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REVIEW ARTICLE

Gold Nanoparticles and their Applications in Cancer Treatment

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Abstract: ***Background*:** Cancer nanotechnology has become a prime field of investigations for the scientists nowadays. There are several nanocarrier systems used for effective cancer therapeutics and gold nanoparticles (GNPs/AuNPs) have become promising vehicles for the delivery of anticancer drugs into their targets. Gold nanoparticles (GNPs/AuNPs) have been explored for tumor targeting, tumor imaging, and photothermal therapy of cancer due to their unique physicohemical and optical characteristics.

***Methods*:** We searched about recent research progress made in the field of gold nanoparticulate systems for effective elimination of cancer. Our main focus was on the use of gold nanoparticles (spherical), gold nanorods, and gold nanostars for improved cancer therapy.

***Results*:** Gold nanoparticles are suited well for cancer therapeutics due to their higher biocompatibility and lesser toxicity. They can be utilized actively or passively both for the targeting of tumor cells.

***Conclusion*:** Recently, gold nanoparticulates have been investigated preclinically for the treatment of cancer. Their clinical practice is still a challenge and it is necessary to carry out clinical practice of gold nanoparticles to make them available in the market. Future advancement in the field of gold nanoparticles will likely produce better results in cancer therapeutics.

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1. INTRODUCTION

Advancement in the field of nanotechnology has improved the therapeutic index in the treatment of dangerous diseases like cancer [1]. The higher availability of nanosized materials with controlled physical and chemical properties has opened a new window in cancer therapeutics [2]. Nanosized materials like nanoparticles show localization in tumor tissues instead of normal tissues due to enhanced permeability and retention (EPR) effect [3]. High loading of various drugs in nanoparticulate system is easy due to their high surface area to volume ratio and hence, enhancement of drug's stability and solubility is observed [4]. Metallic nanoparticles come under the new class of nanoparticles which are explored for diagnostic and therapeutic purposes nowadays [5]. Metallic nanoparticles possess a large number of physcochemical properties which show differences from those of the bulk substances. Special proper-

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ties of metallic nanoparticles can be studied by exploring their melting behavior. Metallic nanoparticles exhibit solid-like appearance at low temperature, while higher temperature incorporates liquid-like properties in their structure. Shape, composition, and size of metallic nanoparticles influence their melting behavior [6]. Various metallic nanoparticles explored for cancer therapeutics are iron oxide, silver, and gold nanoparticles [7]. So, our major aim in this review was to explore therapeutic utility of gold nanoparticles (GNPs) for the treatment of cancer.

Michal Faraday firstly described synthesis of gold nanoparticles (GNPs or AuNPs) in the form multicolored solution through the reaction of gold chloride with sodium citrate [8]. Gold nanoparticles were implemented in immunodiagnosis and histopathology during 1950s because of their capability to bind with protein biologics without change in their physicochemical properties [9]. Gold nanoparticles have been implemented in the field of DNA diagnostics and biosensor technology nowadays in the form of scaffolds [10]. They are also explored for the treatment of rheumatoid arthritis [11], while, radioactive gold nanoparticles are used for eradication of liver carcinoma [12]. Colloidal gold nanoparticles are emerging as effective candidates for targeted elimination of tumor cells [13]. Cancer is currently treated by implementation of three methods namely chemotherapy, radiation therapy, and surgical treatment. Chemotherapy and radiation therapy is used to cause death of cancerous tissues while tumors are removed from their development sites using surgical techniques [14]. Gold nanoparticles can play a vital role in minimizing the serious limitations of conventional cancer treatments [15]. The gold nanoparticulate system causes destruction of cancerous tissues using photothermal therapy. Irradiation of gold nanoparticles with focused impulses of particular wavelength can cause targeted elimination of cancerous tissues [16]. Various advantages of gold nanoparticles over the other nanoparticulate systems are:

- These are inert and non-toxic carrier systems due to the presence of non reactive gold core.
- They are detectable upto low concentration of 10^{-6} M.
- Gold nanoparticles can be formed in monodisperse form having size of 1 - 150 nm [5].

2. CANCER: A BRIEFING ABOUT RECEPTORS AND METABOLISM

Cancer simply represents abnormal and unrestricted growth of cells [17]. Cancerous vasculature shows unique properties like the presence of the leaky nature, the presence of mutated proteins, and alteration in receptor expression [18]. The presence of a large number of cell surface receptors on tumor blood vessels makes them distinct from normal vessels [19]. Cancerous vasculature also show the presence of extracellular matrix proteins [20]. Table **1** enlists various types of receptors implemented to target the cancerous cells and their location in different tumor sites [21].

Alongwith altered receptor's expressions, abnormal cellular metabolism is also a sign of cancer recognition [22]. It was reported in one study that tumor cells show rapid consumption of glucose compared to normal cells and lactic acid production capability even at higher concentrations of oxygen. This process was named as "Warburg effect" [23]. Currently, scientists have revealed that "metabolic reprogramming" is responsible for the generation of abnormal metabolism [24]. Various growth factors, alongwith nutrient conditions play the role of input signals for this reprogramming process [25]. It was reported that activation of PI3K/Akt/mTOR pathway through the series of transduction signals changed the phase of metabolism from quiescent to proliferation. The activation of PI3K/Akt/mTOR pathway promoted the higher carbon flux in combination with glutamine addiction [26]. Due to this process, pyruvate is directly involved in lactic acid production instead of joining the Krebs Cycle and producing Acetyl-CoA by implementing enzyme pyruvate dehydrogenase. Furthermore, various enzymes of Krebs Cycle get mutated, leading to the abnormal oncometabolites formation [27]. Proliferation and drug resistance of cancerous cells is also enhanced due to the production of lactic acid in a low pH environment also [28]. Current research in the elimination of cancer is focused on the molecular therapeutics [29] however, their combination with a potential nanocarrier system is still a field of investigation. Conjugation of such bioactive molecules with nanocarrier like gold nanoparticles may improve their efficacy subject to complete information regarding toxicity profile, cellular dynamics, and intracellular diagnosis of nanocarrier systems [21].

Table 1. Types of receptors used for targeting of various types of tumors [Adapted from Kumar *et al.*, (2013)].

