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Review article

Gold nanoparticles in radiation therapy: an old story yet mesmerizing

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Abstract

Radiotherapy (RT) is generally considered to be one of the most effective cancer treatments. The primary goal of RT is to accurately induce radiation damage to the tumor while limiting radiation toxicity to a level acceptable to normal tissue. This is accomplished by targeting the tumor with radiation. On the other hand, the status of RT procedures as they stand today is not substantial enough to eliminate advanced metastatic and radio-resistant hypoxic tumors. Radiologists and medical physicists all face the same fundamental challenge of improving treatment efficacy while minimizing damage to surrounding healthy tissue. Through a process called radio-sensitization, tumor cells become more sensitive to the damaging effects of radiation. Therefore, radiosensitizers are compounds that are either medicinal or inactive and boost the efficacy of radiation treatment. In the last few years, there has been a surge of interest in the use of formulations to enhance the effectiveness of radiotherapy, especially when employing metallic, primarily gold-based nanoparticles. The aim of combining NPs with radiation therapy is to enhance the differential effect of treatment between normal and malignant cells. Gold nanoparticles (AuNPs) have been the most widely investigated nanoplatforms for use in radiation therapy due to their high X-ray absorption rate and synthetic modifiability, which allows precise control over the physical properties of the particles. We only highlight the radio-sensitization characteristics of gold nanoparticles in cancer treatment in the current review article.

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1. Introduction

Over 50% of cancer patients are believed to undergo radiotherapy (RT) with the intention of curing or managing their condition [1]. Ionizing radiation is the basis of RT. This radiation either directly interacts with DNA as a key cellular target or tangentially interacts with DNA by causing radiolysis of water and generation of free radicals, both of which lead to cellular damage [2]. The ultimate purpose of RT is to delicately deliver radiation damage to tumors while limiting its toxicity to a level tolerable to normal tissues. For this purpose, marked progress has been made in the development of RT, with a focus on cutting-edge technology, providing state-of-the-art radiation delivery tools, such as intensity-modulated radiotherapy (IMRT), stereotactic radiotherapy (SRT) systems, and tomotherapy machines with imaging guidance. Nevertheless, radiotherapy methods are

currently not sufficient to eradicate advanced, radio-resistant, hypoxic tumors. Radiosensitizers can be incorporated into the tumor to increase the efficiency of RT, which is an essential requirement. This may increase tumor sensitivity to radiation, leading to more specific radiation-induced damage and better RT outcomes. Increasing the effectiveness of treatment without causing damage to surrounding healthy tissues is the main task of oncologists, medical scientists, and radiobiologists. The term "radio-sensitization" refers to the process of making malignant cells more vulnerable to radiation damage. For this purpose, radiosensitizers are pharmaceutical or inactive substances that increase the effectiveness of radiation therapy. In order to further differentiate between normal and malignant cells, the combination of NPs with radiation therapy has been considered. The use of formulations, especially those containing metal-based nanoparticles (mainly gold), to improve the efficacy of radiation therapy has increased dramatically in recent years [3].

2. Gold nanoparticles

The scientific community has paid much attention to AuNPs in recent years. The detection and medicinal potential of AuNPs have been widely investigated due to their distinct physical and molecular properties [4-6]. In particular, gold nanoparticles (AuNPs) have gained in popularity due to their many desirable properties, such as their high biocompatibility, their simple synthesis in a wide range of sizes, and their simple surface functionalization through the attachment of ligands necessary to target cancer cells, and organelles therein, or their extended blood circulation time. The enhanced permeability and retention (EPR) effect, caused by tumor vascular leakage and inefficient lymphatic drainage, allows the preferential accumulation and retention of AuNPs at the tumor site [7]. Furthermore, proteins, peptides, polyclonal antibodies, and small compounds can be readily attached to the surface of AuNPs to prevent non-specific absorption and enable tumor-specific targeting [8-11]. AuNPs are widely used as nanocarriers for drug delivery due to their bioinertness, high surface area/volume ratio, and adaptable surface chemistry [12]. Gold nanoparticles (AuNPs) have been the most widely investigated nanoplatforms for use in radiation therapy due to their high X-ray absorption rate and synthetic modifiability, which allows precise control over the physical properties of the particles. Gold nanoparticles have not only been investigated for their potential use in radiotherapy as a radio-sensitizing agent but also in radiofrequency hyperthermia (RFHT), photothermal therapy (PTT), magnetic hyperthermia (MHT), ultrasound hyperthermia (USHT), selective DNA synthesis (SDS), and photodynamic therapy (PDT) [13]. In this study, we specifically focus on the role of gold nanoparticles in radio-sensitizing cancer therapies.

