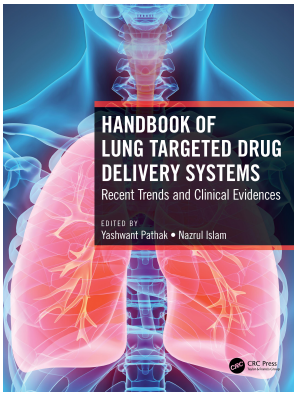

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Anti-cancer Activity of Eco-friendly Gold Nanoparticles against Lung and Liver Cancer Cells

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Anti-cancer Activity of Eco-friendly Gold Nanoparticles against Lung and Liver Cancer Cells

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33.1 Introduction

Cancer is a common term for a kind of genetic disease explained by unrestrained, irregular cell division and invasiveness. The expansion of cancer in the majority of cases resulted from mutations or changes in the expression prototypes of proto-oncogenes, tumor suppressor genes, and genes involved in deoxyribonucleic acid (DNA) repair. The disturbance of pro-apoptotic signaling along with overexpression of several proteins facilitates cell growth and supplementation impedes the expansion of resourceful anti-cancer treatment (1). Most cancers result from the effect of ecological factors, for example, vulnerability to radiation and pollutants, although most prominently, from an unhealthful standard of living, including not enough physical activity, unbalanced diet, tobacco smoke, and trauma. No more than 5–10% of cancer cases are related to hereditary genetics (2,3). The peril of cancer increases notably with age, and many types of this ailment arise increasingly in industrialized countries.

Among all the cancers, lung and liver cancers are the most widespread cancers in the world, and the main cause of cancer fatalities all over the world (4–6). Lung cancer could be categorized into two main subtypes: small cell lung carcinomas (SCLCs) and non small cell lung carcinomas (NSCLCs) as reported by the histological considerations (7,8). The fatality rate of both cancers is too high, and almost every patient dies within a year. The American Cancer Society anticipated that 69410 males and 62470 females would die of lung cancer, while 20300 males and 9930 females would die of liver cancer in the US in 2021 (9).

Contrary to other widespread solid cancers, lung cancer has no well-known techniques for early diagnosis, and the majority of cases are diagnosed at a progressive stage. It accounts for about 14% of all new cancers with a miserable 5-year survival rate of just 15%. On the other hand, most liver cancers are diagnosed during progressive stages, where an invasive strategy is the only therapy with a survival rate of 10–30% (10–12). Latest data indicate that lung cancer is to be expected to exceed breast cancer as the major cause of cancer death among European women by the middle of this decade (13). According to the category of melanoma and stage at the time of diagnosis, lung and liver cancer treatment frequently entails a combination of surgery, chemotherapy, and/or radiations (14–16). Although these techniques have been recognized and practiced in recent decades, they have their downsides and undesirable effects. Surgical retrieval of malignant growth is limited primarily to large, resectable, and easily reached tumors. A chemotherapeutic agent targets quickly dividing cells, and as a result not only destroys cancer cells but kills normal cells such as bone marrow cells as well as immune cells (17). This engenders widespread "collateral damage" in the patient's body. Radiation treatment uses high energy radiation like X-rays and gamma rays to eradicate tumor cells and unavoidably triggers deadly effects on healthy tissues along the radiation path (18).

Regardless of noteworthy progression in its treatment (chemotherapy, surgery, and radiotherapy), cancerous cell suppression remains inadequate, and the rate of survival has not improved to a large extent (12,19).

Taking into account the deficiencies of recent treatment modalities for cancer, a decisive thrust towards upgrading cancer rehabilitation is to explicitly target therapeutic agents to cancer cells while protecting frugal healthy tissues from damage. This is one of the promising focuses of nanotechnology research. Nanotechnology relates to the fabrication of substances having nanoscale dimensions between 1 and 100 nm (20). The smaller size of these nanomaterials empowers their individuality with chemical as well as physical properties that are distinctive from their bulk materials (21). These nanomaterials, attributable to their exclusive physicochemical properties as well as smaller size, have a higher surface to volume ratio, the possibility of surface modification, and discriminatory accessibility to tumor cells, and these novel metal nanoparticles have attracted much attention in the nano-oncology field (22–27). The quick growth in nanomaterials research raises the future perspective of novel diagnostic methods and treatment of diseases in human beings. This division of nanotechnology in the diagnosis of disease, monitoring, and therapy has been referred to as *nanomedicine* by the National Institutes of Health in the USA (20). Presently, cancer nanotechnology has come out as a novel area of medication with the aim to achieve progress in both cancer diagnosis and treatment (28,29). Among numerous nanomaterials

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being considered for nanomedicine applications, this chapter will mainly focus on biosynthesized gold nanoparticles for their anti-cancer activity against lung and liver cancer cells.

33.2 Gold Nanoparticles and Their General Properties

At the moment, there is growing attention to nanoparticles of noble metals (30). The consideration of scientists is mainly focused on gold nanoparticles, which have resourceful properties and potential applications in bioimaging, clinical chemistry, and treatment of cancer, in addition to targeted drug delivery persistently being exemplified.

