Vietnam Journal of Science and Technology ***62*** *(3) (2024) 405-421*

doi:10.15625/2525-2518/19457

Chemical potential and biomedical activity of gold nanoparticles in cancer and drug delivery systems: *an update*

Sandeep Kumar Soni[1,*], Manoj Kumar Solanki[2]

[1]*M.Sc. Chemistry & Inspire (SHE) Scholar, Department of Chemistry, A.P.S. University, Rewa (M.P.), India, 486001*

[2]*Associate Professor & HOD, Department of Chemistry, Rewa Engineering College, Rewa (M.P.), India, 486001*

[*]Emails: *1.*ssoni173555@gmail.com, *2.* manojgecrewa@yahoo.co.in

Received: 21 November 2023; Accepted for publication: 3 March 2024

Abstract. Gold nanoparticles (AuNPs) are broadly utilized in medical fields because of their unique potential, biomedical activity and physicochemical properties. The biocompatible nature, optical properties, and minor cytotoxicity are the key features of AuNPs which make them valuable for biomedical applications. Today, the AuNPs are widely used for cancer therapy, bioimaging, biosensing, radiotherapy, photodynamic therapy and drug delivery systems. The present article illustrates the current progresses in AuNPs synthesis, properties of AuNPs, and various biomedical activities of AuNPs in therapeutic fields and drug delivery systems. Apart from numerous benefits the chemically synthesized AuNPs also create a certain level of toxicity in the living system which represents confronts of AuNPs against biomedical applications. Reducing their cytotoxic nature and development of green AuNPs can lead to the development of new history in the field of medical science and clinical trials. Thus, the present review article deals with a compiled study of various fundamental researches over AuNPs such as their chemical and bio-synthesis, biomedical and therapeutic applications viz. *plasmonic photothermal therapy, photodynamic therapy, folate receptor targeting, targeted drug delivery, etc*. The article also finds some of their confronts against biomedical application because of their cytotoxic nature and their possible future prospects.

*Keywords:*gold nanoparticles, anticancer activity, cancer, nanoparticles, nanotechnology.

Classification numbers: 1.1.5, 1.2.1, 1.2.4, 2.7.1.

1. INTRODUCTION

Nanotechnology is generally defined as the manipulation of matter in at least one dimension, ranging in size from 1 to 100 nm. The term “nanotechnology” was first used by Norio Taniguchi in 1974. It is the engineering of functional system at the molecular level. Nanoparticles are designed for human benefits by appropriate synthesis with uniform size for better distribution. Even though several methods are available to design desired nanoparticles,

the methods followed to synthesize them are dangerous to the environment. To tackle the above problem, we could use eco-friendly green chemistry based nanoparticle preparation methods using different sources like biological organisms such as microorganisms, plant extracts or plant biomass[1]. The critical atomic force microscopic view of AuNPs synthesized with fungal mycelia surface with its low (a) and high (b) resolution is illustrated in Fig. 1 [2].

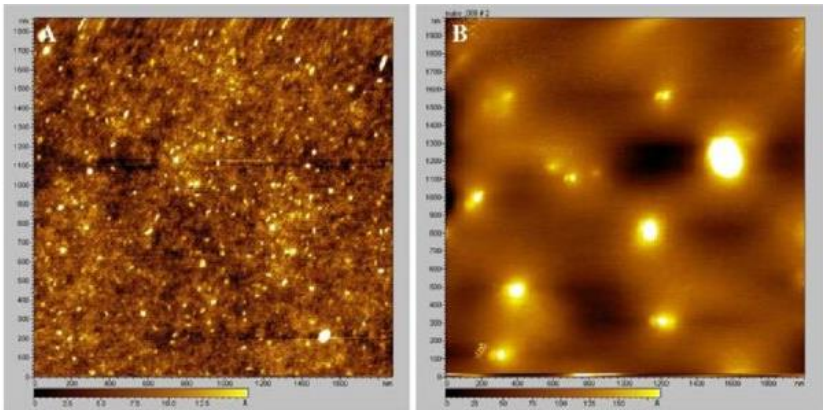

Figure 1. Atomic force microscopic view of fungal mycelia surface synthesized AuNPs (a) low resolution; (b) high resolution. Adapted with modification from [2].

In this review, we have addressed various concerns by explicitly discussing the distinctive aspects in the field of AuNPs. We have incorporated different points that outline the specific contributions, updates, and novel perspectives presented in our work. By doing so, we aim to provide readers with a clear understanding of the value that our review adds to the existing body of literature.

2. CHEMICAL AND BIO-SYNTHESIS OF GOLD NANOPARTICLES (AuNPs)

AuNPs prepared by polysaccharide PST001, an antitumor and immunomodulatory compound isolated from the seed kernels of *Tamarindus indica* (Ti), have been used for various applications in cancer. PST-AuNPs were prepared by a method in which PST001 acted both as a reducing agent and as a capping agent. The PST-AuNPs showed high stability, no obvious aggregation over months and a wide range of pH tolerance. PST-AuNPs not only retained the antitumor effect of PST001 but also showed an enhanced effect even at low concentrations. *In vivo* assays on BALB/c mice revealed that PST-AuNPs exhibited immunomodulatory effects [3]. The AuNPs prepared by chitosan hydrogel exhibited an excellent water absorbing property and could be applied as a drug delivery system for anticancer drug: doxorubicin (DOX) due to its high equilibrium water swelling content [4]. Fluorescent AuNPs were synthesized by fibrillated human insulin under alkaline conditions at physiological temperature (37 °C). The synthesis scheme of AuNPsinvolving chain functionalized cabazole hydrocarbons in which a thiol group acts as the capping material present at the tail end is presented in Fig. 2 [5].

Biogenic gold nanotriangles and spherical silver nanoparticles were synthesized by a simple procedure using *Aloe vera* leaf extract as the reducing agent. This procedure offers control over the size of the gold nanotriangle and thereby a handle to tune their optical properties, particularly the position of the longitudinal surface plasmon resonance. The kinetics of gold nanotriangle formation was followed by UV-vis-NIR absorption spectroscopy and transmission electron microscopy (TEM). The effect of concentration of the reducing agent in

the reaction mixture on the yield and size of the gold nanotriangles was studied using transmission electron microscopy. Dextran stabilized physiological stable AuNPs functionalized with amination could be used to deliver peptide for cell imaging [6].

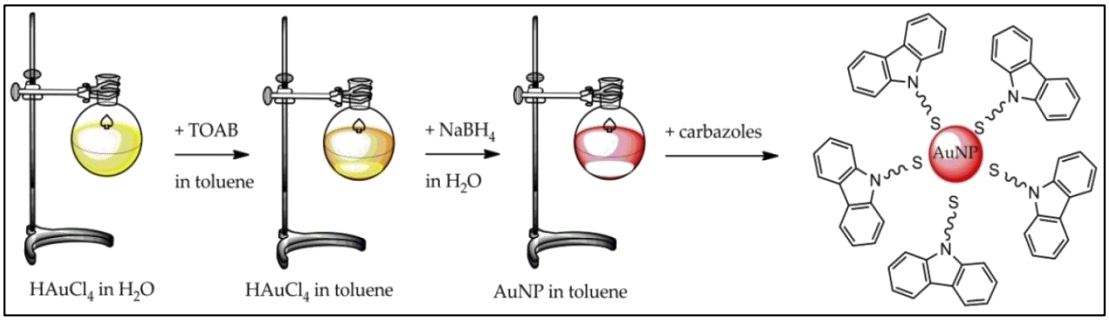

Figure 2. Synthesis scheme of AuNPs with N-thio-alkylcarbazoles in the presence of toluene. Adapted with modification from [5].