3. Mechanisms of radio-sensitization

3.1. Physical enhancement

Due to their increased X-ray absorption cross-section, high-atomic-number AuNPs are ideal candidates for use as efficient radiosensitizers to boost RT (14). Initially, Hainfeld et al. utilized this radio-sensitization ability for cancer treatment. Mice with a subcutaneous breast tumor were injected with 1.9 nm AuNPs (2.7 g Au/kg) and then exposed to X-rays at 20 kVp (30 Gy). The authors reported a significant increase in 1-year survival from 20% with RT alone to 86% with RT + AuNPs, which is promising for further study development in AuNPs-based radiosensitivity (15). The Compton effect and the photoelectric effect are the primary mechanisms by which electrons engage with the matter in the physical phase, which lasts only a few nanoseconds and happens at kV levels. The photoelectric effect involves the release of an inner shell electron after receiving an incident photon by an electron bound to an atom. In the process of filling the empty space, the outer shell electrons emit higher energy photons (fluorescence) and a chain of secondary electrons (Auger electrons) (14). The photoelectric absorption cross-section, which is the main radiation interaction in the kilovolt energy range, is proportional to the square of the atomic number (Z4) and is larger for elements with higher atomic numbers (Z) (16). Since the binding energies of inner-shell electrons in soft tissue are typically on the order of 1 keV or less, and since the average atomic number of organic materials is much lower, the photoelectric effect contributes only a minor amount to the absorption in soft tissue, whereas it is the primary factor in gold ionization events with energies up to hundreds of keV (17). Thus, materials with high Z have a greater tendency to emit secondary radiation (e.g., Auger/photoelectrons), leading to increased generation of free radicals, which in turn cause protein damage and apoptosis/necrosis (18-21). Furthermore,

the environment may capture these electrons, leading to ionization and radical production [22]. At high radiation energy (megavoltage, MV) of therapeutic use, where the Compton effect is common, radiosensitivity by AuNPs has also been demonstrated [17]. When an incident photon collides with an electron that is only loosely bound to it, this phenomenon is known as the Compton effect. Here the photon transfers some of its energy to the electron and causes the electron to leave the molecule [23]. The interaction cross-section between AuNPs and X-ray and ion energy is substantial, up to about 1MeV. In order to demonstrate the radio-sensitizing potential of AuNPs, Zhang et al. used Monte Carlo simulations and found that the radiation beam leaves a reduced dose after passing through the AuNP-containing region, thereby improving the treatment ratio [24].

Experiments demonstrate a radio-sensitization impact despite the much smaller contact cross section at these energies [22]. McMahon et al. [25] demonstrated analytically that the interaction of NPs with secondary species created by the ionization of the water medium, rather than with the radiation itself, is what causes the radio-sensitization observed with photons at these frequencies. Studies using recombinant DNA have demonstrated the physical effects of AuNP radiosensitivity, allowing the assessment of radiation-induced DNA damage at the molecular level in the absence of cellular responses to radiation. This research showed that the energy emitted by AuNPs has a molecular character and that low-energy electrons (LEEs) are essential for the ability of AuNPs to increase the dose. By analyzing the distribution of electrons released from 3 nm AuNPs incorporated into DNA after exposure to 100 kV X-rays, Carter et al. were able to show that the majority of DNA damage was caused by LEE (b 100 eV) with an effective range of 1-10 nm [26]. According to experimental results from plasmid DNA research, secondary LEEs produced by AuNPs cause concentrated energy accumulation close to the nanoparticle, which causes radio-sensitization.

