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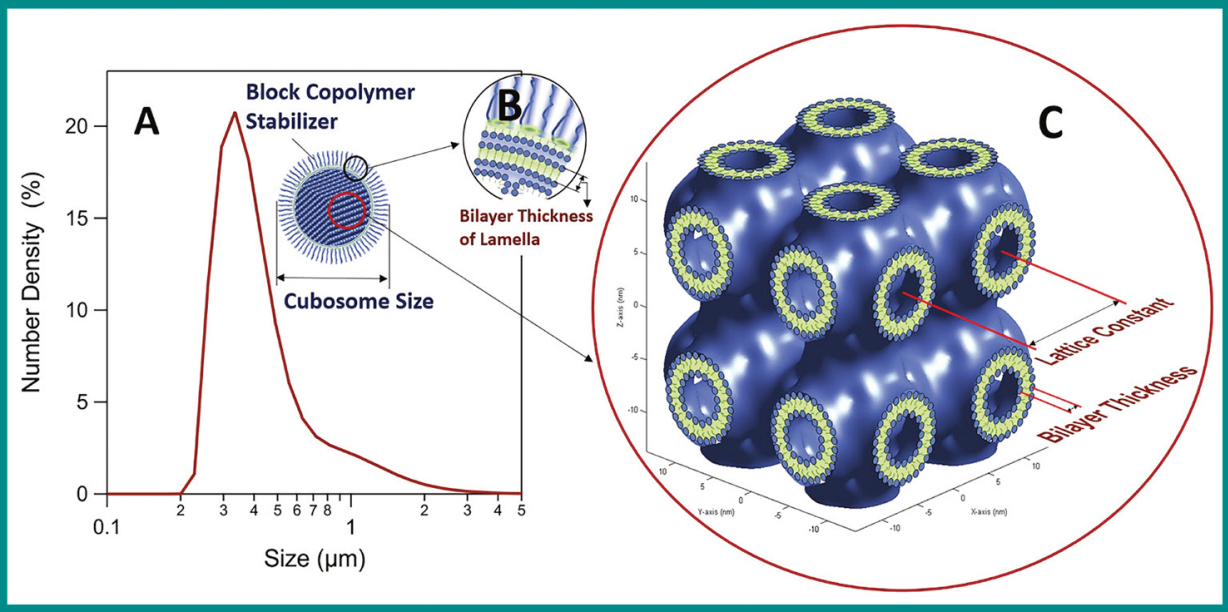

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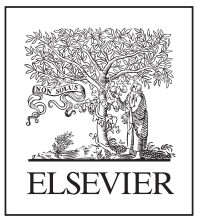

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CONTENTS

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CONTRIBUTORS

M.-I. Aguilar
Monash University, Clayton, VIC, Australia

B. Burja
University Medical Centre Ljubljana, Ljubljana, Slovenia

Z. Capáková
Centre of Polymer Systems, Tomas Bata University in Zlin, Zlin, Czech Republic

S. Čučnik
University Medical Centre Ljubljana; Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia

C.E. Conn
School of Science, College of Science, Engineering and Health, RMIT University, Melbourne, VIC, Australia

C.J. Drummond
School of Science, College of Science, Engineering and Health, RMIT University, Melbourne, VIC, Australia

A. Flašker
Chemical Institute, Ljubljana, Slovenia

J.F. Hancock
McGovern Medical School, University of Texas Health Science Center, Houston, TX, United States

P. Humpolíček
Centre of Polymer Systems, Tomas Bata University in Zlin, Zlin, Czech Republic

A. Iglič
Laboratory of Biophysics, Faculty of Electrical Engineering, University of Ljubljana, Ljubljana, Slovenia

I. Junkar
Josef Stefan Institute, Ljubljana, Slovenia

M. Kulkarni
Laboratory of Biophysics, Faculty of Electrical Engineering, University of Ljubljana, Ljubljana, Slovenia

T.-H. Lee
Monash University, Clayton, VIC, Australia

A. Mazare
Chair of Surface Science and Corrosion, University of Erlangen–Nuremberg, Erlangen, Germany

T.G. Meikle
School of Chemistry, Bio21 Institute, University of Melbourne, Melbourne, VIC, Australia