Types of Receptor	Associated Locations or Tumors
Transferrin receptors	Capillary endothelial cells
Opioid receptors	Capillary endothelial cells
Insulin receptors	Capillary endothelial cells
Low-density lipoprotein receptor related proteins 1 and 2 (LRP-1 and 2)	Capillary endothelial cells
Nicotine receptors	Capillary endothelial cells
Transferrin receptors	Most tumors
Integrin receptors	Most tumors, metastasis
Folate receptor	Most tumors
Endothelial growth factor receptor	Epithelial tumor cells
Vascular endothelial growth factor receptor	Tumor vesicular endothelial cells
Prostate specific membrane antigen receptor	Prostate tumors
Luteinizing hormone-releasing hormone receptor	Breast, ovarian, endometrial, and prostate cancers
Vitamin B12 receptor (cobalamin)	Gastric tumors, Neuroendocrine tumors
Man-6-Phos/ insulin-like receptors	Cancer, melanoma and hepatocellular carcinoma
Nucleolin	Leukemia, colon cancer, Breast cancer, Melanoma
Endolin	Vascular and lymphatic endothelium in tumors
Bombesin receptors	Breast, Prostate, Small cell lung, and Pancreatic cancers
Immunoglobin receptor (Fcγ receptor)	Leukemia
p32 protein (gC1q receptor, hyaluronic acid-184 binding protein)	Surface of lymphatic, myeloid, and several tumor tissue

3. GOLD NANOPARTICLES AS NANO-MEDICINES FOR EFFECTIVE CARCI-NOMA ELIMINATION

There are several properties of gold nanoparticles, which make them suitable for cancer therapeutics [30]**.** The optical characteristics of the gold nanoparticles (GNPs) are unique and they show high absorption efficiency in the absence of photobleaching [31]. They also show very high light absorption and scattering power due to increased surface area at the nanoscale. This characteristic makes them an efficient system for cancer imaging and analysis [32]. Localized surface plasmon resonance characteristic may be present in gold nanomaterials of particular shapes like nanocages, nanorods, and nanostars. This surface plasmon resonance (SPR) effect makes them more valuable in the targeted elimination of carcinoma [33]. SPR effect promotes valence electron vibrations in a solid material when irradiated by incident light of a particular wavelength. At this stage there is light absorption and photon emission at same frequency leading to localized thermal degradation of cancerous cells after accumulation at the target site due to SPR effect [34]. Conventionally used anticancer drugs have low molecular weight along with a median value of HLB promoting their easy partitioning across lipidic membranes. This factor is responsible for rapid distribution of anticancer drugs in the body, including target and non-target

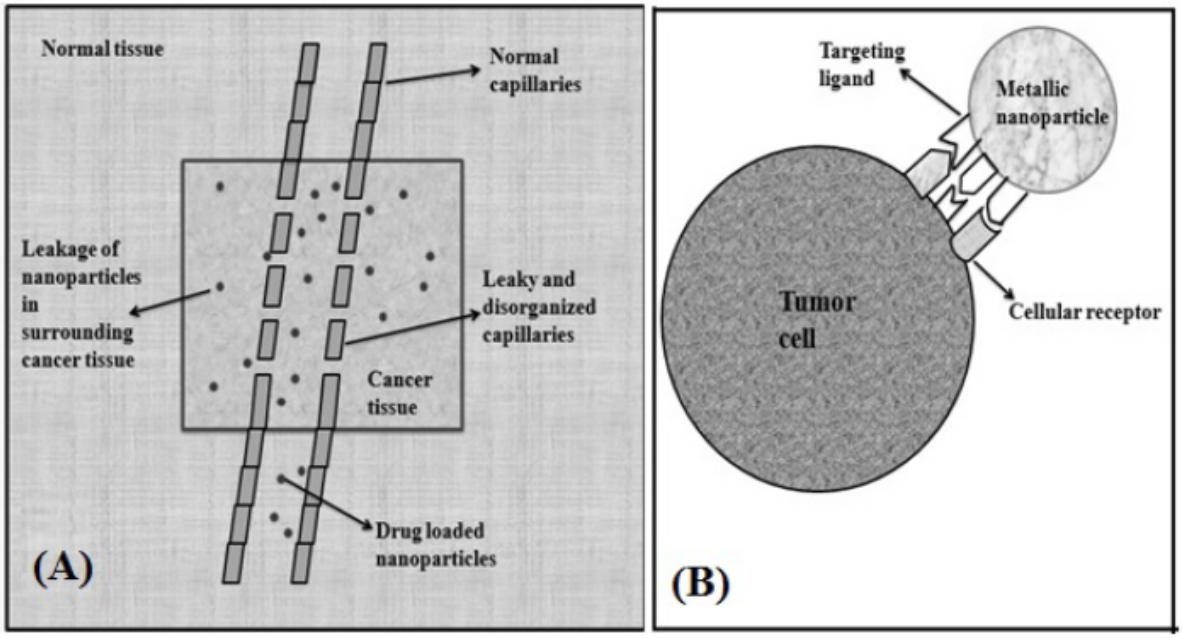

Fig. (1). Cancer tissue targeting using gold nanoparticles. Passive targeting involves localization of nanocarrier system in target tissue using enhanced permeability and retention (EPR) effect (**A**), while active targeting concept involves ligand receptor mediated interaction between nanocarrier and target cell (**B**).

tissues, excessive first pass effect by the liver, and fast renal excretion [35, 36]. Therefore, a nanocarrier system loaded with anticancer drug should not be rapidly cleared from the body and it should allow maximum interaction of drug molecules with the target site [37]. Various factors affecting activity of nanoparticles within vascular compartment are size, density, shape, and surface properties. These factors regulate modulation of circulation time and way of entrance of nanocarrier into the target cellular compartment [38]. So, these factors should be taken into consideration in design of metallic nanoparticles like GNPs.

3.1. Targeting Strategies for Cancer Using Gold Nanoparticles (GNPs)

Gold nanoparticles can target cancer tissues through passive targeting and the active targeting techniques (Fig. **1**) [30]. Targeting through the nanocarriers is only possible when they show resistance towards the uptake by phagocytes of mononuclear phagocyte system (MPS). Nanoparticles are usually taken by the various organs of reticuloendothelial system (RES) and rapidly cleared out from the body [39]. RES uptake of metallic nanoparticles can be avoided by modifying surface properties of nanoparticles like increasing surface hydrophilicity. High surface hydrophilicity block their identification by the RES system and makes them invisible to macrophage [40]. For the purpose, coating of nanoparticles is done with polyethylene glycol (PEG) or its copolymers. Hydrated groups of PEG block interactions between blood opsonins and nanoparticles sterically enhancing their blood circulation time and accumulation in tumor cells [41]. It has been reported in several studies that nanoparticles of size 1 – 2 μm undergo phagocytosis, therefore, the size of metallic nanoparticles like GNPs should be maintained below 100 nm. Neutral surface can also help in the escape from RES system [7]. Passive targeting involves the use of pathological states of cancerous tissue for the distribution of nanoparticles at target location. For example, the higher concentration of enzyme, like alkaline phosphatase, in cancerous tissues is responsible for the drug release from nanoparticles at the target sites [42]. Formation of cancerous tissue leads to the displacement of normal cells. Furthermore, formation of new blood vessels from the existing ones is known as angiogenesis [43]. Resulting tumor vasculature is different showing the presence of abnormal characters in basement membrane [44]. There is formation of leaky blood capillaries due to the incomplete vasculature of cancerous tissues. The leaky vasculature tumor tissues promote high permeability of nanocarrier towards the cancerous cells and absence of lymphatic drainage enhances their