3.2. Chemical enhancement

By participating in radical processes that repair the damage or by breaking DNA bonds, AuNPs play a role in the molecular phase of radiation exposure. Chemical sensitivity of DNA to IR-induced damage and increased radical production and catalysis through the energetic surface of AuNPs are two proposed mechanisms of chemical enhancement depending on the cellular location of AuNPs. While both of these mechanisms have the potential to lead to increased radiosensitivity, the first mechanism requires nuclear localization of AuNPs to enable DNA binding. Photoelectrons and Auger electrons emitted by AuNPs and fluorescent X-rays induce secondary radio-dissociation of water via charge transfer, leading to greater generation of reactive oxygen species (ROS). The superoxides produced by X-ray bombardment were shown to excite the surface atoms of AuNPs, thereby chemically enhancing the radiation effect, as shown by Cheng et al. [27]. Upon bombardment with 100 kV/s X-rays, Misawa et al. found that the concentrations of hydroxyl radicals (•OH) and superoxide anions (O_2^-) in water treated with AuNPs increased by 1.46 and 7.68 folds, respectively [2]. Due to their small size and high curvature, AuNPs disrupt the highly ordered crystalline structure of the gold bulk, which is thought to be responsible for their distinct catalytic properties. The reactive AuNP surface generates radicals due to the change in the electrical arrangement of surface atoms [28].

Notably, cells exposed to 90 kVp and 6 MV X-rays showed radiation-induced ROS production when treated with glucose-coated AuNPs, indicating that AuNP-induced oxidative stress is a practical method for radio-sensitization [29]. Research shows that AuNPs chemically enhance the effects of radiation by stimulating radical reactions and increasing the generation of ROS.

3.3. Biological enhancement

As the initial studies using MV radiations, a growing number of theoretical modeling[30, 31] in-vitro [32-35] and in-vivo [36, 37] studies have exhibited radio-sensitization at the clinically relevant MV energies. In addition to the physical mode of action, the differences between theoretical predictions and experimental data raise the possibility of biological enhancement. Moreover, laboratory data confirmed the function of biological improvement by demonstrating that AuNPs sensitize cells to bleomycin (SER = 1.38), a redox-active substance that causes cell death via oxidative stress and DNA damage. Based on available research, radiosensitivity is thought to occur through three major biological pathways: (1) cell cycle disruption, 2) oxidative stress, and (3) suppression of DNA repair.

Radiolysis of water generates free radicals and reactive oxygen species, which combine with