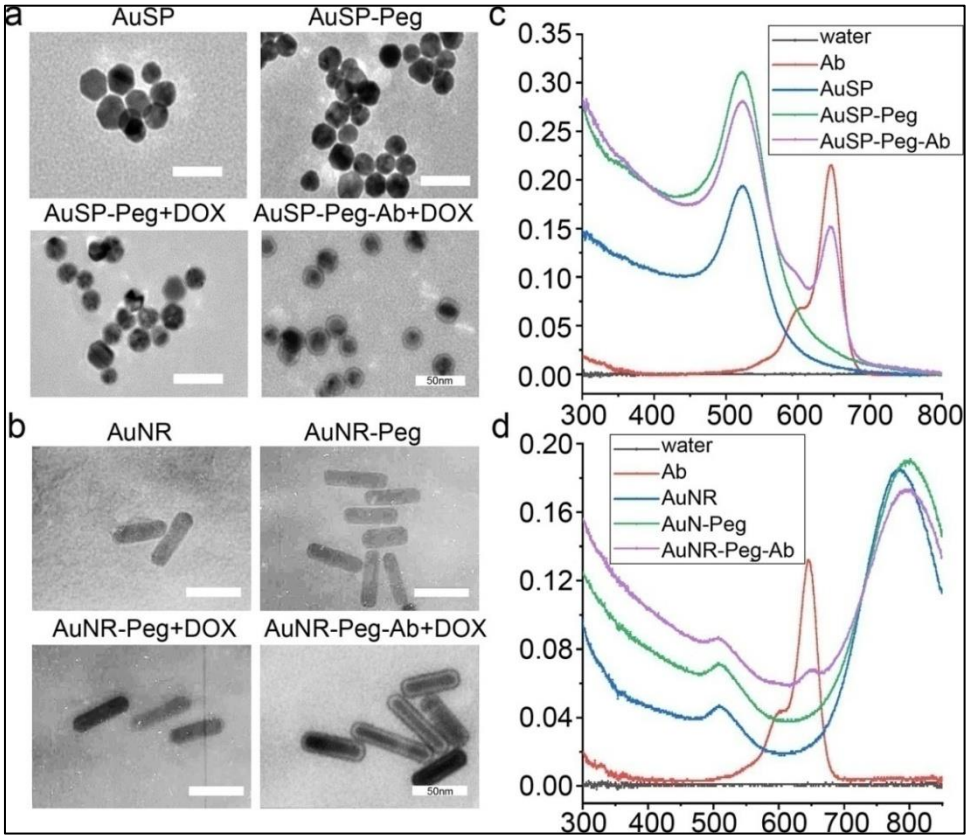

Figure 3. TEM recognition for Au nanosphere and nanorods (Au-PEG, Au-PEG+DOX, AuNR, AuNR-Peg, AuNR-Peg+DOX and AuNR-Peg-Ab+DOX). Adapted with modification from [8].

An eco-friendly simple approach for the synthesis of AuNPs, amenable for large scale commercial production and technical applications using coriander extract as the reducing agent for biosynthesis of AuNPs in the size range from 6.75 to 57.91 nm [7]. A recent study revealed the presence of shells on the surface of Au nanorods and nanosphere. The characterization was

proved by (200,000×) TEM, the capsule thickened with the attachment of antibodies (Ab) (Fig. 3a, b). Figure 3c, d illustrates the production and characterization using spectrophotometer detection [8].

The AuNPs were prepared by tea which contains many phytochemicals. The tea-generated AuNPs (T-AuNPs) demonstrated remarkable *in vitro* stability under physiological conditions and were found to be biocompatible. They had high affinity towards prostate (PC-3) and breast (MCF-7) cancer cells. The results on the cellular internalization of T-AuNPs through endocytosis into the PC-3 and MCF-7 cells were also presented [9]. Physiological stability and biocompatibility of AuNPs provide great opportunities to use these AuNPs for biotechnology and biomedicine [10]. Green chemistry based polyvinylpyrrolidone stabilized AuNPs were prepared in a single step at room temperature by adding sodium hydroxide (NaOH). It acts as an initiator for the reduction of $HAuCl_4$ in aqueous solution. AuNPs (5-15 nm) were prepared by eco-friendly processes of an alkalotolerant actinomycete (*Rhodococcus* sp.) The particles were more concentrated on the cytoplasmic membrane than on the cell wall, possibly due to the reduction of metal ions by enzymes present in the cell wall and on the cytoplasmic membrane. The metal ions were not toxic to the cells and the cells continued to multiply after biosynthesis of the AuNPs [11].

Green AuNPs were prepared by soybean that contains antioxidant phytochemicals and protein extracts. The green AuNPs are nontoxic, physiologically stable and thus provide excellent opportunities for their applications in nanomedicine for molecular imaging and therapy [12]. AuNPs were synthesized using banana peel extract (BPE) as a simple, non-toxic, eco-friendly green material. The BPE mediated nanoparticles displayed efficient antimicrobial activity towards most of the tested fungal and bacterial cultures [13]. The AuNPs prepared by citrate reduction method are unstable in high ionic strength solution, which limits their applications in the biomedical field. The stability of AuNPs was improved by coating gelatin biopolymer and used for the detection of analytes (rose Bengal fluorophore) and surface-enhanced Raman scattering active tags in view of imaging purpose [14].

Biosynthesis of gold and silver nanoparticles was carried out using *Mentha piperita* (Lamiaceae) plant extracts containing menthol as a reducing agent. The prepared silver nanoparticles were spherical in shape with 90 nm size, whereas AuNPs were found to be 150 nm. The synthesized nanoparticles were active against clinically isolated human pathogens, *Staphylococcus aureus* and *Escherichia coli* [15]. The AuNPs could also be prepared by a natural, biocompatible and biodegradable polymer, chitosan, which acts as a reducing agent in the synthesis of AuNPs and also promotes the penetration and uptake of peptide hormone insulin across the mucosa. These studies showed that oral and nasal administration of insulin loaded chitosan reduced AuNPs led to improved pharmacodynamic activity. Thus, chitosan reduced AuNPs loaded with insulin proved to be promising in controlling the postprandial hyperglycemia [16]. The AuNPs based vaccine prepared using a thiol-modified CpG 1668 oligodeoxynucleotide with a spacer consisting of ten adenine nucleotides (A10) was also conjugated to the RFP/AuNP, because CpG 1668 is known to strongly stimulate immune responses through the activation of toll-like receptor 9 (TLR-9). The AuNPs based vaccines exhibited significant antitumor efficacy in RFP-expressing melanoma tumor models. AuNPs have several advantages over other nanoparticulate-based carriers such as nontoxic, biocompatible, non-invasive CT tracking [17].

3. AuNPs IN BIOMEDICAL APPLICATIONS

The modification and fictionalization of AuNPs to improve their physicochemical and biological properties have resulted in many biomedical applications such as diagnosis, imaging, gene and drug delivery.

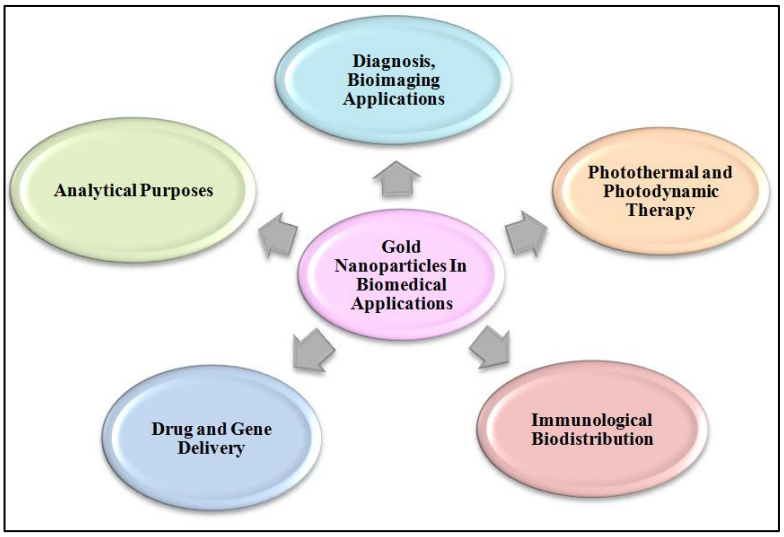

Figure 4. AuNPs in biomedical applications. Adapted with modification from [18].

Table 1. List of functionalized AuNPs used for diagnostic purposes.

Functionalized AuNPs	**Reference**
Colorimetric detection of DNA	[21]
Immunoanalysis of human chorionic gonadotropin	[22]
Immunoanalysis of Shistosoma mansooni circulating antigen	[23]
Determination of anti-rubella antibodies	[24]
Estimation of immunoglobulins	[25]
Estimation thrombin	[26]
Glucose sensing	[27]
Direct detection of cancerous cells	[28]
Detection of Leptospira cells in urine	[29]
Detection of alzheimer’s disease markers	[30]
Immunodiagnostic of papilloma	[31]
Immunodiagnostic of HIV viruses	[32]
Detection of pathologic biomarker for alzheimer’s disease	[33]
Detection of organophosphorus substances and pesticides	[34]
Detection of antibiotics	[35]
Detection of allergens	[36]
Rapid identification and quantification of tumor cells	[37]
Colorimetric detection of DNA	[38]

The eye-catching feature of surface plasmon resonance and interaction with thiol group could be a selective platform to target intracellular release of small molecules and genes for pathological area.Various biomedical applications of AuNPs in different fields of medical science are depicted in Fig. 4 [18].

Targeted drug delivery is classified into two types: 'active' and 'passive'. The term 'passive targeting' most commonly refers to the accumulation of nanoparticles or pharmaceutical substances at a specific site by physiochemical factors (e.g. size, molecular weight), extravasation, or pharmacological factors [18]. In the case of 'active targeting', the nanoparticle or drug molecule is conjugated with a specific active molecule that binds to the desired target cells or tissues. For example, nanoparticles can be targeted to specific phagocytic cells or to tumors [19, 20].