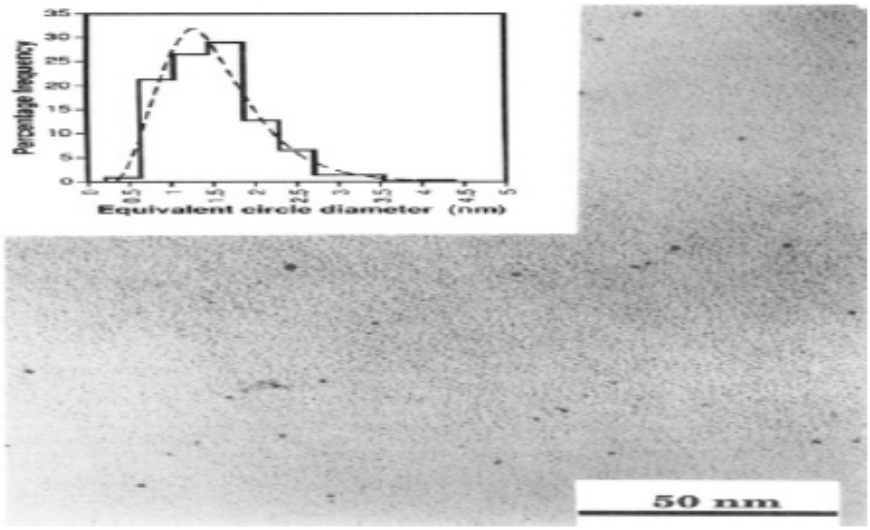

Fig. (2). Representative TEM micrograph of the standard THPC gold sol at a low cluster loading of the carbon film. Inset: Particle size distribution measured from such areas of low cluster loading to minimize coalescence within the specimen. The fit to a log normal curve [(d_g) = 1.42 nm, σ_g = 1.47] is shown. {Used with permission from Duff *et al.*, (1993) [56]}.

accumulation in the tumor cellular area. This phenomenon is called as enhanced permeability and retention (EPR) effect (Fig. **1A**) [45]. Passive targeting through nanoparticulate system does not guarantee 100% targeting of tumor cells [7]. Therefore, active targeting with the help of various molecular targeting ligand is suggested for complete destruction of cancerous cells. Cancer cells may show the presence of various surface receptors that can be actively targeted using metallic nanoparticles GNPs (Fig. **1B**) [46]. Ligands used for active targeting of cancer are antibodies, hormones, lectins, aptamers, and saccharides [47]. Targeting ligand must show effective interaction with receptor present on malignant cell and should have the capability to induce RME (receptor-mediated endocytosis) of nanocarrier [48]. RME can induce intracellular targeting of various targets like nucleus and mitochondria [49]. Firstly, implemented targeting ligands were monoclonal antibodies (MAbs) which induced active targeting of magnetic nanoparticles [50]. HER2/neu receptor present on tumor cells (ovarian and breast) can be targeted by using "Herceptin" which is an FDA approved MAb [51]. Cancerous cells also show overexpression of folate receptor compared to normal cells of the body. Therefore, folic acid and tetrahydrofolate can be used as targeting ligands for active targeting of cancerous cells bearing folate receptor [52]. Nanoparticles like metallic nanoparticles can be turned into highly specific carriers by using multivalent targeting ligand on their surface [53]. Several research works showed enhanced binding capacity of nanoparticles with multivalent targeting ligands [54, 55].

3.2. Conventional Spherical Gold Nanoparticles for Treatment of Cancer

Description of synthesis of conventional spherical gold nanoparticles was given by Duff *et al.*, (1993). They synthesized GNPs by reducing chloroauric acid ($HAuCl_4$) with tetrakis (hydroxymethyl) phosphonium chloride (THPC) in the presence of water. This method resulted in the formation of nanoparticles in the size range of 1-2 nm (Fig. **2**), however, the size increased with the storage time. Glass ware was carefully cleaned with a mixture of 75% 12N HCl and 25% 16N HNO_3 by volume followed by rinsing with ultrapure water [56].

Sykes *et al.*, (2014) evaluated conventional spherical gold nanoparticles (GNPs or AuNPs) developed through citrate reduction and hydroquinone seeded growth method for active and passive targeting of MDA-MB-435 orthotopic xenografts in mice. Transferrin coated AuNPs (active targeting) showed five times faster and two fold higher accumulation compared to poly(ethylene glycol) coated GNPs (passive targeting) coated in tumor cells at the size range of 60 nm (Fig. **3**) [57].

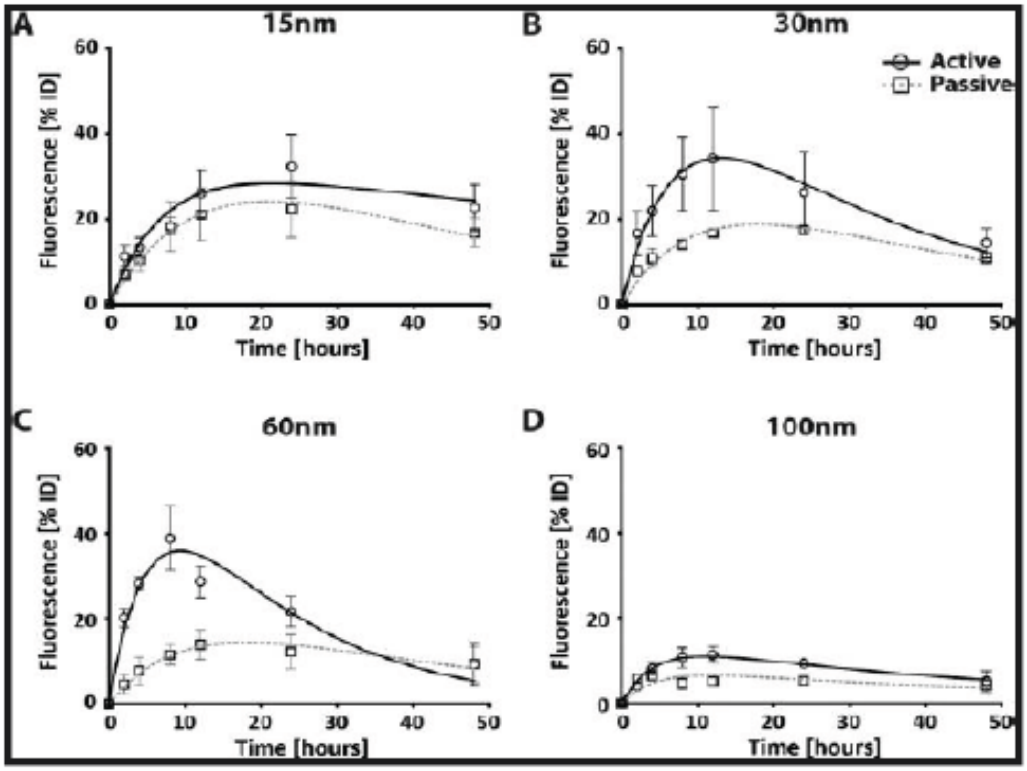

Fig. (3). Kinetic profiles (n > 3) depicting the relative tumor fluorescence for mice injected with passive (dotted) and active (solid) AuNPs over 48 postinjection. Graphs **A**-**D** illustrate tumor uptake of 15-100 nm diameter AuNPs, respectively. Tumor fluorescence (% ID) denotes the relative difference in tumor signal to opposing mouse flank expressed as a percentage of tumor fluorescence immediately after injection. Error bars represent the standard error mean values for each time point. {Used with permission from Sykes *et al.*, (2014) [57]}.