different biological components and destroy cells [38]. Reactive oxygen species (ROS), such as hydrogen peroxide, superoxide radicals (O2-), and hydroxyl radicals (•OH), all of which can damage cells either by causing oxidative stress and cell death (necrosis or apoptosis) or by reacting with biological molecules. Several studies confirm AuNP surface-mediated ROS production, which induces oxidative stress. Pan et al. found that 1.4 nm AuNPs capped with triphenylphosphine mono sulfonate (Au1.4MS) increased ROS production and mitochondrial potential, leading to necrotic cell death [39]. After 24 h of exposure to 2.7 mm tiopronin-coated AuNPs, Cui et al. reported similar observations involving a significant increase in intracellular ROS levels leading to necrosis in HeLa and L929 (fibroblast) cells. This necrosis was observed in HeLa and L929 cells [28]. It is not well known how precisely AuNPs cause reactive responses to stress. However, it is thought to arise primarily through disruption in mitochondrial activity as a result of increased cytoplasmic ROS. According to the research of Wahab et al., 10-15 nm AuNP citrate caused a dose-dependent increase in intracellular ROS levels, which was subsequently associated with up-regulation of caspase 3 and 7, ultimately leading to death through mitochondrial dysfunction [40]. As a result, mitochondria are yet another possible target because disturbance of their membrane potential can result in death. It has been discovered that AuNPs alter the potential of the mitochondrial membrane and also lead to the breakdown of the cardiolipin protein present in the mitochondrial membrane. Increased radical production encouraged by the nanoparticles themselves may be the source of membrane potential depolarization, and cardiolipin oxidation leads to the release of cytochrome c. Both mechanisms have the potential to induce apoptosis, which increases radiosensitivity [41, 42]. Several lines of evidence indicated that AuNP-induced oxidative stress might also result from the suppression of proteins essential for maintaining cellular oxygen homeostasis. In cells treated with tridecapeptide-linked Au25 clusters (Au25peptide9), Liu et al. showed that ROS levels were increased due to suppression of thioredoxin reductase 1 (TrxR1) activity [43]. Depending on the concentration used, Au25peptide9 binds more or less to the glutamic acid-rich region of TrxR1, inhibiting its function and leading to increased levels of intracellular reactive oxygen species (ROS) and subsequent cell death. This new avenue of AuNP-induced oxidative stress necessitates additional research. The capacity of tumor cells to self-repair DNA damage and their position in the cell cycle both play a role in response to γ- or X-rays. Cancer cells treated with Au-based nanoparticles undergo cell cycle resynchronization, and the G0/G1 phase is shortened, and the radiation-sensitive G2/M phase is prolonged [35, 44-46].

Some studies have shown that AuNPs affect cell cycle progression, but others have found no effect [22, 39, 47]. The impacts of 1.9 nm AuNPs (AuroVistTM), for example, were found to vary depending on the cell type tested. While MDA-MB-231 cells did not show any signs of death after being exposed to AuNPs for 48 hours, DU-145 cells underwent apoptosis [48]. Pan et al.[39], found that 1.4 nm triphenyl mono sulfonate-AuNPs had no cell cycle effects, and Cui et al. [47] found that 2.7 nm tiopronin-AuNPs had no cell cycle effects. Thus, additional research is required to completely understand the impacts of nanoparticle characteristics on cell cycle disruptions. Using the γ-H2AX focal assay, which detects one of the early events after double-strand break (DSB) formation, researchers have found evidence that suppression of DNA repair may be a molecular process of radio-sensitization by AuNPs [45]. Incubation of HeLa cells with 50 nm citrate-AuNPs for 4 and 24 hours after irradiation with 220 kVp and 6 MV increased the number of γ-H2AX and 53BP1 foci, according to research by Chithrani et al. Based on these results, it was suggested that a critical mechanism of radio-sensitization is the increase of residual damage in the presence of nanoparticles, indicating a delay in DNA repair [49]. Cui et al. found that cells exposed

to 250 kVp X-rays in the presence of 2.7 nm tiopronin-AuNPs had significantly higher levels of persistent DNA damage 24 hours after irradiation compared to controls, despite there being no change in the initial levels of DNA DSB 30 minutes following the irradiation process [40]. Chen et al. found that BSA-capped AuNPs enhanced radiation-induced damage, resulting in a 2.02- and 1.95-fold rise in γ-H2AX foci at 2 and 4 h post-irradiation, respectively. However, after 4–24 h of incubation, there was no change in DNA double-strand break (DSB), implying that AuNP had no effect on the DNA damage repair mechanism [50]. A definitive answer as to whether or not AuNPs play a role in inhibiting DNA repair has yet to be established in the literature, where conflicting reports abound. This requires further research on the precise function of AuNPs in different DNA repair pathways, as well as the impact of particle properties (e.g., morphology, size, surface chemistry), treatment conditions, biological nature (e.g., cell line), and radiation indices (e.g., radiation source, dose rate parameters, energy, and dosage) in response to radiation-induced DNA damage. Radio-sensitization mechanisms of AuNPs on cells are briefly demonstrated in **Figure 1.**