Gold (Au) was one of the first metals found a few thousand years back. Gold in its purest form is a yellow, bright, dense, soft, and malleable metal, solid under ordinary conditions. It is one of the least reactive chemical substances. Since the beginning, gold was treasured because of its rare occurrence, ease of handling and production, and resistance to corrosion as well as other chemical properties, and, obviously, its inimitable color (31). Medicinal applications of gold and its complex form have a long track record, as well. The initial findings on colloidal gold (colloidal suspension of gold nanoparticles in a fluid) can be found in ancient Arabian, Chinese, and Indian papers from the 4th and 5th centuries BCE, which suggested it for the cure of different illnesses, even though the mechanism of action was not properly understood (32). The first research paper on gold nanoparticles was reported in 1857 by Faraday, which attributed the red color to the colloidal nature of gold nanoparticles and described their light scattering features.(33). After 50 years the visible absorption characteristics of gold nanoparticles were described with Maxwell's electromagnetic equations (33). In the year 1971, British investigators Faulk and Taylor designed an innovative technique of antibody–colloidal gold coupling for the direct electron microscopy imaging of surface antigens of Salmonellae (34). This innovation instigated numerous studies over the next 40 years, dedicated to biomedical applications of gold nanoparticles, particularly identifying different biomacromolecules as a result of the surface functionalization and the distinctive features. The latter are generally linked with controlled systems of production, permitting the acquirement of gold nanoparticles with definite sizes and shapes (35–38).

By virtue of much-optimized techniques for production, allowing the control of size and shape, as well as the dimension of gold nanoparticles, they can be specially developed to acquire specific characteristics. For the finding of features of these nanoparticles, interparticle interactions as well as an assemblage of gold nanoparticle networks have a crucial role (39). The size as well as the shape of gold nanoparticles has an insightful influence on their characteristics, affecting compatibility, mobility, stability, etc. (40–46), and needs to be optimized in respect of the specific biomedical applications. For example, nanoparticles fabricated for drug delivery need to be pretty small to cross physiological barriers or go into the target cells, and pretty big to convey an adequate quantity of therapeutic agents to the target site (47,48).

It is worth mentioning that physical and chemical features of materials in nanometer size are noticeably dissimilar than their analogs in larger forms. For gold, the greatest example of this attribute is the yellow color of the larger form of gold and the wine-red color of the gold nanoparticles which is reliant on their shape as well as characteristics (32). Moreover, colloidal gold, unlike bulk gold, is believed to be very reactive, which significantly expands its application perspectives, offering antioxidant, catalytic, and optoelectronic properties, as well as the potential of surface functionalization (32). Because of the smaller size and larger surface, shape, and crystallinity, nanoparticles have turned out to be outstanding therapeutic compounds as they can effortlessly deliver into the target cells and carry a higher drug load (49).

One essential physical attribute of gold nanoparticles is surface plasmon resonance (SPR). This definite miracle takes place when the frequency of the oscillation of free electrons at the exterior part of nanoparticles resonates with the frequency of the arriving light radiation, resulting in a plasmon band. Accordingly, an electromagnetic field emerges at the surface of gold nanoparticles, allowing surface-enhanced optical features. Gold nanoparticles offer absorption as well as scattering effects, the proportions of which are subject to the size and shape as well as the type of solvent, core charge, temperature, surface ligand, and the closeness of other nanoparticles (50,51), affecting the electron charge density on the surface of the particle. In sphere-shaped gold nanoparticles with sizes smaller than 60 nm, the SPR peak absorbance seems near 500–550 nm, creating their red color (52). An added fascinating effect contingent on the form of gold nanoparticles and linked with surface plasmon bands includes the intonation of fluorescence features of proximate fluorophores. This is attributable to the photoinduced electron transfer (PET) method, fluorescence resonance energy transfer (FRET) phenomenon (53–57), and photothermal characteristics, arising from the light absorption and succeeding nonradiative energy dissipation (58,59). As a consequence, modifying the shape of gold nanoparticles presents fascinating optical characteristics that span the broad visible to near-infrared (NIR) spectrum, converting them into excellent tools for bioimaging and theranostic applications (60,61), and permitting the controlling of morphological features of gold nanoparticles during manufacturing. Gold nanoparticles are extensively employed in biomedical science including for tissue or tumor imaging, photothermal therapy, drug delivery, and immunochromatographic detection of pathogens in clinical specimens, thanks to the SPR (62).

In short, the exploitation of gold nanoparticles is increasingly popular in these fields of research for numerous reasons. First of all, gold nanoparticles are believed to be biologically unreactive and so suitable for in vivo appliances when compared with the highly toxic cadmium as well as silver nanoparticles (63). Further beneficial qualities include the strong optical features of gold nanoparticles because of localized SPR (64), effortlessly controllable surface chemistry, which allows flexibility in addition to surface functional groups (65), and finally, the simplicity in control over particle size along with shape during production (66). Gold nanoparticles can be addressed to be completely multifunctional, with the likelihood

of combining diverse most-wanted functionalities in one molecular-sized package. All of these points promote a great deal of interest and priorities for the utilization of gold nanoparticles relative to other nanoparticles (67). Moreover, gold nanoparticles have proven to be outstanding therapeutic agents as well as drug transporters.