4. BIOMEDICAL ACTIVITIES AND APPLICATION OF AuNPs

4.1. Plasmonic photothermal therapy

Using the popular human epithelium cervical carcinoma (HeLa) cellular line, experts employed bio-compatible folic acid conjugated AuNPs, laser-treated spheres and anisotropic AuNPs with various shapes [39]. By incorporating EMA theory with full-wave electrodynamic simulations, PNCs have been developed to be highly efficient PTAs and offer a semi-quantitative method for determining the resonant frequency along with efficiency in absorption [40]. According to a sophisticated approach, nanorods are the most efficient means of generating heat in isolated contexts. Arrays of nanorods with a length of 91 nm were able to reach hyperthermic values, which are defined as a rise of at least 5 °C, within a volume exceeding 20 μm^3 [41]. According to this research, M2 polarized macrophages have a higher absorption rate of AuNPs than M1 polarized macrophages. This higher absorption rate can be converted into laser activation and destruction of protumoral M2-Mfs without harming anti-tumoral M1-Mfs. Because it can enable the total elimination of protumoral cells and eliminate their support for malignant tumor cells, this result may have a favorable effect on the usage and enhancement of PPTT in the fight against malignancies [42, 43].Under the same conditions of NIR light radiation exposure within 10 min at 300 mW/cm^2, in vitro cell tests showed that all PEGylated AuNPs exhibited minimal cytotoxicity while AuNSTs were particularly effective in producing local hyperthermia [44]. Breast tumor targeting and curative measures are now possible because, to the advancement of chemical synthesizing technology, which has made it possible to synthesize AuNPs with the intended characteristics in a variety of sizes and forms [45, 46]. In vitro along with in vivo, the lower temperature PTT in conjunction with cRGD-GIPG sonodynamic treatment (SDT) exhibitsa strong anticancer effect versus EGFR-TKI-resistant cells of NSCLC [47].A different study put forth a number of preliminary requirements for plasmonic photothermal treatment in vitro. Pre-, during, and post-irradiation characterization, biological specimens, nanotechnologies, and PPTT experiments in vitro are the five primary areas covered by the practice [48]. Chitosan was used as a capping and reducing agent during the synthesis of AuNPs. Different 6MP concentrations were combined with AuNPs. After 48 hours of incubation with 6MP and 6MP loaded AuNPs, cells got exposed to laser [49].

4.2. AuNPs in photodynamic therapy

PDT and PTT are two examples of light-mediated therapies that have been used as minimally invasive methods for tumor ablation. Both techniques can remove malignancies from normal tissues and organs relatively little harm to them. Fig. 5 [50] provides a broad picture of these tissues and organs. Utilizing the peptide FITC-βAAEYLRK,AuNPs functionalized covalently with the photosensitizers C11Pc and PEG were effectively directed towards tumors overexpressing the receptor of epidermal growth factor [51]. The photosensitizers could be administrated intravenously; contact and oral administration arealso possible. The photosensitizer accumulated in tumor area can be irradiated with laser light at the corresponding wavelength leading to a local thermal effect. This effect also causes the formation of highly active radicals, which produces necrosis, apoptosis of target cells and disrupts the nutrition for the tumor and leads to its death by damaging microvessels [52-54].

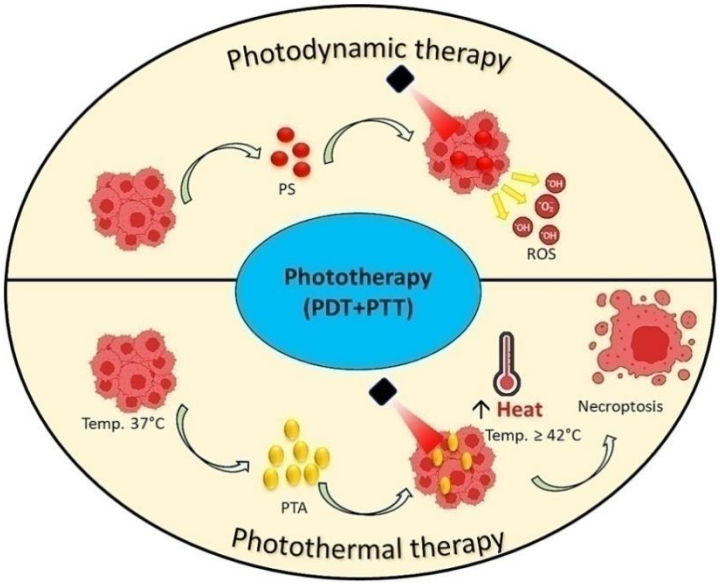

Figure 5. Graphical representation of PDT and PTT with AuNPs. Adapted with modification from [50].

4.3. AuNPs in drug delivery

Nanoparticles have been used in provisional delivery applications, imaging or therapeutic agents, including small and large molecules, gene vectors, biosensor, and nanotubes due to the certain reasons. Nanoparticles with high surface area may favor sites for drug loading and enhance solubility and stability of loaded drugs. The surface functionalized nanoparticles could enhance therapeutic effect with least side effects. Nanoparticles could have multivalent interactions with cell surface receptors or other biomolecules. Nanoparticles could enhance pharmacokinetics and tumor tissue accumulations compared to free drugs. As tumor sites have leaky blood vessels, nanoparticles can accumulate at tumor sites by enhanced permeability and retention effect [55].Accurate and efficient drug administration to the intended place is the goal of ongoing advancements in HGG treatment strategies [56]. While current standard treatments are effective in treating malignant gliomas, it remains unsettling to improve the effectiveness of these tried-and-true methods. In addition to integrating the development of innovative drug

delivery techniques, tools, and materials, some recent researcheshave resolved numerous issues related to drug delivery towards malignant gliomas [57].

4.4. AuNPs in targeted delivery of anticancer drugs

AuNPs can be readily fabricated with sizes commensurate with biomolecules such as proteins and DNA, facilitating their integration into biological systems. Furthermore, the high surface area-to-volume ratio of nanoparticles (NPs) provides dense loading of incorporating targeting and therapeutic materials. Secondly, AuNPs with a wide range of core sizes (1 - 150 nm) can be easily fabricated with controlled disparity, since both size and disparity are key aspects for drug delivery systems. The study also incorporated the targeted delivery based on polymeric AuNPs as shown in Fig. 6 [58].

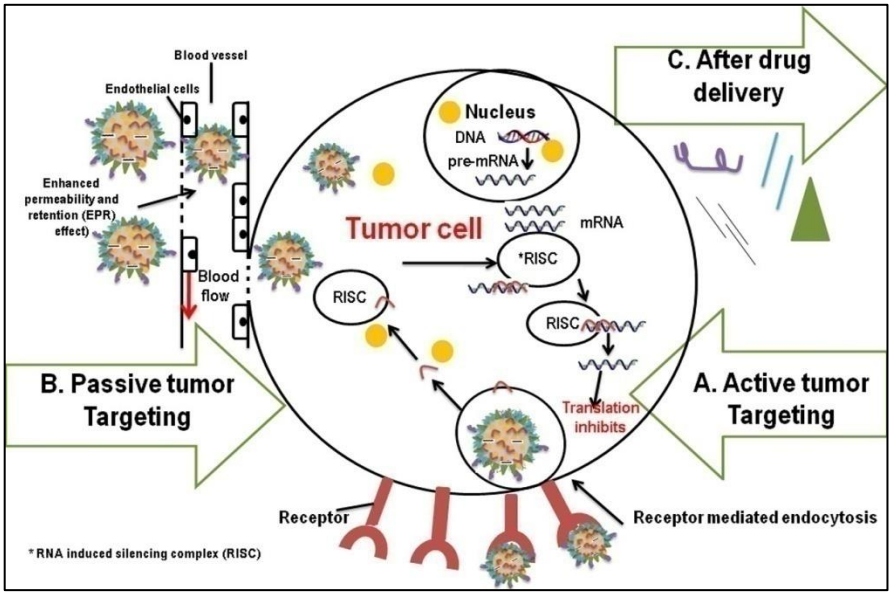

Figure 6. Schematic representation of targeted delivery of polymeric AuNPs with RISC against active tumor cells. Adapted with modification from [58].

The synthesis of a thiol-PEGylated tamoxifen derivative which maintains chemotherapeutic efficacy can also be easily functionalized onthe surface of gold nanoparticles. Breast cancer treatment is an excellent candidate for such methods as 75-80 % of all breast malignancies over express hormone receptors. The presence of soluble and membrane-bound TNF receptors present in solid tumours facilitates active targeting of gold nanoparticle-TNF-PEG conjugates administrated intravenously which leads to the accumulation of TNF at tumor sites directing to promote anti-tumor immunogenic response, malignant vascular leakage, and apoptosis in a variety of cancer cell lines. The conjugates showed significantly reduced toxicity and improved therapeutic efficacy almost by two fold [59]. A large-scale investigation was conducted to confirm that AuNPs can enhance the hepatotherapeutic efficacy of cisplatin over hepatic tumors produced by DENA and to state that AuNPs may mitigate the cisplatin toxicity to the kidneys [60].