4. Morphology, size, surface coating, and functionalization of AuNPs

Biomedical applications have led to the development and use of a wide range of gold nanoparticles, including nanorods, nanospheres, nanocages, nanoshells, and nanostars. Also, these nano-sized particles have various charges and surface coatings such as DNA, polyethylene glycol, amino acids, peptide, and protein, and also they are synthesized in different polarities, including hydrophilic, hydrophobic, and amphiphilic. Numerous important factors, such as the morphology, surface chemistry, size, and concentration of Au nanoparticles, as well as the ionizing radiation and cell type, affected the radiation amplification effect caused by Au nanomaterials. AuNPs in the range of 1–150 nm with diverse morphologies can be easily obtained through shape and size control and exhibit distinct electrical, chemical, and optical properties [7, 11, 12]. In addition, the efficiency with which the cells engulf gold nanoparticles is crucial in triggering the radiation enhancement effect. Cancer cells with higher concentrations of internalized nanoparticles are thought to produce more ROS and increase the level of DNA damage. The uptake of gold nanoparticles of different sizes and shapes by cells has been the subject of a number of studies. For example, previous research has shown that the physical dimensions of spherical gold nanoparticles have a significant effect on their ability to be engulfed by cells. In one study, cells internalized 50 nm nanoparticles at a significantly higher rate than 14.74 nm nanoparticles with 220 kV X-ray beam (the corresponding DEFs for these three groups were 1.43, 1.2, and 1.25, respectively) [49, 51]. Similarly, spherical Au nanoparticles have been found to be more easily internalized by cells than rod- or star-shaped counterparts of the same dimensions [51]. In a similar manner, it has been observed that spherical gold nanoparticles have a greater rate of cellular internalization compared to the rod- or star-shaped gold nanoparticles of a comparable dimension [52]. Another research found that 12.1 and 27.3 nm PEG-coated gold nanoparticles have higher radio-sensitization effects than 4.8 and 46.6 nm counterparts in in-vitro and in-vivo experiments [53]. In order to improve CT imaging and radiosensitivity, Duo et al. discovered that PEGylated AuNPs with an optimal diameter of 13 nm could be used as X-ray theranostic agents [54]. The impact of Au nanoparticles on radiation effectiveness has been studied from a variety of angles, including their size, morphology, and surface coating. For instance, next-generation sensitizers for cancer radiotherapeutic impact have been developed using ultra-small, glutathione-protected gold nanoclusters with high tumor uptake [55, 56]. Only a few comparative studies have addressed how different forms of gold-based nanoparticles affect their biochemical effects in cancer. In a study conducted by Ma et al., they developed gold nano-spikes (GNSs), spherical gold nanoparticles (GNPs), and gold nanorods (GNRs) and functionalized them with polyethylene glycol. These Au nanomaterials had various forms but comparable average sizes (about 50 nm). Their comparative experiments showed that, more or less, with X-ray bombardment, all of these PEGylated gold nanoparticles could increase the death rate of cancer cells. Multiple single-target models obtained sensitivity enhancement ratios (SERs) of 1.62, 1.37, and 1.21 for GNPs, GNSs, and GNRs, respectively, indicating that GNPs are more effective in fighting cancer after X-ray bombardment [57]. Therefore, gold-based nanoparticles with high cellular uptake are needed to produce a