33.3 Surface Modification of Gold Nanoparticles

Surface modification of gold nanoparticles is one important aspect, together with their size and shape, which decides the fate of particles after administration. Surface functionalization has a marked impact on these two criteria, giving protection against aggregation, improved biocompatibility, specified interactions with cells, and targeted transportation and accumulation in preferred organs. They can exhibit an incredible effect on a gold nanoparticle's blood half-life, averting their elimination by the cells of the mononuclear phagocytic system (MPS), also called the reticulo-endothelial system (RES). Nanoparticles without modification following intravenous administration are sometimes speedily recognized and bound by opsonins in the blood, which permits their phagocytosis and elimination by macrophages. Surface functionalization has the ability to "mask" gold nanoparticles from RES, hence guaranteeing long blood circulation time and permitting them to reach the target site (68).

It must be noted that surface functionalization can alter the optical characteristics of gold nanoparticles (69); this should be taken into consideration while designing gold nanoparticles for a specified purpose, such as in radiofrequency or photothermal therapy.

Functionalization might be carried out either via physical adsorption or covalent linking of ligands on the surface of nanoparticles, generally with thiol linkages. Among the most widely utilized compounds for modification of nanogold is poly (ethylene glycol) (PEG), attached covalently with the surface atoms of gold particles. The PEGylation has been proved to improve the biocompatibility of different nanoparticles, extend their blood half-life (70,71), and avert elimination by RES, growing their hydrophilic nature (72,73). Sphere-shaped gold nanoparticles functionalized with PEG exhibited no cytotoxic effect against in vitro cultured human cell lines (74,75), as well as little take-up by RES, comparatively longer blood circulation time, and superior tumor accumulation during in vivo research on mice (76).

At the same time, different surface functionalization has been revealed to eliminate or reduce the cytotoxicity of gold nanoparticles, as a result enabling their risk-free administration into the living being with no detrimental side effects. An example of that comprises gold nanoparticles functionalized with folic acid (77), polyvinylpyrrolidone (PVP) (78), and polyacrylamide (79).

It's important to mention that the surface charge of nanoparticles has an incredible effect on their cytotoxicity. Particles with positive surface charges are generally more lethal, by reason of non-specific interactions with negatively charged cellular membranes (80). It was proved that cationic gold nanoparticles modified with quaternary amines were seven times more deadly to in vitro cultured cells than their anionic equivalents, achieved by the replacement of amine moiety with a carboxyl group (81).

Considering everything, surface functionalization of gold nanoparticles is meant to modify their biodistribution prototypes, allow targeted delivery, and make possible cellular internalization. Examples of that the exploit of folic acid (77), transferrin (82), carbohydrates (83,84), oligonucleotides (85), and specified antibodies (86–88), attached on the surface of nanoparticles. In addition, PEG molecules have been also employed as linkers for various targeting ligands, such as galactose (89) or tumor necrosis factor α (TNFα) (90,91). Though superficially inert changes may significantly affect the accumulation of nanogold in a variety of organs, which must be taken into consideration. For example, it is known that gold nanoparticles coated with gum arabic or maltose display diverse biodistribution patterns in blood, tissues, and urine. Specifically, the uppermost concentration of gold nanoparticles functionalized with gum arabic was accumulated in the liver, while those coated with maltose were found in the lungs (92). As a result, while designing modified nanogold for anti-cancer applications, it is important to consider not only the targeting features of surface moieties, but also their ability to direct the particles to different body regions.

33.4 Gold Nanoparticle-Mediated Drug Delivery

Targeted drug therapy can be a better choice than conventional drug therapy due to the fact that in a targeted drug delivery system, drugs directly target the site of action, reducing the side effects resulting from conventional drugs (93). Principle objectives of formulating anti-cancer agents are to diminish the different side effects resulting from conventional drugs and to get better efficiency as well as selectivity of drugs (94). Targeted drug delivery is the major field of attention for researchers in recent times, and lots of work has been done regarding manufactured systems for targeted drug delivery, for instance, nanoparticles, polymer gels, and quantum dots (95).

Gold nanoparticles have the aptitude of bio-imaging of the effected malignant cells for treatment (96). For impactful drug therapy, it is essential to explore the biological activities of the nanoparticles (62), as gold nanoparticles have distinctive physical as well as chemical features and have a binding attraction for aptamers (97), carboxylic acids (39), proteins, thiols (95), and disulfides; therefore, they have been widely employed in the biosciences, specifically in drug delivery for cancer treatment. Gold nanoparticles follow three major routes for cellular uptake: phagocytosis, receptor-mediated endocytosis, and fluid-phase endocytosis (98).