Prodrug form of widely administered chemotherapeutic drug cisplatin (inert Pt^{4+}) on conjugation with spherical AuNPs achieved efficient cytosolic delivery to bone, lung, cervical,

and prostate cancer cells without endosomal sequestration. Subsequent intracellular reduction of the prodrug caused activation to the cytotoxic Pt^{2+} form, resulting in co-localization of the particles with microtubules and the formation of intrastrand crosslinked nuclear DNA [61]. *In vitro* cytotoxicity was dramatically enhanced compared to that of the free prodrug and active cisplatin form, demonstrating that AuNPs are efficient vehicles for the delivery of prodrugs exhibiting poor cellular uptake. Similarly enhanced potency has also been demonstrated from gold nanoparticle conjugates of oxyplatin [62].

The AuNPs of varying sizes (50, 80, 100 and 150 nm diameter) with or without PEGylation (PEG5000) along with surface grafting of small sugar molecules like galactose (Gal-PEG-NP) become specific for asialoglycoprotein receptors on hepatocytes (liver cells). PEGylation increases circulation life time of the nanoparticles in blood and galactose facilitates the targeting of Gal-PEG-NPs into the liver [63]. The AuNPs coated with hydrophobic inner shell (poly(L-aspartate-doxorubicin) and folic acid coupled hydrophilic PEG outer shell can be used as pH-triggered drug release to acidic environment of tumor tissues [64]. The Au-PEG-TNF coupled with paclitaxel showed enhanced tumor therapy [65]. Researchers have explored doxorubicin conjugates of AuNPs for potential photo triggered release. Loaded DOX (Doxorubicin) was found to be 3.5 times higher than the level achievable using spherical particlesand was effectively retained by the particles over several days in physiologic media and also significantly increased DOX release and cytotoxicity to breast cancer cells. Utilizing long-chain strands of DNA with a customized repeating padlock sequence, researchers commented on the creation of a programmable DNA ribbon. The AuNPs and DNA ribbon can be subsequently linked to produce a hybrid nanomaterial [66]. The development of gold microparticle-based systems for cancer diagnosis and treatment was summed up in another paper. The common mechanism of action of AuNPs against targeted carcinogenic cells is described in Fig.7 [67].

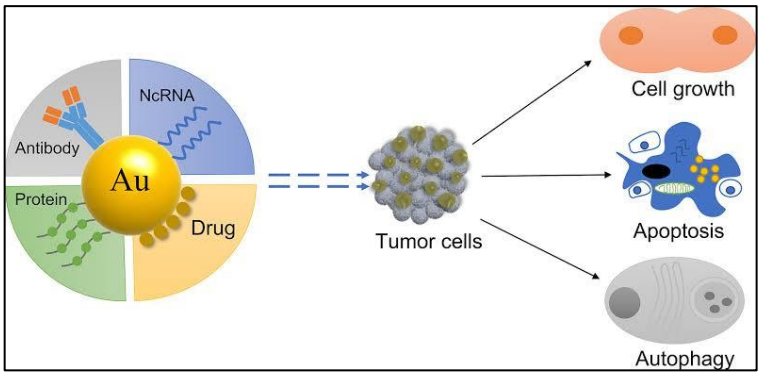

Figure 7. Action of antibody, protein, NcRNA, and drugs based AuNPs composite against targeted cancer cells. Adapted with modification from [67].

The AuNPs functionalized with folic acid and PEG-amines by non-covalent interactions are readily targeted to the folate receptors of cancer cells. Conjugates of folic acid (Fa) with AuNPs could have an important role for folate receptor-targeted drug delivery or targeted therapy in the future [68]. The highly tunable and multivalent surface structures of AuNPs offer the diversity to incorporate multiple therapeutic drugs or biomacromolecules by covalent or non-covalent conjugation on the surface of nanoparticles [69]. A novel conjugation approach has been devised using an extended aptamer design where the extension is complementary to an oligonucleotide sequence attached to the surface of the AuNPs [70].

The AuNPs functionalized with monolayer of zwitterionic ligands provided solubility and prevented cellular uptake. The anticancer drug 5-Fu which was linked to AuNPs through an o-nitrobenzyl group (Au-PCFU) could be effectively cleaved using near-UV (365 nm) irradiation. In the presence of drug, increased light exposure leads to decreased cell viability [71]. A related study demonstrated that the conjugation of histamine, a cell-signaling agent, on AuNPs through carbamate linkage could be dissociated via the photocleavage reaction of the o-nitrobenzyl group upon near-UV irradiation [72]. Effective caging of histamine enabled inhibition of biological activity while attached to AuNPs and complete recovery after photorelease from the particle surface.

Photodynamic therapy (PDT) is another promising non-invasive tumor treatment strategy. A hydrophobic photosensitizing agent phthalocyanine (Pc 4 and Pc 219) is conjugated to AuNPs both by covalent (AuNP-Pc 4) and non-covalent (AuNP-Pc 219) linkages [73]. *In vivo* release of the PDT drug in tumor-bearing mice indicated highly efficient drug delivery, with preferential accumulation in tumor sites. A recent work showed deep penetration of the drug released from AuNP-Pc 4 into tumors within hours. The biodistribution of these AuNPs over a 7-day period indicated renal clearance from mice [74].

The biocompatibility of these particles coupled with appropriate sizes (diameter 10-200 nm) make these systems promising candidates for passive targeting using enhanced permeability and retention (EPR) effect. AuNPs functionalized with zwitterionic ligand could be used to deliver hydrophobic drugsand dyes with non-specific binding to biomacromolcules and cell uptakes proved by ICP-MS [75, 76]. The entrapped payloads were released into MCF-7 cells by membrane mediated diffusion, as demonstrated by both fluorescence microscopy and through drug efficacy with therapeutic guests [77].

4.5. AuNPs in folate receptor targeting

Modern cancer treatment uses chemotherapeutic agents, which are distributed aimlessly into virtually all cells of the body, causing damage to both malignant and normal cells alike, often inducing sufficient toxicity and reducing the patient compliance. To improve patient compliance, we should minimize toxicity to normal cells during cancer chemotherapy,whichcan be achieved by surface functionalized targeting numerous ligands that specifically bind to cancer cells. Currently, folic acid surface functionalized anticancer drug loaded nanoparticles are receiving more attention in cancer chemotherapy treatment [78]. According to a recent research report, U2-AuNP increases the life span of mice harboring GBM by blocking the growth and invasion of U87-EGFRvIII cell lines. In GBM cells, we discovered that U2-AuNP can block the EGFR-related pathway and stop DNA damage repair [79]. The generated unique MTX/Au-GSH-FA NP combination appears to be an exciting option for selective and efficient administration in FR+ cancer therapy, according to its findings [80].

The latter is found primarily on polarized epithelial cells and activated macrophages and preferentially binds and internalizes oxidized folates via receptor-mediated endocytosis [81]. Folic acid is a vitamin required for one-carbon transfer reactions in several metabolic pathways. As it is essential for the biosynthesis of nucleotide bases, this vitamin is consumed in elevated quantities by proliferating cells. Normal cells transport physiological folates across the plasma membrane using either of two membrane associated proteins, the reduced folate carrier or the folate receptor (FR).

The receptor for folic acid primarily constitutes a useful target for tumor-specific drug delivery.It is upregulated in many human cancers, including malignancies of the ovary, brain,

kidney, breast, myeloid cells and lung [82-85]. Access to the folate receptor in those normal tissues that express it, can be severely limited due to its location on the apical (externally-facing) membrane of polarized epithelia, and folate receptor density appears to increase as the stage/grade of the cancer worsens. Thus, cancers that are most difficult to treat by classical methods may be most easily targeted with folate-linked therapeutics [86]. The folate receptor is significantly upregulated in many cancer cells compared to normal tissue. The first *in vivo* study conductedon a positive folate receptor expressing human KB tumor xenografted immunodificient mice by G5 PAMAM dentrimers functionalized with methotrexate (a chemotherapeutic agent structurally similar to folic acid) proved high level accumulation in tumor sites, shown to have significantly lower systemic toxicity and 10-fold higher efficacy compared to free methotrexate at an equal cumulative dose [87]. The delivered folate-conjugated liposomes were used for successful treatment of acute myelogenous leukemia and it was found that the system was capable of evading P-glycoprotein mediated efflux of drug [88].

