoparticles in ovarian cancer

Nanotheranostics refer to the combination of optical multiplexed disease detection and therapeutic monitoring in a single modality, with the ability to escalate nanomedicine closer to a true form of

Table 3. AuNPs-based therapies in ovarian cancer

Type of nanoparticles	Drug	Ligand	Application	Reference
AuNPs	Cisplatin	ALDH1,CD44, CD133, Sox2, MDR1 and ABCG2	-targeting EMT stands as an applicable therapeutic option for surpassing drug resistance in ovarian cancer patients	[131]
Au nanoparticles	-	EGFR	-high anti-cancer activity invitro againstSKOV-3 cells -The overproduction of reactive oxygen species (ROS) was noticed as a vital mediator of AuP NPs-mediated cell death	[132]
Au nanoparticles	as radiosensitizers		-causing an enhancement in the efficiency of RT is the result of exerting radiosensitizers to selectively increase the dose at the tumor site	[133]
Au nanoparticles	Cisplatin	-	-for its long-term therapeutic impact on resistant cancer cells -improved anti-cancer activity was onserved at the low-dose Cis on drug-resistant cancer cells -stands as a suitable strategy for decreasing the side effects of chemotherapy	[134]
Poly-amino acids coated Au nanorod	Doxorubicin	-	-synergistic photodynamic therapy and chemotherapy in ovarian cancer cells - the excessive reactive oxygen species (ROS) generation in DH-GNR (+NIR) might be responsible for the cell apoptosis and cell death	[135]
polypyrrole(PPy) modified Au nanoparticles	-	15P(sequence: SHSWHWLPNLRHYAS)	- the 15PconjugatedPPy modified Au nanoparticles displayed amazing biocompatibility - tumor-targeted impact and the effective photothermal ablation of tumor cells	[136]
Au nanoparticles	Galangin	-	-galangin-AuNPs combination is synergistic in opposition to ovarian carcinoma for inducing cytotoxicity and cell death via apoptosis, this	[137]

Continued Table 3. AuNPs-based therapies in ovarian cancer

Type of nanoparticles	Drug	Ligand	Application	Reference
			mechanism enhancing expression of p53, caspase-8	
AuNPs	ceragenin CSA-131	-	-AuP@CSA-131 applied stronger anti-cancer impacts than free ceragenin, which was pointed out through the improved capability of causing caspase-dependent apoptosis and autophagy processes via reactive oxygen species (ROS)-mediated pathways	[138]
AuNPs	Digitonin	-	-digitonin conjugated Au nanoparticles to annihilate cells through the disruption of membrane	[139]
Fe3O4 NPs and Au NPs	-	-	-Fe3O4@ Thymbra spicata/Au NPs displayed a very low cell viability and high anti-ovarian cancer activities dose-dependently against PA-1, SW-626, and SK-OV-3 cell lines while lacking any cytotoxicity on the normal cell line (HUVEC)	[140]
AuNPs	Doxorubicin + erbB2-siRNA	TRAF(C) (TR)	-target specific delivery in to SK-OV-3 cells via HER2 receptors	[141]
AuNPs	C225+p53DNA	EGFR	-targets EGFR since it has a large number of EGFR receptors and EGFR overexpressing SK-OV-3 cells in ovarian cancer	[142]
AuNPs	Theaflavin+ theaflavin-gallates	quinone motif	-selectively induce apoptosis of tumour cells	[143]
AuNPs	-	folic acid (FA)	-endocytosis of thenanoconjugates	[144]
Branched Au nanoparticles	-	Nanobodies(VHH)	-These nanobodies can form a binding to the HER2 antigen that is severely expressed on breast and ovarian cancer cells	[145]
Au nanoshell–based complex	cyclophosphamide, Adriamycin, melphalan, and cisplatin	anti-HER2+ fluorescence	-dual modal imaging, and photothermal therapy of HER2-overexpressing and drug-resistant ovarian cancer OVCAR3 cells	[145]
cationic Au-Fe3O4 nanoparticles	Cisplatin	aptamer–siRNA chimera+ Notch3 siRNA	-future targeted cancer therapy	[146]