M. Mozetič
Josef Stefan Institute, Ljubljana, Slovenia

K. Mrak-Poljšak
University Medical Centre Ljubljana, Ljubljana, Slovenia

M. Rappolt
School of Food Science and Nutrition, University of Leeds, Leeds, United Kingdom

A. Sadeghpour
School of Food Science and Nutrition, University of Leeds, Leeds, United Kingdom

P.B. Santhosh
Indian Institute of Technology, Chennai, India

D. Sanver
School of Food Science and Nutrition, University of Leeds, Leeds, United Kingdom

P. Schmuki
Chair of Surface Science and Corrosion, University of Erlangen–Nuremberg, Erlangen, Germany

F. Separovic
School of Chemistry, Bio21 Institute, University of Melbourne, Melbourne, VIC, Australia

S. Sodin-Semrl
University Medical Centre Ljubljana, Ljubljana; Faculty of Mathematics, Natural Science and Information Technologies, University of Primorska, Koper, Slovenia

S. Sudhakar
Centre for Biotechnology, Anna University, Chennai, India

M. Tomšič
University Medical Centre Ljubljana; Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Y. Zhou
McGovern Medical School, University of Texas Health Science Center, Houston, TX, United States

P. Žigon
University Medical Centre Ljubljana, Ljubljana, Slovenia

CHAPTER SIX

Gold Nanomaterials: Recent Advances in Cancer Theranostics

S. Sudhakar*, P.B. Santhosh†,1
*Centre for Biotechnology, Anna University, Chennai, India
†Indian Institute of Technology, Chennai, India
[1]Corresponding author: e-mail address: poorni_balaji@yahoo.com

Contents

Abstract

This chapter describes the potential of various shapes of gold nanomaterials such as nanoparticles, nanorods, nanostars, nanocages, and nanoshells in cancer nanotheranostics, i.e., both as diagnostic and therapeutic agent. This study includes the synthesis of different gold nanomaterials using several methods like chemical-, green-, and microbial-mediated synthesis. The ability of gold nanomaterials to absorb light in the near-infrared region and transform it into heat and their unique optical properties make them a promising tool in photothermal cancer therapy. Herein, we present the recent advances and the ability of gold nanomaterials to show its multiple roles in the field of cancer biology.

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1. INTRODUCTION TO DIFFERENT FORMS OF GOLD NANOMATERIALS

Gold nanomaterials have gained huge interest in various biomedical applications and considered to have a promising potential in the field of cancer biology. Based on the synthesis procedure and experimental conditions, various shapes of gold nanomaterials including spherical gold nanoparticles, nanorods, nanoshells, nanocages, nanostars, nanoboxes, nanocubes, nanocrystals, and triangular bipyramids have been investigated [1–7]. In this chapter about gold nanomaterials, first we are going to have a look on synthesis of different shapes of gold nanomaterials and applications as diagnostic and therapeutic agents in cancer.

1.1 Gold Nanoparticles

When compared to many other metallic nanoparticles, noble metals like gold nanoparticles (AuNPs) have distinct electronic and optical properties. When the AuNPs are excited by light at specific wavelengths, the incident photons interact strongly with the conduction band of electrons and cause them to oscillate with resonant frequency. This collective oscillation is known as localized surface plasmon resonance (LSPR) which creates strong and localized electromagnetic fields and allows sensitive detection of changes in dielectric environment surrounding the nanoparticle surface. This property makes them to be prominently utilized in imaging, drug delivery, cosmetics, and in cancer theranostic applications [8,9]. The AuNPs display various colors based on their shape, size, and amount of aggregation of particles [10]. The AuNPs are evolving as an innovative platform for both, cancer targeted imaging and drug delivery usually represented as theranostic application. When irradiated with near-infrared (NIR) light, they induce hyperthermia (increased temperature to kill cancer cells) [11,12]. Furthermore, AuNPs could be successfully and selectively delivered to malignant and benign tumors and could act as carriers for chemotherapeutic drugs like curcumin, and paclitaxel in cancer treatment [13]. Apart from therapeutic applications, AuNPs are employed as imaging agents and biosensors due to their capability to emit photons upon irradiation. The gold nanomaterials of different shapes are schematically represented in Fig. 1.