Many tumor cells overexpress folate receptors (FR) on their surfaces that can be targeted using folic acid (FA) and methotrexate (MTX) derivatives. For example, conjugation of folic acid to AuNPs using a PEG spacer provided selective delivery to FR-positive KB cells [89]. FR has the ability to transport both folic acid and folate-linked cargos of many sorts (i.e., chemotherapeutics, imaging agents, proteins, liposomes, nanoparticles, etc.). Once folate conjugates are bound to a cell surface FR, they are transported into the cell through a process called receptor-mediated endocytosis [90 - 93]. Methotrexate is an analogue of folic acid that has the ability to destroy folate metabolism of cells and has been commonly used as a cytotoxic anticancer drug. The carboxylic groups on the methotrexate molecule can bind to the surface of AuNPs after overnight incubation. The cytotoxic effect of free methotrexate is about seven times lower than that of methotrexate conjugated to AuNPs in the case of Lewis lung carcinoma cells [94]. Due to increased radiosensitization, GNP-LP bonds after gamma ray treatment showed increased toxicity against AR42J cells. In particular, the current work showed that LP can functionalize GNP and that this can lead to preferential delivery and improved radiosensitization in cancerous cells that overexpress SSTR2 [95]. The AuNPs produced having a dimension of less than 100 nm were found to be benign at certain concentration levels and to demonstrate a higher X-ray attenuate amplitude at a comparable level as iodine-based contrast elements [96].

5. CONFRONTS OF AuNPs AGAINST BIOMEDICAL APPLICATIONS

According to reports, toxicity is the main issue with them. Despite the fact that a number of researches suggested that the chemical inertness of the gold metal madeAuNPs comparatively less hazardous. Numerous cell and animal models have been used to demonstrate the toxicity caused by AuNPs. Undoubtedly, numerous factors can significantly affect their biodistribution in vivo and ultimate toxicity. These factors include the basic characteristics of the particles (e.g., size, shape, charged surface, and coating), the experimental setup (e.g., cell and animal model tested, evaluated duration), the administration plan (e.g., administration route, dose, time and times), etc. The toxicity of AuNPs has been found to be influenced by particle size, with smaller particles being found to be more harmful than larger particles [97, 98]. This could be explained by the fact that smaller nanoparticles are more likely to pass through the nucleus pore and the cell membrane, which promotes the production of intracellular ROS and DNA damage [99, 100]. Positively charged particles were said to be more hazardous than their negative or neutral counterparts. It's possible that the electrostatic interaction between positive NPs and a negative cell surface causes cationic AuNPs toxicity by enhancing cellular absorption or disrupting membranes [101, 102]. When exposed to PEGylated AuNPs, mice and rats reacted differently;

while many rats abruptly died several hours after injection, mice showed a strong macrophage response and no fatalities [103]. Although scientists have been working to determine the in vivo toxicity profile of AuNPs, the wide range of characteristics and circumstances in these papers makes it challenging to draw reliable and significant conclusions from them [104].

Although anticancer medications, such as cisplatin or CDDP, have several adverse effects that limit radiation treatment, researchers are looking into using nanoparticles as carriers for tailored drug delivery. Because of their adjustable surface, nontoxicity, or biologic compatibility, gold nanoparticles (AuNPs) are the subject of much research [105].Toxicity can be decreased by switching out hazardous capping agents with appropriate biocompatible ones or by altering them to stop them from dissolving [106]. Materials in this nanoscale level start to exhibit unforeseen properties that could occasionally prove dangerous or beneficial. Nevertheless, some of the main variables that influence the impact of how they're used include their usage regions, formation processes, and the surrounding environment [107]. According to a research, biological cells are destroyed by AuNPs with a size of 2 nm because they oxidatively damage the mitochondrial structure [108]. It was discovered that toxicity depended on shape and size. For instance, it was discovered that while 15 nm AuNPs were non-toxic, 1.4 nm AuNPs were harmful [109]. According to a number of experimental findings, the safety concentration limit is 1012 particles per milliliter, and the toxicity is dose-dependent [110]. The manufacturing process, size/shape, surface charge, and kind of surface coating all affect the nature of the interaction between AuNPs and bio-systems [111]. The AuNPs may thus communicate with subcellular organelle components or proteins, resulting in DNA damage, immunotoxicity, and neurotoxicity. Given their extensive use, it is implied that the biosafety of these products and methods has drawn a lot of attention [112]. The AuNPs' potential for cytotoxicity is dependent on their size, shape, level, and mode of delivery, and other factors [113]. Following injection, the size, charged surface, and surface hydrophobicity of the NPs all influence their in vivo dispersion. It has also been shown how these parameters affect the mononuclear phagocyte system's acceptance of NPs [114]. Studies have examined how the hazardous qualities of nanomaterials relate to their concentrations. Nanomaterials with higher concentrations are more harmful to cells [115].

6. FUTURE PROSPECTIVE

Due to their inherent qualities, AuNPs have attracted particular interest recently. Undoubtedly, significant progress has been made in the synthesis and functionalization of AuNPs, leading to the development of sophisticated diagnostic and therapeutic procedures. In the field of biomedicine, functionalized AuNPs with their unique functional moieties have made significant progress. Due to their SPR effect, AuNPs have been used as contrast agents in bioimaging. Additionally, because of this function, AuNPs can be used as agents for photothermal therapy and radiation therapy in the primary identification and treatment of cancer. Because of their great stability, biocompatibility, minimal cytotoxicity, and huge surface area, AuNPs are good carriers in the customized DDS system, which is an important research area in biomedicine. To optimize AuNP's therapeutic benefits in biomedicine, more research is necessary, with a particular emphasis on assessing the targeting efficiency *of in vivo* and *in vitro* processes.

7. CONCLUSIONS

In present revolutionary era, nanotechnology has played a significant role in the field of biomedical science and clinical supports. AuNPs have demonstrated their potential role in

various biomedical applications such as cancer therapy, drug delivery system, drug targeting, gene therapy, photothermal therapy, radiotherapy, etc. Although AuNPs are not being widely utilized for biomedical applications, researchers are continuing their efforts in the fields of drug delivery and gene therapy, and their studies have shown potential results. Apart from numerous benefits, AuNPs also have certain disadvantages such as cytotoxicity, nonbiodegradability, etc. which need to be investigated in detail for their practical application in biomedical and clinical fields.

Acknowledgements. It is declared that no external funding has been received for this research work.

CRediT authorship contribution statement. Sandeep Kumar Soni: Methodology, Investigation, Funding acquisition. Manoj Kumar Solanki: Formal analysis and Supervision.

Declaration of competing interest. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

1. Shankar S. S., Rai A., Ahmad A., Sastry M. - Rapid synthesis of Au, Ag, and bimetallic Au core– Ag shell nanoparticles using Neem (Azadirachta indica) leaf broth, J. Colloid Interface Sci. **275** (2004) 496-502.
2. Das, S. K., Marsili, E. - A green chemical approach for the synthesis of gold nanoparticles: characterization and mechanistic aspect, Rev. Environ. Sci. Bio/Tech. **9** (2010) 199-204.
3. Joseph M. M., Aravind S. R., Varghese S., Mini S., Sreelekha T. T. - PST-Gold nanoparticles as an effective anticancer agent with immunomodulatory properities, Colloids Surf. B: Biointerfaces **104** (2013) 32-39
4. Chen R., Chen Q., Huo D., Ding Y., Hu Y., Jiang X. - In situ formation of chitosan–gold hybrid hydrogel and its application for drug delivery, Colloids Surf. B: Biointerfaces **97** (2012) 132-137.
5. Saturnino C., Sinicropi M. S., Iacopettab D., Ceramella J., Caruso A. Muia N., Longo P., Rosace G., Galletta M., Ielo I. - N-Thiocarbazole-based gold nanoparticles: Synthesis, characterization and anti-proliferative activity evaluation, IOP Conf. Ser. Mater. Sci. Eng. **459** (2018) 12023.
6. Jang H., Kim Y. K., Ryoo S. R., Kim M. H., Min D. H. - Facile synthesis of robust and biocompatible gold nanoparticles, Chem. Commun. **46** (2010) 583–585.
7. Badri N. K., Sakthivel N. - Coriander leaf mediated biosynthesis of gold nanoparticles, Mater. Lett. **62** (2008) 4588-4590.
8. Hrushikesh M. J., Devika R. B., Kalpana J., Varsha P., Sastry M. - Gold nanoparticles as carriers for efficient transmucosal insulin delivery, Langmuir. **22** (2006) 300-305.
9. Satish K. N., Nripen C., Ravi S., Kavita K., Rajesh R. K., Subramanian T., Swapna M., Raghuraman K., Kattesh V. K. - Green nanotechnology from tea: Phytochemicals in tea as building blocks for production of biocompatible gold nanoparticles, J. Mater. Chem. **19** (2009) 2912-2920.
10. Zhou M., Wang B., Rozynek Z., Xie Z., Fossum J. O., Yu X., Raaen S. - Minute synthesis of extremely stable gold nanoparticles, Nanotechnology **20** (50) (2009) 505606.