The toxic effect of gold nanoparticles is influenced by the size, shape, production method, surface coating, surface charge, and functionalized fragments, however, overall cytotoxicity of gold nanoparticles is tolerable as gold nanoparticles are believed to be nontoxic agents (99). For the resourceful drug delivery system, two factors are most important, and those are drug release and transport. Drugs are loaded on nanocarriers by means

of non-covalent bonds or covalent conjugation with pro-drug, which is treated by the cell. Gold nanoparticles have serviceable flexibility, attributable to their monolayers; as a result they give a well-organized system (100).

33.5 Advantages of Gold Nanoparticle-Mediated Drug Delivery

Gold nanoparticle-mediated drug delivery systems have numerous benefits relative to other nanocarriers as well as to conventional medicines. Gold nanoparticles have been extensively utilized as a cancer antigen and in cancer therapies (101). A few benefits are mentioned here: (i) gold nanoparticles have inimitable physical, chemical (102), and optical properties (49), because of their shape and size (103); (ii) gold nanoparticles have higher surface area (62) which enables compact loading of the drug; (iii) gold nanoparticles are biologically compatible (104) and are easily available for attachment with small biomolecules like amino acids, carboxylic acid, DNA, enzymes, and proteins (105); (iv) gold nanoparticles have well-controlled dispersibility (106); (v) as a result of smaller size and homogeneous dispersion they can effortlessly arrive at the targeted site with blood flow (107); (vi) gold nanoparticles are non-cytotoxic to normal cells (95); and (vii) gold nanoparticles are straightforwardly fabricated by different techniques (Figure 33.1) (108).

33.6 Methods for the Synthesis of Gold Nanoparticles

In most cases, the methods of formulation of gold nanoparticles are similar to those of other particles. There are basically two alternatives for the categorization of production methods. The first option is based upon the method of production (bottom-up or top-down) (109), and the second option comprises the methodology-based strategy (biological, chemical, and physical methods).

One of the leading and most popular chemical processes, developed by Turkevich and his team, involves the reduction of chloroauric acid ($HAuCl_4$) with trisodium citrate (plays an additional role of the ligand for newly fabricated gold nanoparticles) at 100 °C. This reaction allowed the acquirement of aqueous solutions of moderately monodisperse sphere-shaped nanoparticles with sizes ranging from 15 to 150 nm, according to the initial concentration of sodium citrate (110). This technique was the base for the progress of further ones, enabling the highly controlled fabrication of gold nanoparticles in water or organic liquids, exploiting different temperatures and pH values but also various reducing agents, similar to sodium borohydride ($NaBH_4$) (111–113), hydroquinone (114), or aspartate (115). The size of gold nanoparticles can be further stabilized with a variety of stabilizing agents, which also function to defend fabricated nanoparticles from aggregation and to manage their characteristics in a specific manner.

Although Turkevich-based techniques produce generally spherical gold nanoparticles, gold nanoparticles can be achieved in different shapes as well, such as rods (116), cages (117), and tubes (118). The most appropriate technique to manufacture different structures of gold nanoparticles is on the basis of seed-mediated growth (119), including the reduction of gold salts with a powerful reducing agent, which leads the fabrication of seed particles, which are afterward added to the solution containing metal salt in the presence of a structure-directing agent as well as a weak reducing agent. Gold nanostructure's geometric shape can be modified by changing the concentration of seeds, structure-directing agents, and reducing agents.

Moreover, physical techniques using microwaves (120), laser ablation (121), ultrasonic waves (122), and photochemical as well as electrochemical reduction (123,124) have been reviewed for fabricating gold nanoparticles. However,