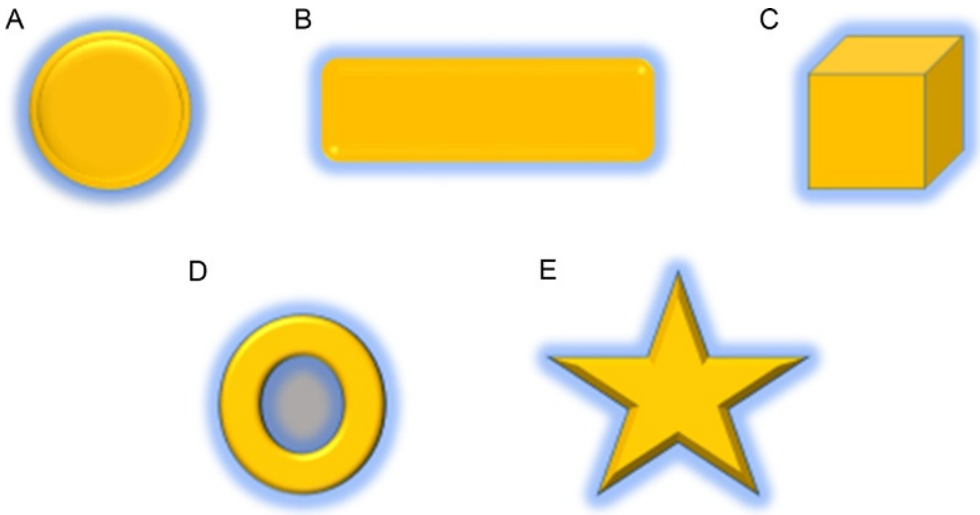

Fig. 1 Schematic presentation of differently shaped gold nanoparticles: (A) nanosphere, (B) nanorod, (C) nanocube, (D) nanoshell, and (E) nanostar.

1.2 Gold Nanorods

When compared to spherical gold particles, the AuNRs have drawn worldwide attention because of their inimitable shape-dependent optical properties. What makes the AuNRs as exclusive materials for biological imaging, sensing, photo thermal therapy, and drug delivery is their ability to possess different plasmon bands [14–17]. Even though, they have attracting features, their usage is restricted because even a small change in the shape, size, and surface nature will alter their properties which in turn affect their biological applications. The major advantages of using AuNRs include their surface plasmon resonance extinction in the NIR region which makes their use appropriately in the medical field for photo thermal therapy, biological sensing, and imaging.

1.3 Gold Nanocages

Next, we move on to a novel nanostructure called gold nanocages (AuNCgs) which are usually characterized by the ultrathin porous walls and hollow interiors. Usually they are prepared by keeping the silver nanoparticles as templates which involves galvanic replacement reaction [18–20]. The penetration depth of light can be maximized in soft tissues, by limiting the light source to NIR region from 650 to 900 nm, where the absorption by hemoglobin and water is negligible. To make AuNCgs suitable for this application, the LSPR peaks can be concisely tuned throughout the visible and NIR regions [21–24]. Prevalently, AuNCgs

are also functionalized with biological molecules to target cancer cells for both photothermal therapy and diagnosis at an early stage [25,26].

1.4 Gold Nanoshells

Gold nanoshells (AuNShs) are composed of a silica core coated by a thin gold metallic shell. One of the interesting properties about the AuNShs is their unique surface plasmon resonance property which can be finely tuned ranging from visible to NIR region. Multiple templates are employed for the formation of hollow AuNShs which includes silica particles [27], metal particles [28–31], etc. The AuNShs have demonstrated their potential in a variety of biomedical applications ranging from substrates for whole-blood immunoassays to photothermal cancer therapy [32–34]. By using magnetic resonance thermal guidance, in vitro cancer cells were successfully ablated using AuNShs. Similar use of AuNShs for photothermal ablation of tumors in mice showed complete regression of tumors with the mice remaining healthy compared with the controls [35–38].

1.5 Gold Nanostars

The gold nanostars (AuNSts) have multiple sharp branch structure which sharply increases the electromagnetic field. The AuNSts also have unique plasmon bands which are tunable from visible to NIR region. The fabrication of AuNSts has been driven by the interest on the LSPR response to the environment, especially on sharp tips and edges, where light can be highly concentrated [39–43]. Because of their exclusive property, they serve as effective tools in the field of nanomedicine. Furthermore, AuNSts also display stronger surface-enhanced resonance spectrum activity than gold spheres or even rods.