11. Fan L., Wang W., Wang Z., Zhao M. - Gold nanoparticles enhance antibody effect through direct cancer cell cytotoxicity by differential regulation of phagocytosis, Nature comm. **12** (1) (2021) 6371.
12. Ravi S., Satish K. N., Nripen C., Kavita K., Swapna M., Rajesh R. K., Wade V. W., Raghuraman K., Kattesh V. K. - Soybeans as a phytochemical reservoir for the production and stabilization of biocompatible gold nanoparticles, Small **4** (9) (2008) 1425-1436.
13. Ashok B., Bhagyashree J, Ameeta R., Smita Z. - Banana peel extract mediated synthesis of gold nanoparticles, Colloids Surf. B: Biointerfaces **80** (2010) 45-50.
14. Suarasan S., Focsan M., Maniu D., Astilean S. - Gelatine nanogold bioconjucate as effective plasmonic platform for SERS detection and targeting, Colloids Surf. B: Biointerfaces **103** (2013) 475-481.
15. Mubarak A. D., Thajuddin N., Jeganathan K., Gunasekaran M. - Plant extract mediated synthesis of silver and gold nanoparticles and its antibacterial activity against clinically isolated pathogens, Colloids and Surf B: Biointerfaces **85** (2011) 360-365.
16. Joshi H. M., Bhumkar D. R,Joshi K., Pokharkar V.,Sastry M. - Gold nanoparticles as carriers for efficient transmucosal insulin delivery, Langmuir **22** (2006) 300-305.
17. Lee I. H., Kwon H. K., An S., Kim D., Kim S., Yu M. K., Lee J. H., Lee T. S., Im S. H., Jon S. - Imageable antigen-presenting gold nanoparticle vaccines for effective cancer immunotherapy in vivo, Angew. Chem. Int. Ed. **51** (2012) 8800-8805
18. Vasir J. K., Reddy M. K., Labhasetwar V. D. - Nanosystems in drug targeting: opportunities and challenges, Current Nanosci **1** (2005) 47-64.
19. Pissuwan D., Valenzuela S. M., Killingsworth M. C., Xu X., Cortie M. B. - Targeted destruction of murine macrophage cells with bioconjugated gold nanorods, J. Nanopart. Res. **9** (2007) 1109-1124.
20. Bhattacharya R., Patra C. R., Earl A., Wang S., Katarya A., Lu L., Kizhakkedathu J. N., Yaszemski M. J., Greipp P. R., Mukhopadhyay D., Mukherjee P. - Attaching folic acid on gold nanoparticles using noncovalent interaction via different polyethylene glycol backbones and targeting of cancer cells, Nanomedi **3** (3) (2007) 224-238.
21. Mirkin C. A., Letsinger R. L., Mucic R. C., Storhoff J. J. - A DNA-based method for rationally assembling nanoparticles into macroscopic materials, Nature **382** (1996) 607-609.
22. Leuvering J. H., Goverde B. C., Thal P. J., Schuurs A. H. - A homogeneous sol particle immunoassay for human chorionic gonadotrophin using monoclonal antibodies, J. Immunol. Methods **60** (1983) 9-23.
23. Deelder A. M., Dozy M. H. - Applicability of sol particle immunoassay (SPIA) for detection of schistosoma mansoni circulating antigens, Acta Leiden **48** (1982) 17-22.
24. Wielaard F., Denissen A., van der V. L, Rutjes I. - A sol-particle immunoassay for determination of anti rubella antibodies; development and clinical validation, J. Virol. Methods **17** (1987) 149-158.
25. Zeisler R., Stone S. F., Viscidi R. P., Cerny E. H. - Sol particle immunoassays using colloidal gold and neutron activation, J. Radioanal. Nucl. Chem. **167** (1993) 445-452.
26. Pavlov V., Xiao Y., Shlyahovsky B., Willner I. - Aptamer functionalized Au nanoparticles for the amplified optical detection of thrombin, J. Am. Chem. Soc. **126** (2004) 11768- 11769

27. Aslan K., Lakowicz J. R., Geddes C. D. - Nanogold Plasmon resonance based glucose sensing, Anal. Biochem. **330** (2004) 145-155.
28. Medley C. D., Smith J. E., Tang Z., Wu Y., Bamrungsap S., Tan W. - Gold nanoparticle based colorimetric assay for the direct detection of cancerous cells, Anal. Chem. **80** (2008) 1067-1072.
29. Chirathaworn C., Chantaramalai T., Sereemaspun A., Kongthong N., Suwancharoen D. - Detection of leptospira in urine using anti leptospira coated gold nanoparticles. Comp. Immunol, Microbiol. Infect. Dis. **34** (2011) 31-34.
30. Neely A., Perry C., Varisli B., Singh A. K., Arbneshi T., Senapati D., Kalluri J. R., Ray P. C. - Ultrasensitive and highly selective detection of Alzheimer's disease biomarker using two-photon rayleigh scattering properties of gold nanoparticle, ACS Nano **3** (2009) 2834-2840.
31. Baek T. J., Park P. Y., Han K. N., Kwon H. T., Seong G. H. - Development of a photodiode array biochip using a bipolar semiconductor and its application to detection of human papilloma virus, Anal. Bioanal. Chem. **390** (2008) 1373-1378.
32. Mahmoud K. A., Luong J. H. - Impedance method for detecting HIV-1 protease and screening for its inhibitors using ferrocene-peptide conjugate/Au nanoparticle/single-walled carbon nanotube modified electrode, Anal. Chem. **80** (2008) 7056-7062.
33. Georganopoulou D. G., Chang L., Nam J. M., Thaxton C. S., Mufson E. J., Klein W. L., Mirkin C. A. - Nanoparticle-based detection in cerebral spinal fluid of a soluble pathogenic biomarker for Alzheimer's disease, Proc. Natl. Acad. Sci. U. S. A. **102** (2005) 2273-2276.
34. Haes A. J., Chang L., Klein W. L., Van Duyne R. P. - Detection of a biomarker for Alzheimer's disease from synthetic and clinical samples using a nanoscale optical biosensor, J. Am. Chem. Soc. **127** (2005) 2264-2271.
35. Simonian A. L., Good T. A., Wang S. S, Wild J. R. - Nanoparticles based optical biosensors for the direct detection of organophosphate chemical warfare agents and pesticides, Anal. Chim. Acta. **534** (2005) 69-77.
36. Boghaert E. R., Khandke K. M., Sridharan L., Dougher M., DiJoseph J. F., Kunz A., Hamann P. R., Moran J., Chaudhary I., Damle N. K. - Determination of pharmacokinetic values of calicheamicin-antibody conjugates in mice by plasmon resonance analysis of small (5 microl) blood samples, Cancer Chemother. Pharmacol. **61** (2008) 1027-1035.
37. Maier I., Morgan M. R., Lindner W., Pittner F. - Optical resonance-enhanced absorption based near-field immunochip biosensor for allergen detection, Anal. Chem. **80** (2008) 2694-2703.
38. De la E. A., Sánchez-Espinel C., Díaz-Freitas B., González-Fernández A., Maltez-da Costa M., Merkoçi A. - Rapid identification and quantification of tumor cells using an electrocatalytic method based on gold nanoparticles,Anal. Chem. **81** (2009) 10268-10274.
39. Guerrero-Florez V., Mendez-Sanchez S. C., Patrón-Soberano O. A., Rodríguez-González V., Blach, D., Martínez, F. - Gold nanoparticle-mediated generation of reactive oxygen species during plasmonic photothermal therapy: A comparative study for different particle sizes, shapes, and surface conjugations, J. of Mate. Chem. B **8** (14) (2020) 2862-2875.