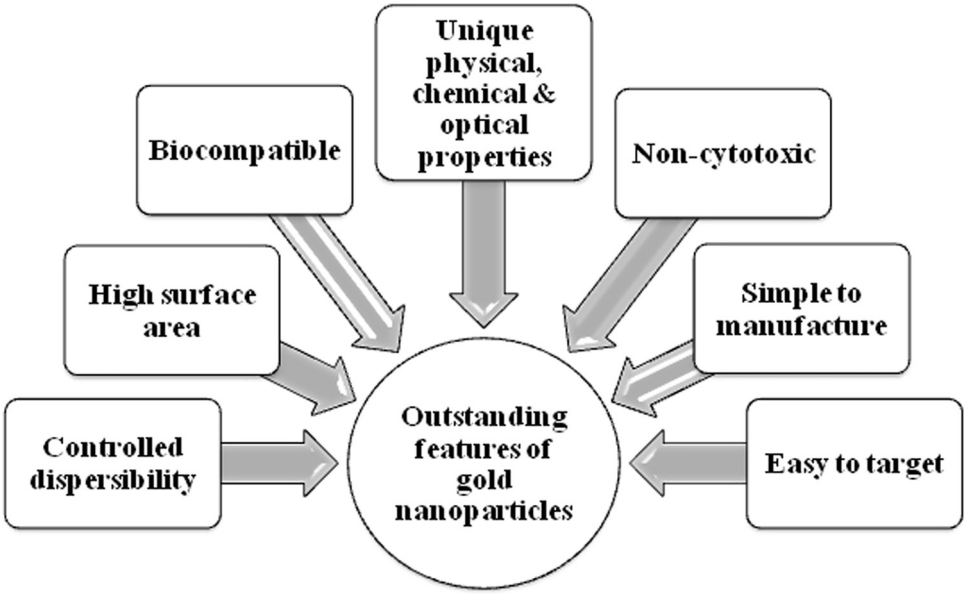

FIGURE 33.1 Outstanding Features of Gold Nanoparticles

seeing as different physical as well as chemical procedures prepared for the production of nanoparticles would be somewhat costly and detrimental to the environment, "green synthesis" techniques have grown to be the main attention of researchers with a view to elaborating an environment-friendly and non-hazardous means of gold nanoparticles fabrication (125). Numerous substrates and reducing compounds have been fruitfully implemented for the safe production of gold nanoparticles, including chitosan (126), extracts from citrus fruit juice (127), eggshell membrane (128), and edible mushrooms (129). In recent times, *Bacillus licheniformis* has been exploited for the fabrication of 10–100 nm gold nanocubes in much smoother conditions relative to classical chemical techniques (130), indicating the probability of the application of different bacterial strains for this process.

33.7 Clinical Applications of Gold Nanoparticles for Lung and Liver Cancer

Gold nanoparticles have distinctive electric and magnetic properties attributable to their size and shape. As a result they have received enormous consideration in research areas, principally in the fields of biological tagging, biomedical imaging, biological and chemical sensing, DNA labeling photothermal therapy (104), photoacoustic imaging and microscopy (131), catalysis, tracking and drug delivery (106), and cancer therapy (103). Gold nanoparticles have been extensively studied for lung as well as liver cancer therapy and diagnosis because of their astonishing and inimitable properties. The synthesized gold nanoparticles induce a dose-dependent inhibition activity against lung and liver cells. A number of the approved chemotherapeutic agents have induced side effects and high cost. For that reason, there is an important need to develop alternative medicines against this lethal ailment. Synthesized gold nanoparticles to fulfill the need for new therapeutic treatments were discovered and some of the potential applications of gold nanoparticles in lung and liver cancer discussed in this section.

Zeng and colleagues formulated gold nanoparticles from *Magnolia officinalis*, which is recognized as an eco-friendly and less toxic technique. The size of nanoparticles is recognized by dynamic light scattering analysis and it shows a value of 128 nm. Besides, energy dispersive X-ray analysis, high-resolution transmission electron microscopy, and atomic force microscopy describe the shape of the gold nanoparticles which are present in the complex materials. The anti-cancer efficiency of gold nanoparticles has been assessed in the human lung cancer cell line (A549). Gold nanoparticles successfully persuade apoptosis and cytotoxicity by intonating intrinsic apoptotic gene expressions in A549 cells. As a result, the gold nanoparticles produced from *Magnolia officinalis* show confirmation of anti-cancer effects (132).

The potential cytotoxicity of mannosylerythritol lipid-gold nanoparticles on human liver cancer cells (HepG2) was studied by the 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide, a tetrazole (MTT) assay using different concentrations (10, 25, 50, 75, 100, 125, and 150 μg/mL) exposed for 24 and 48 hours. The HepG2 cell population was progressively decreased with an increased mannosylerythritol lipid-gold nanoparticle concentration and treating time. Noticeably, mannosylerythritol lipid-gold nanoparticles established potential cytotoxicity on HepG2 cells, the IC50 values were 75 and 100 μg/mL for 24 and 48 hours, respectively. The highest concentration of mannosylerythritol lipid-gold nanoparticles has inhibited cell growth by about 89% (133).

The anti-cancer effects of gold nanoparticles with *Cordyceps militaris* extract against the hepatocellular carcinoma HepG2 cells was investigated by Ji and colleagues. Gold nanoparticle extract produces reactive oxygen species and induces damage to the mitochondrial membrane potential in the hepatocellular carcinoma HepG2 cells. The gold nanoparticle extracts have a tendency to begin the apoptosis by activating the Bax, Bid, and caspases, and inhibiting the activation of anti-apoptotic Bcl-2 in the HepG2 cells. These results established that the gold nanoparticles with *Cordyceps militaris* would be a capable chemotherapeutic drug against hepatocellular carcinoma cells (134).

Latha and colleagues produced bio-inspired gold nanoparticles using the leaf extract of *Justicia adhatoda* and evaluated the anti-cancer activity on A549 cells. The bio-synthesized gold nanoparticles were confirmed and characterized by using different spectral studies like UV-Vis spectrum, FTIR analysis, scanning electron microscope with EDAX, transmission electron microscope, and surface-enhanced Raman spectroscopy. The cell viability was verified by the MTT reduction assay. Additionally, cytomorphology and the nuclear morphological study of the A549 cell line were examined under a fluorescence microscope. UV-Vis spectrum verified SPR peak at 547 nm, transmission electron microscopy as well as scanning electron microscopy analysis demonstrated the monodispersed sphere shape, and its average size in the range of 40.1 nm was observed. Fascinatingly, the produced gold nanoparticles confirmed a potent anti-proliferation effect on the A549 lung cancer cell. Cell morphology was monitored and cell death has resulted from apoptosis as revealed by propidium iodide staining. This investigation confirms the anti-cancer potential of biosynthesized gold nanoparticles. So synthesized gold nanoparticles can be employed for the treatment of A549 cells and it can be exploited for drug delivery in the future (135).