Furthermore, immobilization of doxorubicin (DOX) was carried out by Madhusudhan *et al.*, (2014) on gold nanoparticles (GNPs) modified with carboxymethyl chitosan (CMC) capping. Prepared system showed interaction between carboxylic group of CMC and amino group of DOX on the surface of GNPs. DOX-CMC-GNPs showed higher absorption of the drug in the cervical cancer cells compared to free DOX and effective release of the drug was observed in the acidic pH of target cancer cells [58]. Later on, Afifi *et al.*, (2014) evaluated the anti-tumor efficacy of XAV939 conjugated GNPs *in-vitro* against human oral squamous cell carcinoma (HSC-3) cells. Cellular uptake studies revealed higher targeted accumulation of the XAV939-GNPs conjugate in HSC-3 cells compared to free form at the same content. Developed conjugate also showed two orders of magnitude enhanced cytotoxicity *in-vitro* compared to free XAV939 (Fig. **4**) [59].

A brief overview of research work done on conventional spherical gold nanoparticles for tumor eradication is given in Table **2**.

3.3. Role of Gold Nanorods (Novel Gold Based Carriers) in Cancer Therapeutics

Gold nanorods are modified gold based carrier system used for drug delivery [68]. Gold nanorods can be manufactured by implementing the seed mediated growth method. This is a two step synthesis method where the first step involves formation of seed suspension using sodium borohydride, gold salt, and cetyltrimethylammonium bromide (CTAB). In the second step suspension formed previously is added to a growth solution having ascorbic acid, gold salt, CTAB, and varying content of silver nitrate to result gold nanorods [69]. Fig. (**5**) showed transmission electron microscope (TEM) images of gold nanorods with different plasmon band energies.

Ren *et al.*, (2013) developed paclitaxel (PTX) loaded gold nanorods (Au-NRs) for photothermal eradication of cancer. Drug loaded gold nanorods were stabilized by combining poly(ethylene glycol) (PEG) branched with 11-mercaptoundecanoic acid (MUA). MUA-PEG/PTX/Au-NRs were found effective against KB-3-1 and A549 cell line

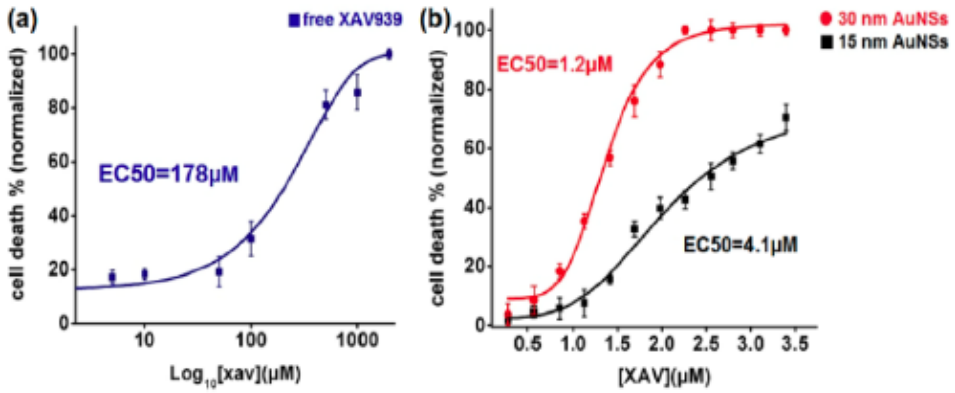

Fig. (4). Dose-dependent curves for cellular cytotoxicity of HSC-3 cells incubated with free (**a**) and ligated XAV939 to 15 and 30 nm AuNSs for 96 h (**b**). EC50 values for the free and bioconjugated XAV939 were 178, 4.1, and 1.2 μM, respectively. The conjugated form exhibits 2 orders of magnitude increased potency when compared to the free drug ($P < 0.05$). {Used with permission from Afifi *et al.*, (2014) [59]}.

Table 2. Role of conventional spherical gold nanoparticles in cancer treatment.

Drug	Targeting Type/ Ligand Used	Animal Model/Route of Administration	Key Findings	References
5-Fluorouracil (5-FU)	Active targeting/ thioglycolic acid (TGA) and glutathione (GSH)	----------	5-FU/GSH-gold nanoparticles showed pH dependant controlled drug release and two fold higher cytotoxic effect *in-vitro* compared to free drug	[60]
Temozolomide (TMZ)	Passive targeting/---- ----	Male BALB/c mice/ intratracheal route	TMZ loaded gold nanoparticles (GNPs) and liposome-embedded gold nanoparticles (LGNPs) showed equivalent stability and safety profile *in-vitro*, however, *in-vivo* lung antitumor effect was higher in LGNPs	[61]
TGF-β1 antibody and methotrexate	Active targeting/ folic acid	----------	Folate, methotrexate, and gold nanoparticles (GNPs) in the ratio 5: 5: 9 showed highest *in-vitro* cytotoxic effect against MDA-MB-231 (breast cancer) cells and coating of TGF-β1 antibody to the GNPs reduced 30% extracellular level of TGF-β1	[62]
Gallic acid	Passive targeting/---- ----	----------	Gallic acid (GA) – gold nanoparticle (GNPs) conjugate showed higher *in-vitro* cytotoxic effect against cervical cancer cells infected with HPV type 16 (SiHa) or 18 (HeLa) at a concentration of 150 μM and size 15 nm and GA - GNPs conjugate was found less toxic to normal cells compared to free gallic acid	[63]

(Table 2) contd….