40. Chen J., Gong M., Fan Y., Feng J., Han L., Xin, H. L., Yin Y.- Collective plasmon coupling in gold nanoparticle clusters for highly efficient photothermal therapy, ACS nano **16**(1) (2022) 910-920.
41. Manrique-Bedoya S., Abdul-Moqueet M., Lopez P., Gray T., Disiena M., Locker A., Mayer K. M. - Multiphysics modeling of plasmonic photothermal heating effects in gold nanoparticles and nanoparticle arrays, The J. of Phy. Chem. **124** (31) (2020) 17172-17182.
42. Ali H. R., Selim S. A., Aili D. - Effects of macrophage polarization on gold nanoparticle-assisted plasmonic photothermal therapy, RSC Adv. **11**(40) (2021) 25047-25056.
43. Gupta N., Malviya, R. - Understanding and advancement in gold nanoparticle targeted photothermal therapy of cancer, Biochimica et Biophysica Acta (BBA)-Rev. on Cancer **1875** (2) (2021) 188532.
44. Yang W., Xia B., Wang L., Ma S., Liang H., Wang D., Huang J. - Shape effects of gold nanoparticles in photothermal cancer therapy, Mat. Today Sust. **13** (2021) 100078.
45. Dheyab M. A., Aziz A. A., Khaniabadi P. M., Jameel M. S., Oladzadabbasabadi N., Rahman, A. A., Mehrdel B. - Gold nanoparticles-based photothermal therapy for breast cancer, Photodiagnosis and photodynamic therapy (2023) 103312
46. Figueiredo A. Q., Rodrigues C. F., Fernandes N., Correia I. J., Moreira A. F. - In situ formation of alginic acid-gold nanohybrids for application in cancer photothermal therapy, Biotech. J. (2023) 2300019
47. Lv W., Wu H., Zhang Y., Li H., Shu H., Su, C., Nie F. - cRGD-targeted gold-based nanoparticles overcome EGFR-TKI resistance of NSCLCvia low-temperature photothermal therapy combined with sonodynamic therapy, Biomat. Sci. **11** (5) (2023) 1677-1691.
48. Villuendas H., Vilches C., Quidant R. - Standardization of In Vitro Studies for Plasmonic Photothermal therapy, ACS Nanosci. Au. **3** (5) (2023) 347-352.
49. Faid A. H., Shouman S. A., Thabet N. A., Badr Y. A., Sliem M. A. - Laser enhanced combinatorial chemo-photothermal therapy of green synthesis gold nanoparticles loaded with 6 mercaptopurine on breast cancer model, J. Pharm. Innov. **18** (1) (2023) 44-148.
50. Gupta T., Pawar B., Vasdev N., Pawar V., Tekade R. K. - Carbonaceous Nanomaterials for Phototherapy of Cancer, Technol. Cancer Res. Treat. (2023) 22.
51. Goddard Z. R., Beekman A. M., Cominetti M. M., O'Connell M. A., Chambrier I., Cook M. J., Searcey M. - Peptide directed phthalocyanine–gold nanoparticles for selective photodynamic therapy of EGFR overexpressing cancers, RSC Med. Chem. **12** (2) (2021) 288-292.
52. Shang L., Zhou X., Zhang J., Shi Y., Zhong L. - Metal nanoparticles for photodynamic therapy: A potential treatment for breast cancer, Molecules **26** (21) (2021) 6532.
53. Wilson B. C. - Handbook of Photonics for Biomedical Science, ed. V. V. Tuchin, CRC Press, Boca Raton (2010) 649-686.
54. Wilson R. - The use of gold nanoparticles in diagnostics and detection, Chem. Soc. Rev. **37** (2008) 2028-2045.
55. Maeda H., Wu J., Sawa T., Matsumura Y., Hori K. - Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review, J. Controlled Release **65** (2000) 271-284.

56. Kurawattimath V., Wilson B., Geetha K. M. - Nanoparticle-based drug delivery across the blood-brain barrier for treating malignant brain glioma, OpenNano (2023) 100128.
57. Carreón González J. L., García Casillas P. E., Chapa González C. - Gold Nanoparticles as Drug Carriers: The Role of Silica and PEG as Surface Coatings in Optimizing Drug Loading, Micromach **14** (2) (2023) 451.
58. Masood F. - Polymeric nanoparticles for targeted drug delivery system for cancer therapy, Mat. Sci. Eng. C **60**(2016) 569-578.
59. Paciotti G. F., Kingston D. G. I., Tamarkin L. - Colloidal gold nanoparticles: A novel nanoparticles platform for developing multifunctional tumor targeted drug delivery vector, Drug Dev. Res. **67** (2006) 47-54.
60. Hassanen E. I., Korany R. M., Bakeer A. M. - Cisplatin-conjugatedgoldnanoparticles-based drug delivery system for targeting hepatic tumors, J. of Biochem. and Mole. Toxico **35** (5) (2021) e22722.
61. Dhar S., Daniel W. L., Giljohann D. A., Mirkin C. A., Lippard S. J. - Polyvalent oligonucleotide gold nanoparticle conjugates as delivery vehicles for platinum(IV) warheads, J. Am. Chem. Soc. **131** (2009) 14652-14653.
62. Brown S. D., Nativo P., Smith J. A., Stirling D., Edwards P. R., Venugopal B., Flint D. J., Plumb J. A., Graham D., Wheate N. J. - Gold nanoparticles for the improved anticancer drug delivery of the active component of oxaliplatin, J. Am. Chem. Soc. **132** (2010) 4678-4684.
63. Pun S. H., Davis M. E. - Development of a nonviral gene delivery vehicle for systemic application, Bioconjugate Chem. **13** (3) (2002) 630-639.
64. Lee E. S., Oh K. T., Kim D., Youn Y. S., Bae Y. H. - Tumor pH responsive flower like micelles of poly(L-lactic acid)-b-poly(ethylene glycol)-b-poly(L-histidine), J. Controlled Release **123** (2007) 19-26.
65. Paciotti G. F., Myer L., Weinreich D., Goia D., Pavel N., McLaughlin R. E., Tamarkin L. - Colloidal gold: a novel nanoparticle vector for tumor directed drug delivery, Drug Deliv. **11** (3) (2004) 169-183.
66. Zhang S., Chen C., Xue C., Chang D., Xu H., Salena B. J., Wu Z. S. - Ribbon of DNA lattice on gold nanoparticles for selective drug delivery to cancer cells, Angewandte Chemie Inter. Ed. **59** (34) (2020) 14584-14592.
67. Fan M., Han Y., Gao S., Yan H., Cao L., Li Z., Zhang J. - Ultrasmall gold nanoparticles in cancer diagnosis and therapy, Theranostics **10** (11) (2020) 4944.
68. Ghosh P., Han G., De M., Kim C. K., Rotello V. M. - Gold nanoparticles in delivery applications, Adv. Drug Deliv. Rev. **60** (2008) 1307-1315.
69. Kim C. K., Ghosh P., Pagliuca C., Zhu Z. J., Menichetti S., Rotello V. M. - Entrapment of hydrophobic drugs in nanoparticle monolayers with efficient release into cancer cells, J. Am. Chem. Soc. **131** (2009) 1360-1361.
70. Javier D. J., Nitin N., Levy M., Ellington A., Richards-Kortum R. - Aptamer targeted gold nanoparticles as molecular specific contrast agents for reflectance imaging, Bioconjugate Chem. **19** (2008) 1309-1312.
71. Agasti S. S., Chompoosor A., You C. C., Ghosh P., Kim C. K., Rotello V. M. - Photoregulated release of caged anticancer drugs from gold nanoparticles, J. Am. Chem. Soc. **131** (2009) 5728-5729.

72. Nakanishi J., Nakayama H., Shimizu T., Ishida H., Kikuchi Y., Yamaguchi K., Horiike Y. - Light regulated activation of cellular signaling by gold nanoparticles that capture and release amines, J. Am. Chem. Soc. **131** (11) (2009) 3822-3823.
73. Chen R., Chen Q., Huo D., Ding Y., Hu Y., Jiang X. - In situ formation of chitosan–gold hybrid hydrogel and its application for drug delivery, Colloids Surf. B: Biointerfaces **97** (2012) 132-137.
74. Chen Y. H., Tsai C. Y., Huang P. Y., Chang M. Y., Cheng P. C., Chou C. H., Chen D. H., Wang C. R., Shiau A. L., Wu C. L. - Methotrexate conjugated to gold nanoparticles inhibits tumor growth in a syngeneic lung tumor model, Mol. Pharm. **4** (5) (2007) 713-22.
75. Matsumura Y., Maeda H. - A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs, Cancer Res. **46** (1986) 6387-6392.
76. Torchilin V. - Tumor delivery of macromolecular drugs based on the EPR effect, Adv. Drug Deliv. Rev. **63** (2011) 131-135.
77. Kim C. K., Ghosh P., Pagliuca C., Zhu Z. J., Menichetti S., Rotello V. M. - Entrapment of hydrophobic drugs in nanoparticle monolayers with efficient release into cancer cells, J. Am. Chem. Soc. **131** (2009) 1360-1361.
78. Low P. S., Henne W. A., Doorneweerd D. D. - Discovery and development of folic-acid-based receptor targeting for imaging and therapy of cancer and inflammatory diseases, Acc. Chem. Res. **41** (2008)120-129.
79. Peng L., Liang Y., Zhong X., Liang Z., Tian Y., Li S., Zhang X. - Aptamer-conjugated gold nanoparticles targeting epidermal growth factor receptor variant III for the treatment of glioblastoma, Inter. J. of Nanomed (2020) 1363-1372.
80. Yücel O., Şengelen A., Emik S., Önay-Uçar E., Arda N., Gürdağ G. - Folic acid-modified methotrexate-conjugated gold nanoparticles as nano-sized trojans for drug delivery to folate receptor-positive cancer cells, Nanotech. **31** (35) (2020) 355101.
81. Turk M. J., Breur G. J., Widmer W. R., Paulos C. M., Xu L. C., Grote L. A., Low P. S. - Folate targeted imaging of activated macrophages in rats with adjuvant-induced arthritis, Arthritis Rheum **46** (7) (2002) 1947-55.
82. Antony A. C. - The biological chemistry of folate receptors, Blood. **79** (1992) 2807-2820.
83. Elnakat H., Ratnam M. - Distribution, functionality and gene regulation of folate receptor isoforms: implications in targeted therapy, Adv. Drug Deliv. Rev. **56** (8) (2004) 1067-1084.
84. Shmeeda H., Mak L., Tzemach D., Astrahan P., Tarshish M., Gabizon A. - Intracellular uptake and intracavitary targeting of folate conjugated liposomes in a mouse lymphoma model with up-regulated folate receptors, Mol. Cancer Ther. **5** (4) (2006) 818-824.
85. Garin-Chesa P., Campbell I., Saigo P. E., Lewis J. L. Jr Old L. J., Rettig W. J. - Trophoblast and ovarian cancer antigen LK26 Sensitivity and specificity in immunopathology and molecular identification as a folate binding protein, Am. J. Pathol. **142** (1993) 557-567.
86. Toffoli G., Cernigoi C., Russo A., Gallo A., Bagnoli M., Boiocchi M. - Overexpression of folate binding protein in ovarian cancers, Int. J. Cancer. **74** (1997) 193-198.