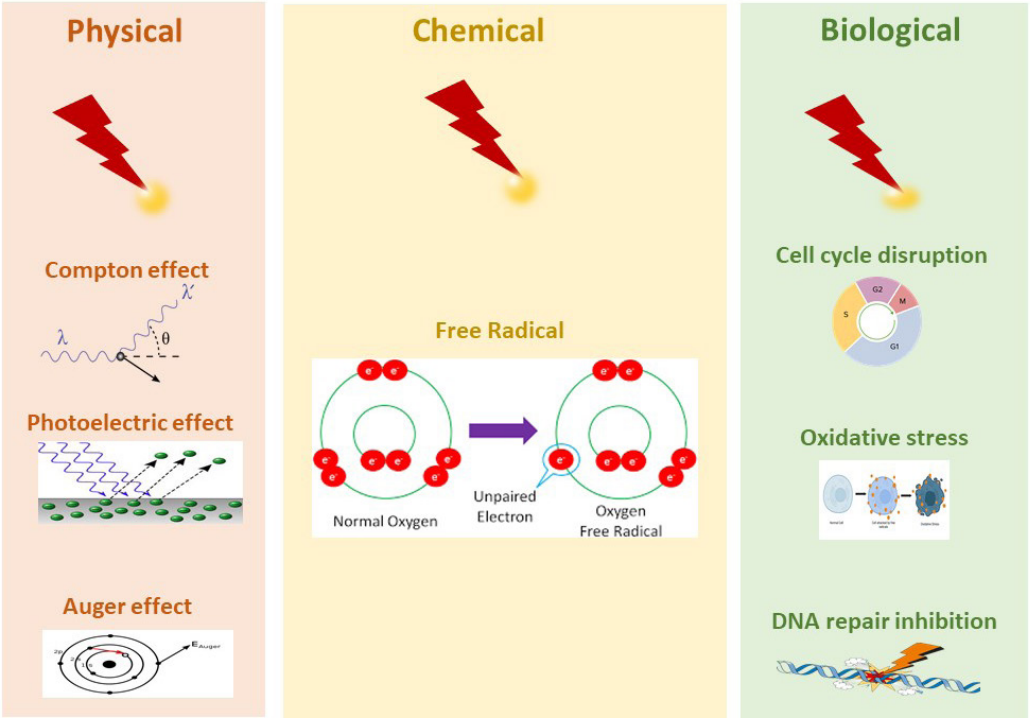

Figure 1. Radio-sensitization mechanisms of AuNPs on tumor cells

powerful radio-sensitizing effect in cancer radiation. Small AuNPs have been found to be more catalytically active than larger particles, leading to the generation of more ROS and increased mortality [19, 58, 59] .

4.1. In-vitro and in-vivo studies

There has been exponential growth in the field of AuNP radiosensitivity since 2004 when Heinfeld et al. provided the first experimental proof of the effects of increasing the radiation dose of AuNPs in-vivo [15]. In this research, the combination of 1.9 nm AuNPs and 30 Gy irradiation (250 kVp X-rays) dramatically increased the one-year survival of mice with subcutaneous EMT-6 breast cancer from 20% with X-rays alone to 50% with 1.35 g Au/kg, and further to 86% with a greater dosage of AuNPs (2.7 g Au/kg). Since this groundbreaking research, numerous studies have shown that AuNPs can successfully expose cells to kilovolt (kV) and megavolt (MV) radiation both in-vitro **(Table 1)** and in vivo **(Table 2).**

4.2. Clinical applications

The field of AuNP-based radio-sensitization has grown significantly as a consequence of multidisciplinary study that includes radiation biology, physics, formulation sciences, and chemistry. Despite numerous advances in discovering new nanoparticle formulations for preclinical research, their translation into clinics has faced challenges. To date, two forms of gold nanoparticles have been tested against some types of cancer. CYT-6091 (NCT00356980, NCT00436410) is composed of PEGylated colloidal AuNPs used for the delivery of the recombinant human tumor necrosis factor-alpha (rhTNF) against lung cancer. In addition, silica Core-Au shell nanoparticles (AuroShell®) have been examined for photothermal ablation against head and neck carcinoma (NCT01679470). Phase I clinical trials of CYT-6091 showed that gold was delivered to tumors, and there were no major dose-limiting side effects [70]. For the treatment of non-small cell lung cancer, Phase II clinical trials are being accomplished with CYT-6091 along with the standard of care second-line therapy. These findings provide encouraging evidence for the possible therapeutic compatibility of AuNPs. However, the clinical evaluation of AuNPs for radiosensitizing applications has not yet been investigated. One of the obstacles to the practical application of AuNPs for RT is the lack of in-vivo evidence of their radiotherapeutic effect.