Drug	Targeting Type/ Ligand Used	Animal Model/Route of Administration	Key Findings	References
Doxorubicin hydrochloride	Active targeting/ thiol-terminated polyethylene glycol (PEG)	Female BALB/c mice/intravenous	Targeted magnetic nanoparticles of size 22 nm loaded with drug showed better *in-vivo* accumulation in target cancerous tissue and less toxicity towards normal tissues compared to passive target delivery system	[64]
----------	Active targeting/ anti FAT1 antibody (clone mAB198.3)	BALB/c athymic nude mice/ intravenous	Negatively charged gold nanoparticles of size 20 nm functionalized with FAT1 antibody (clone mAB198.3) showed higher uptake in colon cancer cells compared to simple GNPs as confirmed in *in-vivo* bioimaging analysis	[65]
Resveratrol	Passive targeting/----------	----------	Resveratrol conjugated gold nanoparticles showed higher inhibitory effect towards phosphoinositide 3-kinase/Akt (PI3K/Akt), nuclear transcription factor-κB (NF-κB), matrix metalloproteinase-9 (MMP-9) and stimulatory effect towards extracellular signal-regulated kinase *in-vitro* indicating their efficacy in the treatment of breast carcinoma	[66]
Small interfering RNA (siRNA)	Passive targeting/----------	----------	Catechol-conjugated polyethyleneimine (PEI) coated gold nanoparticles showed high cellular uptake and reduction in cellular toxicity *in vitro* due to reduction in density of primary amine group of system compared to uncoated GNPs	[67]

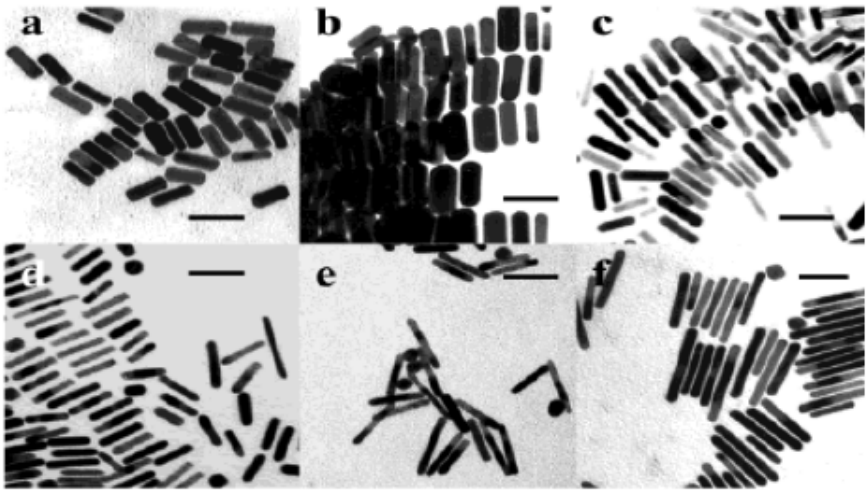

Fig. (5). TEM images of gold NRs with plasmon band energies at (**a**) 700, (**b**) 760, (**c**) 790, (**d**) 880, (**e**) 1130, and (**f**) 1250 nm. The scale bar is 50 nm. {Used with permission from Nikoobakht and El-Sayed, (2003) [69]}.

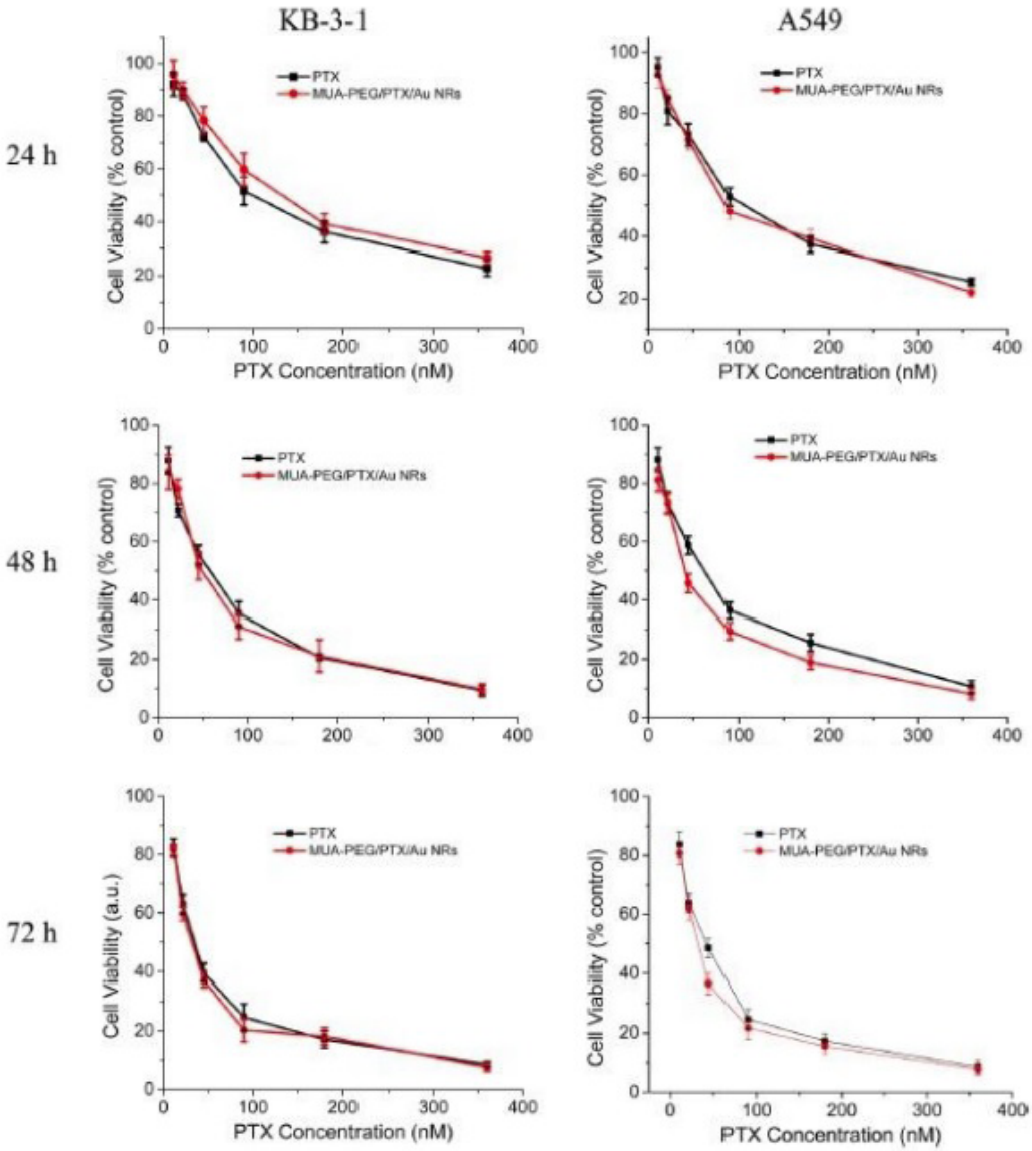

Fig. (6). Cytotoxicity of free PTX and MUA-PEG/PTX/Au NRs in KB-3-1 and A549 cells after 24, 48, and 72 h incubation. The results are mean values ± SD of triplicate experiments. The MUA-PEG/PTX/Au NRs showed comparable anticancer activity to the free PTX in both cell lines. The concentration of MUA-PEG/PTX/Au NRs was expressed as equivalent PTX concentration. {Used with permission from Ren *et al.*, (2013) [70]}.

in-vitro due to the efficient drug release upto 72 h (Fig. **6**) [70].