2. SYNTHESIS OF DIFFERENT FORMS OF GOLD NANOMATERIALS

2.1 Chemical-Mediated Synthesis of Gold Nanomaterials

2.1.1 Synthesis of Gold Nanoparticles

The simplest protocol commonly used for the groundwork of AuNPs is the facile reduction of gold salt in aqueous medium using sodium citrate [44,45], in which Au^{3+} ions are reduced to neutral gold atoms which slowly precipitates to form nanometer-sized gold particles. The widely used reducing agents for the synthesis of AuNPs include aminoboranes, borohydrides, hydrazine, hydroxylamine, formaldehyde, polyols, sugars, saturated and

unsaturated alcohols, hydrogen peroxide, citric and oxalic acids, carbon monoxide, sulfites, acetylene, and hydrogen [46–48]. A variety of stabilizers such as phosphorus ligands, trisodium citrate dihydrate, nitrogen-based ligands, sulfur ligands, dendrimers, oxygen-based ligands, polymers, and surfactants are used to impart the colloidal stability to AuNPs [49,50]. Synthesis of AuNPs by citrate-stabilized method, introduced by Turkevich, is the most popular method in which trisodium citrate dihydrate is added to the boiling chloroauric acid under vigorous stirring, leading to the formation of wine-red colloidal suspension after a few minutes [51,52]. To improve this method, Frens altered the ratio of gold and trisodium citrate, resulting in the synthesis of AuNPs of wide size range (from 15 to 150 nm) [46]. The size of the AuNPs obtained using Brust–Schiffrin method ranges from 2 to 5 nm, which is much smaller in size than particles synthesized by Turkevich method. Another popular technique for synthesis of AuNPs is seed growth method where one can easily control the size and shape of the particle. Usually, it involves two steps, preparation of small sized AuNPs followed by addition of seeds to the growth solution.

2.1.2 Synthesis of Gold Nanorods

In general, AuNRs are produced using cetyltrimethyl ammonium bromide (CTAB) which acts as both reducing and stabilizing agent to produce homogeneous AuNRs with high yield [53–56,4,57–61]. The LSPR resonances of AuNRs are generally observed both in the visible and NIR region [62–70]. Since CTAB is cytotoxic, various biocompatible agents like proteins and lipids are being used to provide stability, reduce cytotoxicity, and to retain its properties. A number of studies have focused on surface modification of AuNRs to address the above mentioned issues. An intrinsic problem in the synthesis of AuNRs using conventional method is its meager efficiency to convert chloroauric acid into nanorods. Reports have shown that only 15% of gold seeds are usually converted into the rods. The AuNRs yield could be increased by preparing the AuNRs in consecutive supernatant solutions. There is an urgent need for novel synthetic protocols in order to make the synthesis process more scalable and efficient as AuNRs progress greatly toward commercial applications.

2.1.3 Synthesis of Gold Nanocages

Recently, AuNCgs with hollow interiors, porous walls, and tunable LSPR in the NIR region have become a new promising platform for therapeutic applications. The unique structures of AuNCgs make them well suited for

drug encapsulation and photothermal controlled drug release with high spatial and temporal resolution. The AuNCgs are generally synthesized through a simple galvanic replacement reaction between solutions containing salts of metal precursors and Ag nanostructures prepared through polyol reduction. The reduced metal deposits on the surface of the AuNCgs, adopting their underlying cubic form. Concurrent with this deposition, the interior Ag is oxidized and removed, together with alloying and dealloying, AuNCgs are produced. [71].

2.1.4 Synthesis of Gold Nanoshells

The commonly used method for the synthesis of gold nanoshells (AuNShs) involves the reduction of chloroauric acid with ascorbic acid at ambient temperature on presynthesized gold nanoseeds and in the presence of surfactants (in most cases CTAB). A general one-pot synthetic strategy for the synthesis of hollow AuNShs includes the reduction of chloroauric acid in 3-aminopropyltriethoxysilane in water suspension [72]. The AuNShs show a high photothermal conversion efficiency (up to 45%) and excellent stability under laser irradiation.