Gold nanoparticles were manufactured using the cetyltrimethylammonium bromide technique and surface properties were enhanced with PVP. The PVP–gold nanoparticles were exploited as a flourishing carrier for doxorubicin delivery for the treatment of lung cancer. Researchers demonstrated the anti-cancer activity doxorubicin conjugated with PVP coated gold nanoparticles against A549, H460, and H520 lung cancer cells, and outcomes signified that doxorubicin gold nanoparticles efficiently inhibit the propagation of lung cancer cells and promotes p53 mediated mitochondria-dependent apoptosis. Furthermore, doxorubicin gold nanoparticles upregulate the expression of several tumor suppressor genes, proving the capacity of the potential anti-cancer agent in cancer therapy (136).

The steady bioactive gold nanoparticles were produced using *Marsilea quadrifolia* leaf extract. The photochemical found in the extract of *Marsilea quadrifolia* reduces the gold ions into metallic nanoparticles. The biogenic gold nanoparticles show

signs of a significant in vitro antioxidant activity and cytotoxicity effect against A549 cancer cells. These biogenic gold nanoparticles are estimated to serve as potent anti-cancer agents and so can be employed in biomedical appliances (137).

Investigators depicted a combination of chemotherapy and improved radiotherapy for in vitro management of lung cancer with gold nanoparticles stabilized by an apigenin-a bioactive gradient that has been explored for cancer treatments. Following interaction with lung cancer cells, the nanoparticles were able to stimulate cell apoptosis, inhibit cell proliferation, and capture cancer cells in G0/G1 phases in a dose-dependent manner. When a treatment combination of X-rays and gold nanoparticles was used, a synergistic anti-cancer effect was observed from chemotherapeutic functions of apigenin and the superior radiation killing effect generated by nanoparticles and X-ray interactions. This study might present a hopeful therapeutic approach for cancer treatment which puts together the benefits of both radiation and chemotherapy (138).

Guo and colleagues formulated PEG-coated gold nanoparticles of two different sizes, 14.4 and 30.5 nm, by a chemical reduction reaction and investigated the radiation enhancing effects in liver cancer cell lines. They investigated cellular uptake, blood stability, cytotoxicity, and radiation therapy. A 3–5 nm red shift of SPR caused by interactions between PEG-coated gold nanoparticles as well as plasma revealed their excellent stability. The in vitro bio-distribution assay indicated PEG-coated gold nanoparticles had high distribution in the cancer cells; almost 10^3 nanoparticles were observed in a single cell. The transmission electron microscopy direct observation demonstrated that PEG-coated gold nanoparticles hybridized with blood proteins constituted a 30–50 nm gold-protein corona. Gold nanoparticles were undergoing endocytosis by cytoplasmic vesicles, located in the intracellular area, and displayed concentration-dependent cell viability. Furthermore, these gold nanoparticles showed little toxicity at the concentration of 10^{-4} M. In vitro radiation therapy indicated that the gold nanoparticles appreciably enhanced the irradiation effect and diminished the endurance of two kinds of liver cancer cells. As a result, PEG-coated gold nanoparticles can be addressed as a prospective agent in liver cancer radiation therapy (139).

Indocyanine green loaded gold nanorod@liposome core-shell nanoparticles showed to be effectiveness in detecting tumor, and surgery guidance in orthotopic liver cancer mouse models by using photoacoustic and fluorescence dual-modality imaging probe. Researchers also investigated their efficacy for tumor detection as well as surgery guidance in orthotopic liver cancer mouse models by using a photoacoustic and fluorescence dual-modality imaging probe. This novel dual-modality nanoprobe gives hope for timely detection, enhances the surgical outcomes of liver cancer, and has immense potential for medical translation (140).

Gold nanoparticles linked with albumin as energetic vectors were utilized to focus liver cells for the development of an alive liver cancer model without any ethical obstacles to evaluate the discriminating features and counteractive capacity of these nanosystems in cancer patients. In order to achieve this goal, samples from cancerous patients were perfused out of the body (ex vivo). The albumin conjugated gold nanoparticles were administered intra-arterially into the model, and delivery of the nanoconjugate to the malignant tissue was established through capillary bedding. Their outcomes demonstrated that albumin conjugated gold nanoparticles build up through receptor-mediated endocytosis triggered to generate a laser-based therapeutic effect at the tumor site, but were not sufficient to have an effect on the healthy parenchyma tissue around it (141).

Aurolase®, made by Nanospectra, is silica-gold nanoshells coated with PEG and created to thermally clear the solid tumors following stimulation with a near infra-r-ed source of light. The absorption of light results in an increase in the local temperature, and it thermally destroys the solid tumors. AuroLase® particles were employed in localized therapy for the management of primary or metastatic lung tumors recently in the clinical trial (142).