Recently, Wang *et al.*, (2017) evaluated docetaxel (DTX) loaded poly(lactic-co-glycolic acid) (PLGA) based gold naorods (GNRs) with manganese dioxide (MnO_2) core shell *in-vitro* and *in-vivo* in female kunmig mice using photothermal therapy. Magnetic resonance imaging (MRI) and X-ray CT scan analysis revealed highest drug release by the prepared system at target tissues after four hours of administration in animal model. PLGA/GNRs/DTX@MnO_2 system also showed prolonged drug release in the cancerous tissue area through implementation of radiofrequency hyperthermia and MnO_2 degradation [71]. Furthermore, Manivasagan *et al.*, (2017) evaluated gold nanorods (AuNRs) coated with fucoidan (Fu) and conjugated with anti-EGFR antibody as effective as an effective photothermal ablation agent in mice bearing tumor. Prepared system showed excellent *in-vitro* ablation efficiency towards MDA-MB-231 cells. Administration of anti-EGFR-Fu-AuNRs followed by irradiation of tumor with 808 nm laser showed complete tumor recovery and prevention of tumor recurrence in animal model (Fig. **7**) [72].

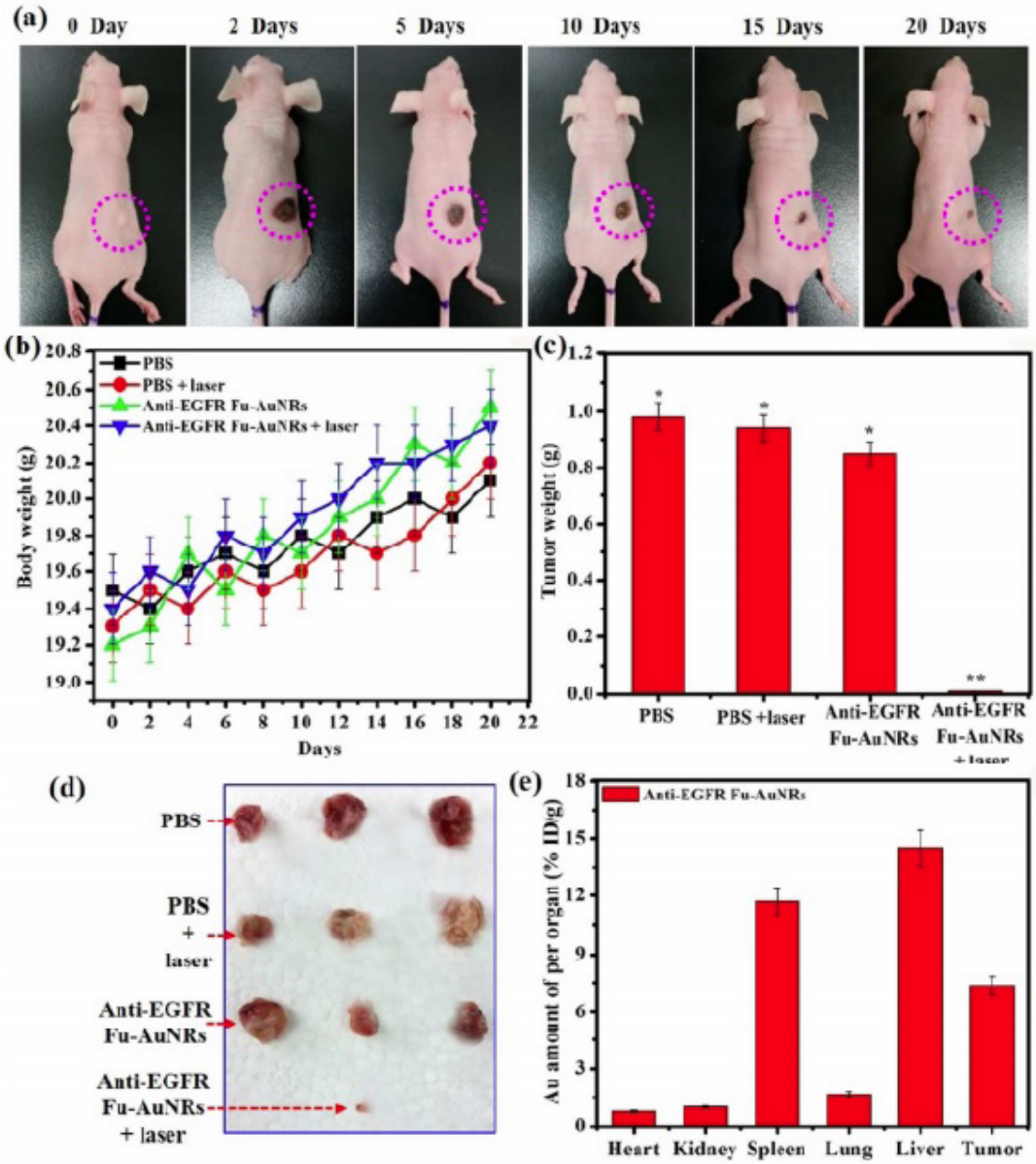

Fig. (7). (**a**) Representative photographs of tumors in mice taken at 0 day before treatments and 2, 5, 10, 15, and 20 days after treatments of anti-EGFR Fu-AuNRs under 808-nm NIR laser irradiation at 2.0 W/cm2 for 5 min. (**b**) Body weight of mice at different treatments indicated in 20 days. Data are expressed as mean ± SD of the three experiments. (**c**) The final tumor weight was acquired after sacrifice of mice. Data is expressed as mean ± SD of the three experiments (* significant $p < 0.05$; ** highly significant $p < 0.01$). (**d**) The digital photographs of relevant tumors originated from each group of mice. (**e**) Biodistribution of nanoparticles (Au concentration %ID/g) in tumor tissues and organs at 24 h after the intravenous injection. Data are expressed as mean ± SD of the three experiments. {Used with permission from Manivasagan *et al.*, (2017) [72]}.

Role of gold nanorods in effective tumor elimination is explained in Table **3**.

3.4. Role of Gold Nanostars (Novel Gold based Carriers) in Cancer Therapeutics

Gold nanostars are also categorized as novel gold based carrier systems which are synthesized through chloroauric acid (HAuCl4) in *N*,*N*-dimethylformamide (DMF) solution containing poly(vinylpyrrolidone) (PVP) in higher concentration along with gold nanoparticles seeds [81]. Fig. (**8**) describes morphology of gold nanostars in the form of transmission electron microscope (TEM) images [82]. Dam *et al.*, (2014) *in-vitro* efficacy of nucleolin-specific DNA aptamer AS1411 (Apt) loaded gold nanostars (AuNS) in various cancer

Table 3. Gold nanorods as effective carriers for tumor elimination.