2.1.5 Synthesis of Gold Nanostars

The AuNSts are synthesized by anisotropic growth process, by altering the growth rates along the specific crystallographic directions [73]. The shape of AuNSts could be controlled by varying the concentration of silver nitrate. The stirring speed, pH, and the ratios of ascorbic acid, silver nitrate, and chloroauric acid determine the size and shape of the AuNSts. Murphy and coworkers have studied the influence of reducing agent by replacing bromide ions of CTAB with its chloride equivalent to achieve a better control over size [74]. Few groups have used hydroxylamine sulfate in the preparation of polycrystalline-branched AuNSts in a stepwise growth approach with sizes ranging from 48 up to 186 nm [75]. It is also reported that addition of polyvinyl pyrrolidone with 15 nm chloroauric acid solution leads to the formation of highly branched AuNSts [76]. Recently, a simple one-step synthesis of AuNSts using hydroxylamine as a reducing agent was reported [77]. The controlled synthesis of high-yield AuNSts ranging from 45 to 116 nm was reported by Khoury and Vo-Dinh [78]. The AuNSts were synthesized by extending the protocol reported by Liz-Marzan *et al.* [79], in order to enable size control of the stars from approximately 45 to 116 nm in size. This size range translates to tuning capabilities of the longitudinal plasmon peak in the NIR region from around 725 to 850 nm. They have used 20 nm

polyvinylpyrrolidone-coated gold seeds in ethanol and investigated the growth of AuNSts as a function of time during the synthesis by monitoring the spectrum of the AuNSts suspension and by imaging morphological changes of stars from time to time via transmission electron microscopy.

2.2 Green Synthesis of Gold Nanomaterials

Even though there are several methods like thermal decomposition, sonochemical, microwave irradiation, chemical reduction, electrochemical ablation for the synthesis of gold nanomaterials, many of these routine methods use hazardous chemicals. Hence, synthesis of nanoparticles in an ecofriendly way is essential. The green synthesis method is more advantageous when compared to other conventional methods which requires extended and high cost for downstream processing. The main components in plants responsible for the reduction of gold ions are usually phenols, proteins, and flavonoids which also acts as a stabilizing agent by capping the nanoparticles. Researchers have explored industrially and botanically important plants for the synthesis of nanoparticles. The active ingredients present in the plant extracts will provide special surface characteristics to the nanoparticles. Citrus maxima fruit extracts are widely used for the inexpensive synthesis of AuNPs [80]. Ghodake *et al.* [81] demonstrated casein hydrolytic peptides (CHPs)-mediated synthesis of crystalline AuNPs. The mechanism behind the nanoparticle formation is attributed to the catalytic properties of hydroxyl groups present in the CHPs. The CHPs are capable of forming a monolayer on the surface of AuNPs via electrostatic interactions, thus playing an important role in long-term stability. Yana *et al.* [82] reported a facile, one-pot green synthesis of biomaterial-supported AuNPs using cellulose with superior catalytic activity. In general, cellulose-mediated AuNPs with a size range of 5–10 nm are prepared by heating the aqueous mixture of chloroauric acid, with cellulose and poly ethylene glycol. Nazirova *et al.* [83] reported water-soluble luminescent AuNPs with average size 2.3 nm synthesized from *N*-(4-imidazolyl) methylchitosan. The biological activity of imidazolyl-containing polymers and their capability to bind proteins and drugs have huge applications in the field of bioimaging, biomolecules detection, catalysis, and drug delivery. Suarasana *et al.* [84] reported the one-pot, green synthesis of AuNPs using gelatin biopolymer having unique reducing, stabilizing, and eminent growth controlling ability. Sadeghi *et al.* [85] reported that the plant *Stevia rebaudiana* have higher amount of polyphenols and flavonoids which makes them more