87. Gruner B. A., Weitman S. D. - The folate receptor as a potential therapeutic anticancer target, Invest. New Drugs. **16** (1998) 205-219.
88. Kukowska-Latallo J. F., Candido K. A., Cao Z., Nigavekar S. S., Majoros I. J., Thomas T. P., Balogh L. P., Khan M. K., Baker J. R. - Nanoparticle targeting of anticancer drug improves therapeutic response in animal model of human epithelial cancer, Cancer Res. **65** (12) (2005) 5317-5324.
89. Ratnam M., Hao H., Zheng X., Wang H., Qi H., Lee R., Pan X. - Receptor induction and targeted drug delivery: a new antileukaemia strategy, Expert Opin. Biol. Ther. **3** (4) (2003) 563-574.
90. Dixit V., Van den B. J., Sherman D. M., Thompson D. H., Andres R. P. - Synthesis and grafting of thioctic acid-PEG-folate conjugates onto Au nanoparticles for selective targeting of folate receptor-positive tumor cells, Bioconjugate Chem. **17** (2006) 603-609.
91. Kamen B. A., Capdevila A. - Receptor mediated folate accumulation is regulated by the cellular folate content, Proc. Natl. Acad. Sci. USA **83** (1986) 5983-5987.
92. Antony A. C., Kane M. A., Portillo R. M., Elwood P. C., Kolhouse J. F. - Studies of the role of a particulate folate binding protein in the uptake of 5-methyltetrahydrofolate by cultured human KB cells, J. Biol. Chem. **260** (1985) 14911-14917.
93. Leamon C. P., Reddy J. A. -Folate-targeted chemotherapy, Adv. Drug Deliv. Rev. **56** (21) (2004) 1127-1141.
94. Leamon C. P., Reddy J. A., Vlahov I. R., Westrick E., Dawson A., Dorton R., Vetzel M., Santhapuram H. K., and Wang Y. - Preclinical antitumor activity of a novel folate targeted dual drug conjugate, Mol. Pharm. **4** (5) (2007) 659-667.
95. Shelar S. B., Barick K. C., Dutta B., Basu M., Hassan P. A. - Selective targeting of gold nanoparticles for radiosensitization of somatostatin 2 receptor-expressing cancer cells, J. of Drug Deli. Sci. Technol. **82** (2023) 104381.
96. Malekzadeh R., Ghorbani M., Faghani P., Abdollahi B. B., Mortezazadeh T., Farhood B. - Fabrication of targeted gold nanoparticle as potential contrast agent in molecular CT imaging, J. of Radiation Res. App. Sci. **16** (1) (2023) 100490.
97. Patra C. R., Bhattacharya R., Mukherjee P. - Fabrication and functional characterization of gold nanoconjugates for potential application in ovarian cancer, J. Mater. Chem. **20** (2010) 547-554.
98. Rambanapasi C., Zeevaart J. R., Buntting H. - Bioaccumulation and Subchronic Toxicity of 14 nm Gold Nanoparticles in Rats, Molecules **21** (6) (2016) 763.
99. Lasagna R. C., Gonzalez R. D., Barria M. A. - Bioaccumulation and toxicity of gold nanoparticles after repeated administration in mice, Biochem Biophys Res. Commun. **393** (4) (2010) 649-655.
100. Glazer E. S., Zhu C., Hamir A. N., Borne A., Thompson C. S., Curley S. A. - Biodistribution and acute toxicity of naked gold nanoparticles in a rabbit hepatic tumor model, Nanotoxicology **5** (4) (2011) 459-468.
101. Dam D. H., Culver K. S., Kandela I.- Biodistribution and in vivo toxicity of aptamer-loaded gold nanostars, Nanomedicine **11** (3) (2015) 671-679.
102. Enea M., Pereira E., Silva D. D. - Study of the intestinal uptake and permeability of gold nanoparticles using both in vitro and in vivo approaches, Nanotechnology **31**(19) (2020) 195-202.

103. Li X., Hu Z., Ma J. - The systematic evaluation of size-dependent toxicity and multi-time biodistribution of gold nanoparticles, Colloids Surf B Biointerfaces **167** (2018) 260-266.
104. Engstrom A. M., Faase R. A., Marquart G. W., Baio J. E., Mackiewicz M. R., Harper S. L. - Size-Dependent Interactions of Lipid-Coated Gold Nanoparticles: developing a Better Mechanistic Understanding Through Model Cell Membranes and in vivo Toxicity, Int. J. Nanomedicine **15** (2020) 4091-4104.
105. Wróblewska A. M., Gos N., Zajda J., Ruzik L., Matczuk M.- Drawbacks in the efficient monitoring of gold nanoparticle-based cisplatin delivery systems formation by HPLC–ICP-MS, Metallomics **15** (1) (2023) mfad002.
106. Ginzburg L., *et al.*-Synergistic toxicity produced by mixtures of biocompatible gold nanoparticles and widely used surfactants, ACS nano **12** (6) (2018) 5312-5322.
107. Sharma C., Bansal D., Bhatnagar D., Gautam S., Goyal N. - Advanced Nanomaterials: From Properties and Perspective Applications to Their Interlinked Confronts. In Advanced Functional Nanoparticles" Boon or Bane" for Environment Remediation Applications: Combating Environmental Issues Cham, Springer Intern. Pub. (2023) 1-26.
108. Li X., Hu Z., Ma J., *et al.* - The systematic evaluation of size-dependent toxicity and multi-time biodistribution of gold nanoparticles,Colloids Surf B Biointerfaces **167 (**2018) 260-266.
109. Bansal S. A., Kumar V., Karimi J., Singh A. P., Kumar S. - Role of gold nanoparticles in advanced biomedical applications, Nanoscale Adv. **2** (9) (2020) 3764-3787.
110. Tsoli M., Kuhn H., Brandau W., Esche H., Schmid G. - Cellular uptake and toxicity of Au55 clusters, Small **1**(8-9) (2005) 841-844.
111. Dykman Lev A., Nikolai G. K. - Gold nanoparticles in biology and medicine: recent advances and prospects, Acta Naturae **9** (2011) 34-55.
112. Chatterjee P., Chauhan N., Jain U. - Confronting antibiotic-resistant pathogens: The drug delivery potential of nanoparticle swords, Microbial Pathogen (2023) 106499.
113. Xiong P., Huang X., Ye N., Lu Q., Zhang G., Peng S., Wang H., Liu Y. - Cytotoxicity of Metal-based Nanoparticles: From Mechanisms and Methods of Evaluation to Pathological Manifestations, Adv. Sci. **9** (2022) 2106049.
114. Xu L., Wang Y. Y., Huang J., Chen C. Y., Wang Z. X., Xie H. - Silver Nanoparticles: Synthesis, Medical Applications and Biosafety, Theranostics **10**(2020) 8996-9031.
115. Joseph T. M., Mahapatra D. K., Esmaeili A., Piszczyk Ł., Hasanin M. S., Kattali M., Haponiuk J., Thomas S. - Nanoparticles: Taking a Unique Positionin Medicine, Nanomat **13** (2023) 574.