Table 1. Example of in vitro experimental results

Nanoparticles	Tumor cell lines	Radiation	Sensitizer enhancement ratio (SER)	Mechanism of radiosensitizing	References
Gold Nanoparticles with Acid-Triggered Aggregation	Human breast cancer (MCF-7)	Gamma radiation of 137Cs (photon energy 662 keV)	1.73	DNA damage, Cells distributed in the G2/M phase, Induction of apoptosis	[60]
Gold Nanoparticles	Human head and neck carcinoma (HSC-3)	150 kV X-ray	No report	Induction of apoptosis	[61]
AuNPs Encapsulated within PEG-CUR	Mouse mammary cancer cells (4T1)	6 MV X-rays	No report	ROS generation, Inhibition of proliferation	[62]
Gold Nanoparticles	Colon cancer (HT-29)	9 MV X-rays	1.4	Induction of apoptosis	[63]
Folic acid conjugated gold nanoparticles	Colorectal cancer (HT-29)	6 MV X-rays	No report	Inducing caspase 3 gene expression, Malondialdehyde generation	[64]
Star-AuNPst-PEG	Prostate Cancers (PC3)	7.5 Gy of 6 MV X-rays	1.67	Induction of apoptosis, ROS generation	[49]

Table 2. Example of in vitro experimental results

Nanoparticles	Tumor Model	Radiation	Sensitizer enhancement ratio (SER)	Mechanism of radiosensitizing	References
Au NPs@PEG	Glioma	160 KVp-X-ray	1.74	Inhibition the process of tumor invasion, proliferation, and migration.	[65]
Au@SA-QBA	Murine hepatic carcinoma	X-ray	1.33	Inducting tumor vascular normalization, Enhancing tumor perfusion, Relieve tumor hypoxia	[66]
Gd2O3@BSA-Au NPs	Murine breast cancer	6 MV X-rays	No report	Inhibition of tumor growth	[33]
Bi2S3-Au-BSA-FA hybrids	Murine breast cancer	6 MV X-rays	No report	Inhibition of tumor growth, Cell death	[67]
11-Mercaptoundecanoic acid coated gold nanoparticles (mAuNPs)	Murine melanoma	Carbon ion beam (190 MeV/u)	1.94	Inhibition of tumor growth, Increasing tumor tissue apoptosis	[68]
Goserelin-conjugated gold nanorods (gGNRs)	Prostat Cancer	250 KVp-X-ray	No report	Tumor Growth Inhibition	[69]

Numerous theoretical and practical investigations using recombinant DNA and biological systems have proven the radio-sensitizing potential of AuNPs. While significant progress has been made in-vitro, it is difficult to translate this success to in-vivo. Furthermore, many formulations lack colloidal stability and necessitate intra-tumoral administration to reduce the negative impacts of particle aggregation and guarantee sufficient gold concentration at tumor sites. Another important obstacle in the therapeutic application of AuNPs is the possibility of long-term toxicity due to the long-term residence of the particles in the liver. In order to increase the therapeutic usefulness of AuNP radiosensitizers, it is critical to determine the variables that affect the in vivo radiation amplification effects of AuNPs and integrate these characteristics into formulation design.

5. Conclusion

Radiation is one of the most common cancer treatments. However, since it has disadvantages, its combination with other drugs may improve the effectiveness of the treatment. Nanoparticles can be used as a means to enhance the therapeutic effects of chemotherapy. Compared to the many nano-platforms that have been investigated for use in radiotherapy, gold nanoparticles may represent one of the greatest possibilities for combination with radiotherapy.

Declaration of interest

The authors declare no competing interests.

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