Drug	Targeting Type/ Ligand Used	Animal Model/Route of Administration	Key Findings	References
Nutlin-3	Active targeting/ folic acid (FA)	----------	Gold nanorods containing α,β-poly(N-2-hydroxyethyl)-D,L-aspartamide functionalized with folic acid showed high *in-vitro* uptake in U2OS cancer cells and showed double drug release in acidic pH (simulating the cancer cell condition) compared to conventional system	[73]
---------	Active targeting/ trastuzumab (Herceptin)	Female athymic nude mice/ intravenous	Porphyrin- trastuzumab conjugated gold nanorods showed selective destruction of HER2-positive cancer using photothermal ablation through near-infrared laser and reduced toxic effects in the mouse model infected with tumor	[74]
----------	Passive targeting/----------	Male BALB/c nude mice/ intravenous	Polysarcosine coated gold nanorods showed longer circulation time compared to conventional PEG coated gold nanorods and complete destruction of tumor at the single time irradiation of near infrared (NIR) laser in experimental animal	[75]
Doxorubicin (DOX)	Active targeting/ Low density lipoprotein receptor (LDLR) targeted peptide-RLT (R)	BALB/c-nu male nude mice/ intravenous	DOX/DNA/PEG/R conjugated gold nanorods showed 1.7 fold increased apoptosis rate *in-vitro* and high activity against PC-3 tumor cells *in-vivo* by application of (NIR) laser compared to free DOX	[76]
----------	Passive targeting/----------	----------	Platinum coated gold nanorods were found highly cytotoxic against MCF-cells (human breast cancer cells) *in-vitro* at a low exposure and they also enhanced the activity of caspase-3 and caspase-9 enzymes promoting quick cancer cell death	[77]
----------	Active targeting/ tumour-specific DNA aptamer (KW16-13)	----------	Gold nanorods conjugated to KW16-13 showed excellent internalization in MCF10CA1h (breast cancer cells) and less uptake in normal MCF10A cells *in-vitro* and NIR irradiation promoted cancer cell death upto 96% which was very high compared to conventional gold nanorods therapy	[78]

(Table 3) contd….

Drug	Targeting Type/ Ligand Used	Animal Model/Route of Administration	Key Findings	References
Doxorubicin (DOX)	Active targeting/ transferrin (Tf)	----------	DOX-Tf-gold nanorods showed 48% and 46% *in-vitro* cytotoxic effect respectively against A549 and HCC827 cells which was higher compared to non targeted system *i.e.* DOX- gold nanorods (36% for A549 and 39% for HCC827 cells)	[79]
Cisplatin (Pt)	Active targeting/ folic acid (FA)	Nude mice/ intravenous	Pt/Fa-gold nanorods showed *in-vivo* rise in temperature upon 655 nm NIR irradiation causing effective inhibition of proliferation of aggressive triple negative breast cancer cells and were found effective compared to conventional system (Pt-gold nanorods)	[80]

cell lines. The developed system showed effective internalization in the cancer cells and 200% down-regulation of antiapoptotic Bcl-2 mRNA expression. Light triggered release of aptamers showed two fold rise in activity of caspase enzyme and 40% reduction in cell viability [83].

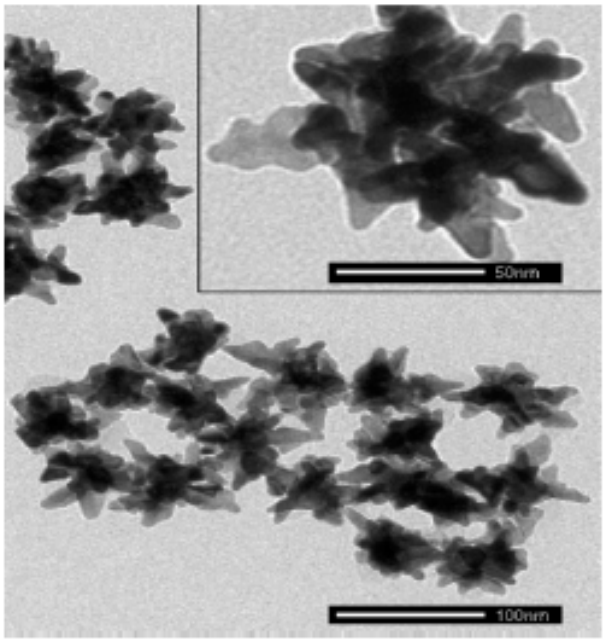

Fig. (8). Typical TEM images of gold nanostars, synthesized via addition of 135 μL of Au seed (main image) and 45 μL of Au seed (inset). The inset is presented at this magnification to detail the star morphology for an enhanced perspective of their 3-dimensional structure. {Used with permission from Khoury and Vo-Dinh, 2008 [82]}.

Furthermore, Wang *et al.*, (2015) evaluated gold nanostars for combined photothermal and photodynamic therapy against breast cancer. Gold nanostars were effectively internalized into MCF-7 cells and a near infra red (NIR) light irradiation caused excellent DNA damage and reduction of cellular glutathione level in MCF-7 cells *in-vitro*. Similar results were obtained *in-vivo* in tumor bearing mice [84]. Wang *et al.*, (2014) developed reduced graphene oxide (rGO) supported gold nanostars (AuNS) for enhanced SERS (surface-enhanced Raman scattering) sensing and delivery of doxorubicin (DOX). The developed rGO-AuNS system showed improved stability compared to conventional AuNS system. Implementation of SERS to rGO-AuNS enhanced DOX loading to system and also produced its pH dependant release. Fig. (**9**) describes the mechanism of DOX release from rGO-AuNS system by the implementation of SERS [85].

Table **4** describes utility of gold nanostars for the effective elimination of cancer.

4. INTELLECTUAL PROPERTY RIGHTS (IPR) RELATED TO USE OF NANOMEDICINE FOR TREATMENT OF BRAIN CANCER

Various patents regarding use of gold nanoparticles for effective treatment of cancer are given in Table **5**.