The anti-cancer effect of gold nanoparticles against HepG-2 and A549 cell lines was investigated by Rajeshkumar. Results demonstrated that the good cytotoxic activity observed with gold nanoparticles against the cancer cells. The concentration of gold nanoparticles has a significant role in anti-cancer activity. The gold nanoparticles are having the good results against A549 in that 100 μg show fine results followed by 50, 25 and 1 μg. The lowest inhibitory action was observed form the concentration of 10 μg (143).

An in vitro and in vivo research study of gum arabic-conjugated gold nanoparticles and laser combination explained that this approach decreases cell viability as well as the activity of histone deacetylase in HepG2 cells. The findings stated that gum arabic-conjugated gold nanoparticles, with or without laser radiation, may cause apoptosis in cancer cells by activating death receptors (DR5), caspase-3, and in addition suppress pre-neoplastic lesions and primary markers (placental glutathione S-transferase). Moreover, gum arabic–conjugated gold nanoparticle stimulation with laser lessens tumor necrosis factor-α levels. That's why the gum arabic–conjugated gold nanoparticles in combination with laser stimulated the extrinsic pathway of apoptosis and repressed swelling that can stop liver pre-neoplastic lesions (144).

Serum albumin as a simple gold nanoparticle transporter was utilized to augment laser thermal extirpation of HepG2 cells, and therapeutic effects were demonstrated. To reveal the discriminatory internalization of serum albumin gold nanoparticles into HepG2 cells by focusing the Gp60 receptors, darkfield microscopy in addition to immunochemical staining was employed. Their outcomes explained that serum albumin gold nanoparticles resulted in an intracellular uptake rise in liver cancer cells by targeting Gp60 receptors selectively, and it was established that after laser irradiation, gold nanoparticle photoexcitation caused apoptosis by activating caspase-3 (145).

Fibronectin plays a vital role in the extracellular matrix structure and functioning of the normal cells, though, in circumstances like lung carcinoma, its manifestation augments, particularly in NSCLCs. In the present study, researchers linked gold nanoparticles to the human fibronectin antibody (anti-hFN) to form a colorimetric nano biosensor for detecting fibronectin present in the extracellular matrix of cultured cells. For comparison of alterations in color caused by aggregation of gold nanoparticles because of an elevated quantity of fibronectin, three different cell lines, specifically A549 (target cells), AGO-1522 (control cells), and Nalm-6 (negative control cells) were

utilized. Their construct was capable of sensing an augmented level of fibronectin, which was identifiable visually by alteration in color and might be established by spectrophotometer, as well (146).

Research in 2014 confirmed that gold nanoparticles fabricated with *Cajanus cajan* phytochemical [3-butoxy-2-hydroxypropyl 2-(2,4-dihydroxyphenyl) acetate] have an ability to provoke apoptosis in liver cancer HepG2 cells (147).

In one more study, a hybrid system made up of gold nanoparticles and the liposomes was exploited to assess the efficacy of paclitaxel in liver cancer treatment. Achieve this goal, two drug delivery systems were analyzed, one by the hybrid system and the other by gold nanoparticles devoid of liposomes. The outcomes of this research confirmed the effectiveness of the hybrid system to be superior to the gold nanoparticles without liposomes in three characteristics of stability, solubility, as well as targeting of liver cells (148). As it was stated, surface modification is imperative to transform a few nanomaterials' distinctiveness. The glycol chitosan layered gold nanoparticles demonstrated a tumor-targeting computed tomography contrast agent in the malignant liver cancer model (149).

The epidermal growth factor receptor (EGFR) is a particular hot topic in cancer therapy, and it can be exclusively targeted with the monoclonal antibody, cetuximab. Cetuximab obstructs signal transduction by coupling to the external arena of EGFR, blocking ligand binding (150–152). In addition to colorectal cancer and head and neck cancer, NSCLC is the third main cancer class for which cetuximab has been assessed. Cetuximab was exploited for the management of EGFR-expressing NSCLC in phase II and III trials, principally in combination with radiotherapy or chemotherapy. Nevertheless, the curative effect of cetuximab in EGFR high-expressing NSCLC is still unsatisfactory. In the present research, investigators stated that the linkage of cetuximab with gold nanoparticles augments the cytotoxicity of cetuximab in NSCLC both in vitro and in vivo. The NSCLC cell lines A549 ($EGFR^{high}$) and H1299 ($EGFR^{low}$) were utilized to explore diverse responses to cetuximab, IgG–gold nanoparticles, and cetuximab–gold nanoparticles. The anti-tumor properties of cetuximab–gold nanoparticles were investigated in vivo by setting up a tumor xenograft model in nude mice. In general, the therapeutic effect of cetuximab–gold nanoparticles was greater in $EGFR^{high}$ A549 cells in comparison to $EGFR^{low}$ H1299 cells. The cytotoxic effect of cetuximab–gold nanoparticles in A549 cells was raised dose-dependently. Cetuximab–gold nanoparticles notably restrained A549 cell propagation and relocation capability, and sped up apoptosis relative to cetuximab, and this effect was most likely attributable to superior EGFR endocytosis and the successive repression of the downstream signaling pathway. Conclusively in the tumor xenograft of nude mice, treatment with cetuximab–gold nanoparticles also resulted in a noteworthy diminution in tumor weight and volume with little toxicity. Their results indicate that a cetuximab–gold nanoparticles conjugate has a hopeful prospect for targeted therapy of EGFR positive NSCLC patients (153).