Table 1 Green Synthesis of Gold Nanoparticles Using Different Plant Sources

Plants	Size of the Particle (nm)	Shapes	References
Acanthella elongata	15	Spherical	[87]
Sugar beet pulp	20	Triangular	[88]
Cinnamomun zyelanicum	20	Spherical	[89]
Zingiber officinale	5–15	Spherical	[90]
Olive leaf extract	50–100	Spherical, triangular	[91]
Coriander leaf extract	6–58	Spherical, triangular	[92]
Cassia auriculata	38	Spherical, triangular	[93]
Hibiscus rosasinensis	15–25	Spherical, triangular, hexagonal	[94]
Terminalia chebula	50–100	Spherical	[95]
Rosa hybrida	35	Spherical	[96]
Morinda citrifolia	10–40	Triangular	[97]
Tamarind leaf extract	20	Spherical	[98]
Palm oil mill effluent	50	Spherical	[99]

specific to act as reducing agent in the synthesis of AuNPs. Yuan *et al.* [86] reported a facile and rapid a single-pot synthesis process for AuNPs using capsicum. The synthesis of AuNps of various shapes from different plant sources is shown in Table 1.

2.3 Microbial Synthesis of Gold Nanomaterials

Synthesis of nanomaterials using microorganisms is an emerging field of industrial microbiology. Biological approaches using either unicellular or multicellular organisms for the synthesis of gold nanomaterials are simple, viable, and ecofriendly alternate to chemical methods. Different biological entities like bacteria, fungi, algae, yeast, and plants are drastically studied for their ability to synthesize metal nanoparticles for various pharmacological applications (Table 2) [109].

There are two ways by which AuNPs can be synthesized by microbes, either extracellularly or intracellularly. The most popular method is extracellular synthesis, as it eliminates numerous downstream processing steps

Table 2 Microbial Synthesis of Gold Nanoparticles of Different Sizes

Microorganism	Size of the Particle (nm)	References
Bacillus subtilis	5–25	[100]
Sulfate-reducing bacteria	15–200	[101]
Shewanella algae	10	[102]
Escherichia coli DH5α	10–20	[103]
Pseudomonas stutzeri	200	[104]
Corynebacterium	10	[105]
Rhodobacter	10–20	[106]
Bacillus sp.	10	[107]
Pseudomonas aeruginosa	17.2	[108]

during the synthesis. The usual procedure followed is to centrifuge the second day well-grown culture to discard the biomass and add the supernatant to chloroauric acid. The enzymes like NADH dehydrogenase, NADPH-dependent sulfite reductase in the microbes act as reducing agents [110]. After bioreduction, the AuNPs can be collected by similar methodologies as in plant extract-mediated synthesis. Cell-free viable approach for synthesis of AuNPs using *Escherichia coli* has also been reported [111]. Despite the stability, biological nanoparticles are usually not monodisperse, and the rate of synthesis is slow. To overcome these problems, several factors such as microbial cultivation methods and the extraction techniques have to be optimized, and the combinatorial approach such as photobiological methods may be used. In the case of intracellular-mediated synthesis process, the particles are released to the external environment either by ultrasound treatment or by adding apt detergents. *Geobacter ferrireducens*, a Fe (III) reducing bacterium, reduces and precipitates the gold in periplasmic space intracellularly. Similarly, in the presence hydrogen gas microbes like Shewanella algae, mesophilic bacteria reduce Au^{+3} ions in anaerobic conditions. *Plectonema boryanum*, a filamentous cyanobacterium, precipitates AuNPs in abiotic and cyanobacterial systems. *Escherichia coli* DH5α-mediated bioreduction of chloroauric acid to Au^{0} nanoparticles has been reported recently [112]. The accumulated particles on the cell surface were mostly spherical. These cell-bound nanoparticles have been reported for promising applications in realizing the direct electrochemistry of hemoglobin and other proteins [113]. Similarly, the bioreduction of trivalent aurum was also reported in

photosynthetic bacterium, *Rhodobacter capsulatus* which showed biosorption capacity of 92.43 mg chloroauric acid/g dry weight in the logarithmic phase of its growth. The carotenoids and NADPH-dependent enzymes embedded in plasma membrane and/or secreted extracellularly were found to be involved in the biosorption and bioreduction of Au^{+3} to Au^{0} on the plasma membrane and also extracellularly [100]. Owing to the rich biodiversity of microbes, their potential as biological materials for nanoparticle synthesis is yet to be fully explored.