Continued Table 3. AuNPs-based therapies in ovarian cancer

Type of nanoparticles	Drug	Ligand	Application	Reference
AuNPs		malicious exosomes	-surpassing MDR -Targeting the tumor microenvironment	[147]
AuNPs	fungal asparaginase	-	-cytotoxicity impact of nano biocomposite was observed to be higher against ovarian cancer	[148]
AuNPs	cetuximab (C225)	anti-EGFR+ anti-FR	-target to cancer cells will be further improved	[149]
AuNPs	bleomycin + doxorubicin	-	-reducing cancer drug resistance -decreasing systemic drug toxicity -improving the results of chemotherapy	[150]
AuNPs	Doxorubicin	-	- promising drug delivery systems for overcoming chemoresistance	[151]

personalized medicine [152]. The delivery of efficient treatments to cancer patients is beginning to face alterations due to the development of targeted cancer therapies, which implicate the rise of nanomedicine as a cutting-edge field in regards to the objective of personalized medicine[74]. The amazing potential of AuNPs in the roles of drug delivery, diagnostics, and imaging carriers is undeniable. Multifunctional hybrid AuNPs were designed for multimodal imaging, diagnosis, and treatment optimization. AuNPs are divided into several subtypes and despite their variances, some of their distinct types can be an excellent choice for specific cancer theranostics applications due to their different features. Next to being biocompatible, AuNPS contain a strong surface plasmon resonance (SPR) peak with the option of being tuned from visible to near-infrared (NIR), which can be easily functionalized through the addition of various molecules to their surfaces [153, 154]. The accommodation of a diverse and straightforward chemistry facilities the simple attaching of numerous biomolecules to the surfaces of these nanoparticles and therefore, they can be a suitable option for cancer theranostics. Peptides, small-molecular-weight chemicals, aptamers, and monoclonal antibodies were added to the surface of AuNPs to improve their tumor-targeting capabilities. The interaction of an electromagnetic wave with conduction electrons results in the creation of a metal, which is an optical phenomenon known as SPR and stands as another attribute of AuNPs. This product has been exerted for multimodality imaging, tumor targeting, and therapeutic delivery(Fig. 1). Au nanoparticles can also function as anticancer drug carriers due to their enhanced permeability and retention (EPR) effects that facilitate their aggregation at tumor sites. Furthermore, the surface of Au nanoparticles can be easily modified to provide the binding of targeted groups and offer active targeting properties to the carriers. Moreover, the rate of drug bioavailability and treatment efficacy can be improved by the application of Au nanoparticles as carriers. Drugs and genes can be simultaneously delivered through the usage of functionalized Au nanoparticle[162-164]. Also, delivery systems based on Au nanoparticles can intelligently release drugs and gene by considering the redox sensitivity, pH sensitivity, thermo-sensitivity, and other factors [165]. Table 4 demonstrates some of the theranostic applications based on Au nanoparticles in ovarian cancer.

THERANOSTIC & FUTURE PERSPECTIVES

There are unquestionable proofs for the great potential of AuNPs in functioning as drug delivery, diagnostics, and imaging vectors. However, their rate of progress is still considerably slower than that of desired and despite the significant attempts for introducing AuNPs into clinical frameworks, only a few clinical trials have been conducted. Although this product is typically regarded to be biocompatible, yet a number of studies reported the observance of toxicity based on size, shape, and surface coating