In recent times, Barash and colleagues recommended a nanodevice rooted in gold nanoparticle sensors that categorize the lung cancer histology by identifying the lung cancer–specific prototypes of volatile organic compound profiles. It aims to distinguish between healthy and lung cancer cells, SCLCs and NSCLCs, and subtypes of NSCLS (154).

There are three common tumor markers of liver cancer, namely alpha-fetoprotein, alpha-fetoprotein variants, and abnormal prothrombin, recognized with three electrochemical redox species with individual voltammetric peaks. In the present research, the electrochemical signals were concurrently attained at different peak potentials, and gold nanoparticle–coated carbon nanotubes were exploited to get better signal response (155). Microorganism-assisted fabricated gold nanoparticles were utilized to explore liver cancer cells by combining them with liver cancer cell surface-specific antibodies. An investigation confirmed that the antibody-conjugated gold nanoparticles attached explicitly to the surface antigens of the cancer cells could productively distinguish normal cell populations from cancerous cells (156).

Arvizo and colleagues coupled the dendrimer-entrapped gold nanoparticles to anti-EGFR antibodies and particularly targeted overexpressed EGFR in NSCLC-type lung cancer cells and facilitated early lung cancer detection (157).

An electrochemical-based immune sensor method has been established to quantitatively test human lung cancer-linked antigens utilizing an (alpha-enolase) ENO1 antibody combined with gold nanoparticles for lung cancer identification (158). In the same way, based on electrochemical and contact angle measurements, a highly susceptible and fast technique has been established for the identification of different cancer cells, including lung and liver cancer (159). Furthermore, Medley and his research team employed the gold nanoparticle–conjugated aptamer for the calorimetric assay for the direct detection of lung cancer cells (160).

The majority of the traditional diagnostic strategies for lung cancer are costly and imprecise. Therefore a novel method has been established for the detection of lung cancer from an exhaled breath sample utilizing an array of sensors anchored in gold nanoparticles. The constitution of volatile organic compounds in exhaled breath is diverse in healthy human beings in comparison to lung cancer patients. Around 42 volatile organic compounds have been discovered, which are employed as lung cancer biomarkers (161). In a similar manner, hollow gold nanospheres have been exploited to fabricate a very susceptible and fast immunoassay system for lung cancer identification which is 100–1000 times more responsive than enzyme-linked immunosorbent assay having a limit of detection 1–10 pg/mL. This surface-enhanced Raman scattering-based immunoassay system makes use of the hollow gold nanospheres for the immunoanalysis of lung cancer markers and carcinoembryonic antigens, whereas magnetic beads are utilized as an immunocomplex-supporting substrate (162). In addition, gold nanoparticles in combination with methotrexate, an analog of folic acid, also generated a cytotoxic effect in Lewis lung carcinoma (163).

Finally, gold nanoparticles delivery systems have shown hopeful outcomes in lung and liver cancer therapy because of their unique features. Together with a growing understanding based on the characteristics and effects of gold nanoparticles, they are at present potential tools for lung and liver cancer therapy.

33.8 Conclusion

Attributable to the swift expansion of nanotechnology over the last several decades, a wide range of particles of different shapes, sizes, and structures are currently available to investigators. Because of distinctive physicochemical and biological properties, gold nanoparticles are of particularly interest in medical appliances, especially for anti-cancer treatment. A great variety of promising production techniques allow for getting gold nanoparticles with definite architecture and characteristics, according to the intended use. Furthermore, their reactivity makes possible further functionalization and modification, additionally enhancing bioavailability and expanding the scope of medical appliances of gold nanoparticles. Plentiful and varied physicochemical properties of gold nanoparticles highlighted in this chapter, differentiating them from other nanoparticles, give us hope for their use, particularly with regard to drug delivery devices and imaging techniques. Gold nanoparticles are employed as sensitive probes in the detection as well as imaging of tumors for diagnostic purposes, delivery agents for the precise targeting of chemotherapeutic medicines to cancer cells, and enhancing agents in plasmonic photothermal therapy and radiation therapy for the eradication of lung and liver cancer cells. Functionalized gold nanoparticles with a variety of biomolecules for example amino acids, carboxylic acids, and proteins, have been employed in cancer treatment and present an outstanding drug delivery system. In the case of lung and liver cancer, there are abundant studies into the utilization of gold nanoparticles. Gold nanoparticle delivery systems have shown hopeful outcomes in lung and liver cancer therapy because of their high surface loading ability of drugs. This inspires hope for the progress of innovative cancer treatment methods, providing an excellent substitute for the most frequently used chemotherapeutics.

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