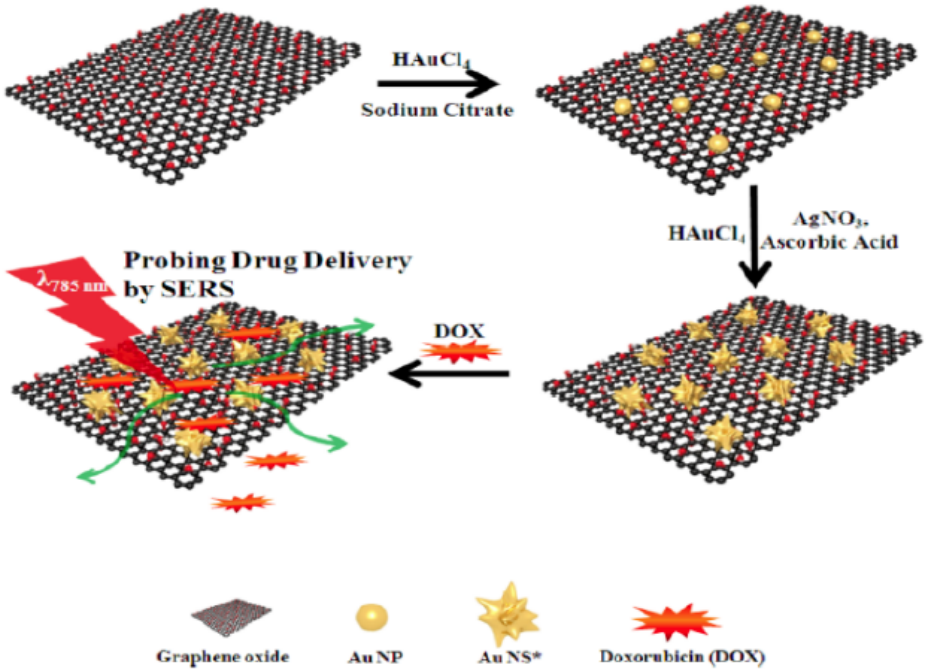

Fig. (9). Schematic Illustration of the Reduced Graphene Oxide-Nanostar (rGO-NS) Nanocomposite for Drug Delivery probed by SERS. {Used with permission from Wang *et al.*, (2014) [85]}.

Table 4. Role of gold nanostars for cancer treatment.

Drug	Targeting Type/ Ligand Used	Animal Model/Route of Administration	Key Findings	References
----------	Passive targeting/------	Female athymic nude mice/ intratumoral	Dual plasmonic gold nanostars (DPGNS) showed increased photoacoustic amplitude by attachment of silica coating over them and higher activity against tumor xenografts *in-vivo* at 1064 nm laser	[86]
Gemcitabine -5 – monophosphate (GMP)	Passive targeting/------	Female athymic nude mice/ intravenous	Gold nanostar (AuNS) core with a shell of metal-drug coordination polymer (CP) showed effective MRI (magnetic resonance imaging) analysis of tumor and maximum antitumor effect when the tumor site irradiated with 808 NIR laser	[87]
Mitoxantrone (MTX)	Passive targeting/------	Female athymic nude mice/ intravenous	MTX conjugated gold nanords showed effective accumulation in lung tumor site after 5 h of administration at a dose of 200 µg/ml as detected by *in-vivo* surface-enhanced Raman scattering (SERS)	[88]

(Table 4) contd….

Drug	Targeting Type/ Ligand Used	Animal Model/Route of Administration	Key Findings	References
----------	Active targeting/ CD44v6 monoclonal antibodies	Female athymic nude mice/ intravenous	Photoacoustic imaging showed accumulation of CD44v6 conjugated gold nanostars in gastric cancer cell in-vivo after 4 h of administration and near infra red (NIR) irradiation (740 nm) caused effective reduction in gastric tumor size	[89]
----------	Active targeting/ G-quadruplex DNA aptamer AS1411 (Apt)	Female Sprague–Dawley rats/ intravenous bolus	Gold nanostars coated with ligand G-quadruplex DNA aptamer AS1411 showed no acute toxicity even at higher dose of 48 mg/kg and they also showed five times more accumulation in breast cancer cells compared to fibrosarcoma cells	[90]

Table 5. List of patents regarding the use of gold nanoparticles for treatment of cancer.

Title of Patent	Brief Description	Inventors	Patent Number	Ref. no.
Amine passivated nanoparticles for cancer treatment and imaging	This invention describes a method of preparation of gold nanoparticles passivated with amines and their utility for cancer imaging and treatment	Shunji Egusa, Yogen Saunthararajah	WO2015123654 A1	[91]
Targeted nanoparticles for cancer diagnosis and treatment	This patent provides information about method of development of gold nanoparticles for cancer treatment and imaging by acting positron emission tomography tracer	Jien Chen, Wilson Roa	US20100034735 A1	[92]
Method of bonding gold nanoparticles with diethylenetriamine pentaacetic acid	This invention describes preparation method of gold nanoparticles conjugated to diethylenetriamine penta-acetic acid for high biocompatibility and increased surface area for effective cancer treatment	Chun-Chia Cheng, Shiau-Shiun Guan	US9238082 B2	[93]
Modified gold nanoparticles for therapy	This invention describes utility of gold nanoparticles containing microRNAs for the treatment of cancer	Aaron E. Foster, Laura B. Carprin, Adham S. Bear, Rebekah Drezek, Adam Yuh Lin	US20140086828 A1	[94]

(Table 5) contd….

Title of Patent	Brief Description	Inventors	Patent Number	Ref. no.
Nanoparticles assisted ultrasound for breast cancer therapy	This invention describes method of preparation of gold nanoparticles containing anticancer drug and monoclonal antibody as a targeting ligand for breast cancer treatment	Olga K. Kosheleva, Peter Lai, Nelson G. Chen, Michael Hriao, Chung-Hsuan Chen	US9427466 B2	[95]
Method of fabricating anticancer drug having doxorubicin bonded with gold nanoparticles	This invention deals with method of preparation of doxorubicin conjugated gold nanoparticles and evaluation their biocompatibility and tumor accumulation capacity	Chun-Chia Cheng, Tsai-Yueh Luo	US20160287723 A1	[96]
Nanoparticles enhanced proton computed tomography and proton therapy	This patent describes a method of preparation of gold nanoparticles conjugated with antibody as a ligand and their efficacy to improve proton computed tomography and proton therapy	Reinhard Schulte	US20070031337 A1	[97]
Anti-VEGF antibody/fragment conjugated gold nanoparticles, and fabrication and therapeutic methods	This invention describes development method of ligand (Anti-VEGF antibody) conjugated gold nanoparticles of size 20 nm and their biological evaluation	Dean P. Hainsworth, Raghuraman Kannan, Kattesh V. Katti, Ravi Shukla	WO2012054564 A2	[98]

CONCLUSION

Gold nanoparticulate systems satisfy all the criteria that a nanocarrier must have for effective cancer elimination. They can be explored as photothermal heat generating agents or drug targeting vehicles for cancer therapeutics. Significant research work carried out recently show efficacy of gold nanoparticles in chemical sensing, tumor imaging, and delivery of anticancer drugs. They can also be categorized as self cancer theranostic *i.e.* having the capability to kill cancer cells alone without conjugation of any anticancer drug. Various properties of gold nanoparticles like the ease of surface modification, high surface area, and photothermal behavior make them novel delivery vehicles in oncology research. Furthermore, their photothermal character and surface plasmon absorption behavior in the near infra red region makes them excellent tumor imaging agent. However, for enhancing their clinical efficacy countering of issues like dose optimization, immunogenicity, and size and shape related toxic behavior is required. Furthermore, their clinical evaluation will determine the entry of gold nanoparticulate based systems in the market.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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