3. DIAGNOSTIC AND IMAGING APPLICATIONS OF GOLD NANOMATERIALS

As discussed earlier, gold nanomaterials have unique properties which attract researchers to focus their studies in the field of tumor molecular imaging and diagnostics. Herein, Zhou and Jia [114] reported a facile approach in which polyethylenimine (PEI) modified with polyethylene glycol (PEG), a cost effective template, is used for the synthesis of folic acid (FA)-targeted multifunctional AuNPs. The PEI was consecutively modified with FA-linked PEG, PEG monomethyl ether and with fluorescein isothiocyanate for the synthesis of AuNPs. The prepared AuNPs were noncytotoxic and colloidally stable. They acted as novel nanoprobe for targeted CT imaging of FAR-expressing cancer cells. Lozano *et al.* [115] demonstrated the hybrid vesicular systems composed of liposomes and AuNRs aid in deep tissue detection, therapy, and monitoring in living animals using multispectral optoacoustic tomography [116].

Gallina *et al.* [117] reported that fluorescent, biocompatible, aptamer-conjugated AuNRs act as perfect agents for diagnostics and therapeutics. Bioconjugation of AuNRs with anticancer oligonucleotide AS1411 was employed and the aptamer-conjugated AuNRs acted as ideal cancer-selective multifunctional probes for imaging. Huang *et al.* [12] reported the synthesis of multifunctional nanoprobes in which silica functionalized gold was decorated with FA molecule which displayed strong computed tomography imaging and X-ray attenuation. Vo-Dinh and coworkers reported the synthesis of AuNSts for in vivo imaging with adjustable geometry. They exhibited strong two-photon photoluminescence process which is confirmed by the quadratic dependence of the luminescence signal up to excitation power which may originate from electron–hole-recombination. They also reported TPL imaging on BT549 cancer cells by wheat germ agglutinin-functionalized AuNSts for imaging.

The reconstituted images appeared white due to the emission of red, blue, and green channels by AuNSts [118].

Tracking of AuNPs needs some fluorescent label but the imaging and tracking of AuNSts are possible without the need of fluorophores due to their unique strong two-photon action cross sections (TPACS) [119]. Due to the high TPACS of nanostars, tracking the motion of PEGylated AuNSts in blood vessels is also possible. In medicine, novel techniques with high specificity, such as positron emission tomography, require probe labeling and offer low spatial resolution which can be obtained by AuNSts. Photoacoustic microscopy is an emerging imaging modality that combines both rich optical absorption and high ultrasonic resolution in a single-imaging modality [120], and it is based on the use of highly absorbance nanoparticles. It also provides in vivo functional imaging information at clinically relevant penetration depths. Recently, AuNSts have been effectively used as enhancing agents in photoacoustic imaging [121].

Nie and coworkers reported the three-dimensional image reconstruction using AuNSts [122]. The AuNSts conjugated with cyclic RGD (Arg-Gly-Asp) peptides and anticancer drug doxorubicin (DOX) were studied in different tumor cell lines, and in vivo imaging was done using S180 tumor-bearing mouse model cells (MDA-MB-231) [123]. The fluorescence images of Au-RGD-DOX after incubating with MDA-MB-231cells for 8 h were collected in order to understand the intracellular kinetics of the multifunctional nanoparticles. The obtained data clearly indicated that Au-RGD-DOX or released DOX entered the nucleus with only a small fraction remaining in the cytoplasm. The AuNSts with size less than 100 nm can accumulate selectively in tumors via the enhanced permeability and retention effect which is due to the increased leakiness of blood vasculature in tumors [124–126]. Combining this statement and their unique properties, AuNSts are considered to be suitable platforms for multimodal imaging for cancer diagnostics.

4. THERAPEUTIC AND DRUG DELIVERY APPLICATIONS OF GOLD NANOMATERIALS

From spheres to rods, different geometrical configurations of gold nanomaterials have been used as drug delivery agents. The tumor targeting ligands associated with AuNPs have shown improved tumor targeting and enhanced cellular uptake efficiency. In addition to delivering