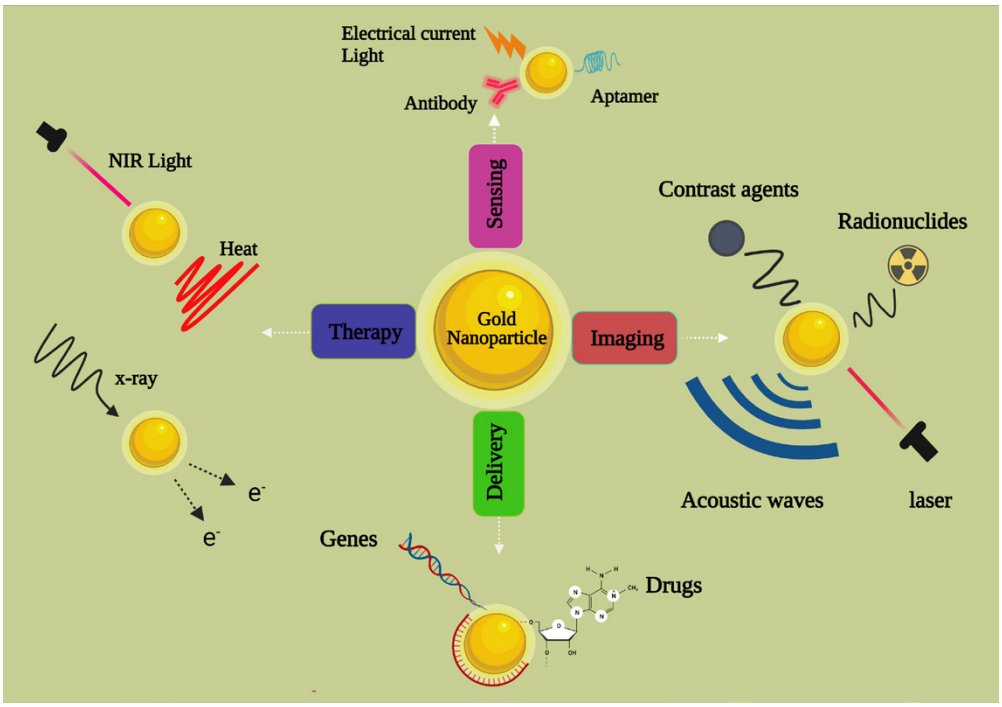

Fig. 1. Application of AuNPs in multimodality imaging, tumor targeting, and therapeutic delivery.

Table 4. Theranostics based on AuNPs in ovarian cancer

Types of Au nanoparticles	Treatment method	Diagnostic agent	Ligand	Various diagnostic methods	Reference
Au nanoparticles	paclitaxel (PTX)	rhodamine B linked beta-cyclodextrin (β-CD)	biotin receptor	fluorescence	[155]
Au nanoshell	Photothermal	-	HER2 receptor	Fluorescence+ magnetic resonance imaging	[156]
magnetic and Au NPs (MNPs and GNPs	photothermal/photodynamic therapy	radioisotopes (125I, 111In, 64Cu, 68Ga, 99mTc)	-	PET/SPECT	[157]
Au nanostars	photothermal therapy (PTT)	-	nanobodies against epidermal growth factor 2 and blocking agents3	photoacoustic imaging (PAI) and computed tomography (CT)	[158]
dendrimer-entrapped Au nanoparticles (Au DENPs)	α-tocopheryl succinate (α-TOS)	fluorescein isothiocyanate (FI)	folic acid (FA)	computed tomography (CT)	[159]
Au nanoparticles	Ultrasound	-	glypican-3 protein (GPC-3)	ultrasound	[108]
Au nanorods (GNRs)	combined photoacoustic (PA)/ Raman spectroscopy (SERS)	-	-	combined photoacoustic (PA)/ Raman spectroscopy (SERS)	[160]
Au nanostars	Photothermal	-	folic acid (FA)	SERS	[161]
Au nanoparticle coated reduced graphene oxide	photothermal Therapy	-	-	photoacoustic Imaging	[106]

among the varying parameters. Other concerns implicate their limited penetration depth that inhibits imaging and PTT implementation, non-biodegradability that can result in bioaccumulation in various tissues and organs, and non-porousness that might cause bioaccumulation in a variety of tissues and organs and turn drug encapsulation and release into a challenge [166, 167]. Nevertheless, comprehensive characterization is required since the pharmacokinetics and biocompatibility of AuNPs can be different depending on the type of applied conjugation. The conduction of further long-term toxicity studies, as well as detailed assessments into the mechanisms of AuNPs interaction with biological systems. stand as a necessity and must be increased. Similar to nano theranostics techniques and their application in clinics, there is still a long way before the complete preparation and availability of nanotechnology platforms for the usage of clinicians[74, 168].

CONCLUSIONS

Au nanoparticles proved to contain a high potential for diagnosis, treating and improving the living conditions of patients with ovarian cancer. Gold nanoparticles can be exerted in a variety of methods for the early detection of this disease. They can be also integrated with different imaging modes and provide a more accurate diagnosis of cancer, which is a crucial factor in the success of following treatments. Using novel methods of cancer treatment instead of traditional procedures (surgery - chemotherapy) can lead to a reduction in the unwanted side effects of chemotherapy, surpassing the obstacle of drug resistance, and preventing disease recurrence to some extent in order to avert the death of patients. It is expected that a faster and greater rate of improvement would be achieved through the utilization of Au nanoparticles as carriers for drug delivery and other therapeutic agents throughout the treatment of patients with ovarian cancer. In fact, this product can prevent the inducement of unwanted toxicity to normal tissues by transporting the drug and its delivery to the desired location, which would consequently cause more toxicity to the target site. Furthermore, the application of Au nanoparticles can guarantee a longer circulation in the blood, which would improve the obtained therapeutic efficiency when combined with successful targeting. Gold nanoparticles can stand as a new horizon for the integration of diagnostic and treatment methods and facilitate the design of personalized medicine, which emphasizes on the necessity of further comprehensive research to demonstrate its effectiveness.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest

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