chemotherapeutic agents successfully to the tumor site, PEGylated AuNPs with human transferrin exert photothermal therapy upon irradiation. Taghdisi *et al.* [124] reported a modified polyvalent aptamers–Daunorubicin-AuNPs complex which exhibited efficient drug loading, tumor targeting, and controllable delivery of anticancer drug to tumor cells. Marques *et al.* [127] reported the polymeric AuNPs as a potential carrier system for drug delivery. Surface modification of AuNPs by polymers plays a significant role in conjugating the therapeutic entities for drug delivery via ionic, covalent bonding, or by physical adsorption. The anticancer drugs can be loaded in AuNPs by adopting various methods. For instance, the drug can be either attached to the capping agent or loaded inside the AuNPs. The AuNCgs and AuNShs have higher drug loading efficiency due to the presence of hollow spaces. By utilizing these strategies, various therapeutic drugs have been successfully delivered using AuNCus and gold AuNShs. Many drugs including doxorubicin, paclitaxel, docetaxel, tamoxifen, oxaliplatin, and 3-mercaptopropionic acid have been successfully loaded in gold nanomaterials and used for anticancer therapy. Zhang *et al.* [128] reported the polymer encapsulated, doxorubicin-loaded AuNRs coupled the photothermal properties of AuNRs and the thermo and pH responsive properties of polymers. This nanocomposite provides an ideally versatile platform to simultaneously deliver heat and anticancer drugs in a laser-activation mechanism with facile control of the area, time, and dosage.

Iodice *et al.* [129] reported that poly (lactic acid-co-glycolic acid) (PLGA)-coated AuNPs exhibited direct cytotoxic effect on breast cancer cells (SUM-159) and in glioblastoma multiform cells (U87-MG). Betzer *et al.* [130] proposed a theranostic approach for the detection and therapy of head and neck cancer. Huang *et al.* [12] reported that plasmonic photothermal therapy acts as a promising cancer treatment and causes cell death, mainly via apoptosis and necrosis. The AuNRs displayed significant reduction in viability of breast, oral, and liver cancer cell lines. Yang *et al.* [131] reported that the chitosan-coated AuNRs tagged with siRNA (small interfering RNA) inhibited the oncogene expression in MDA-MB-231 triple-negative breast cancer cells, and moreover their anticancer efficacy was enhanced through NIR-mediated photothermal ablation. Zhong [132] reported FA-conjugated AuNRs were effectively used in photoacoustic therapy for selectively killing cancer cells within few seconds. Vo-Dinh *et al.* [78] reported photothermal ablation in SKBR3 cells by AuNSts. Zou *et al.* [75] synthesized dual-aptamer-modified AuNSts for photothermal therapy in prostate cancers. These studies have confirmed that

different types of gold nanomaterials act as promising materials for photothermal cancer application.

5. CONCLUSION AND PERSPECTIVES

On the whole, different types of gold nanomaterials including nanoparticles, nanorods, nanocages, nanostars, and nanoshells have shown multifunctional potential in tumor imaging, tumor targeting, and drug delivery and therapy. The synthesis of gold nanomaterials with tunable sizes and surface properties aims to reduce their toxicity, decrease their non-specific cellular uptake, and to increase their targeting efficiency. They are also used to improve the contrast in MRI and to enhance their load to target tumor cells in drug delivery. Their unique optical properties and their multifunctional potential to simultaneously diagnose and treat tumors enhance their reliability and versatility in the field of theranostics. The identification and synthesis of biocompatible cross-linking polymers will increase the stability and scope of gold nanomaterials in cancer treatment. The use of NIR rays and gold nanomaterials will be beneficial to target tumors that are located deep inside the body. To increase their half-life, stealth nanoparticles with improved characteristics have to be designed which will have prolonged circulation rates to facilitate the uptake of gold nanomaterials into cancer cells. The direction of future research regarding gold nanomaterials should focus on the need to overcome these hurdles and to develop novel therapies to provide solutions for the current problems. Promising clinical trials have given considerable hope that gold nanomaterials with improved characters help to develop safe and efficient tumor treatment/eradication methods in the near future.

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Note: Page numbers followed by "*f*" indicate figures, and "*t*" indicate tables.

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Cover image: Structural analysis of mesosomes formulated with 10 w% Dimodan U/J (an industrial source of monoglyceride) and stabilized by 0.5 w% F127 block copolymer. A) Size distribution curve obtained from light scattering experiments showing the formation of about 300 nm-sized droplets. B) A schematic representation of the droplet interface and a proposed molecular organisation demonstrating the co-existence of fluid lamellar and cubic phase. C) 3-D electron density map reconstructed from the small angle X-ray scattering data of empty cubosomes.

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