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REVIEW PAPER

Gold nanoparticles as cancer theranostic agent

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ABSTRACT

The application of nanotechnology in medicine involves using nanomaterials to develop novel therapeutic and diagnostic modalities. Given the unique physiochemical and optical properties of gold nanoparticle (GNP) such as good biocompatibility, nontoxic nature, surface properties and comparative stability, it has been widely studied in medicine, especially as a cancer theranostic agent.

This review focuses on recent progresses in the field of gold nanostructures in cancer treatment and diagnosis. As far as cancer detection is concerned, several studies have indicated that GNPs can be used for X-ray, MR and optical imaging. With regard to cancer treatment, most studies have investigated the effect of GNPs in different treatment modalities like photothermal therapy, photodynamic therapy, sonodynamic therapy, drug delivery, and radiotherapy.

In this paper, we have focused on reviewing the role of GNPs in improving radiotherapy efficiency as radiosensitizers. For optimization of parameters influencing the radiosensitization of GNPs, several studies have been undertaken in different scientific routes. We categorize these studies into three categories; Monte Carlo simulation, cellular studies and animal studies. Finally, according to findings reported by different researchers, the physical and biological mechanism of GNPs in generating radiosensitizing effect is discussed.

Keywords: *Drug delivery, Gold nanoparticles, Photothermal therapy, Photodynamic therapy, Radiosensitizer, Sonodynamic therapy*

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INTRODUCTION

Nanotechnology is defined as the production and application of materials with dimensions in the 1-100nm range [1-3]. Over the past decades, different nanoscale materials have been developed with special structures and properties for biomedical application [4]. Because of their comparable size with biological molecules, nanoparticles can enter human cells and interact with biomolecules both on the surface and inside the cells [5]. Nanomedicine is the application of nanotechnology in medicine that focuses on the use of nanomaterials to develop new methods for the diagnosis and treatment of a wide range of diseases [5]. Advances in nanomedicine have led to the design and synthesis of organic and inorganic nanostructures in the form of nanotubes, nanorods, nanowires, nanocages, nanoshells, nanodisks and other geometries for biomedical applications. In recent years, a number of nanoscale structures with special chemical, physical and biological properties have been proposed. With their defined geometries, surface properties, conductivities, and susceptibility, these structures can react to environmental factors such as heat, light and radiation [6].

For the purpose of diagnosis and treatment of various diseases in humans, researches around the world are actively working on nanomedicine. The highest share of papers on application of nanomaterials in medicine has made by the USA during 2001-2012 (28.8%) followed by China (20.47%), and Japan (12.81%), respectively [7]. As reported by the European Science and Technology Observatory, more than 150 companies are working on the application of nanoparticles in the medicine to accomplish more effective diagnosis0 and treatment [8].

The leading cause of death in human societies because of cancer is more than 760 million deaths every year [9, 10]. As such, cancer is an area of

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particular interest in nanomedicine. According to reports released by the National Cancer Institute (NCI), the application of nanostructures in medicine can make tremendous contribution to cancer prevention, diagnosis, and treatment [11].

There are several cancer treatment methods including surgery, chemotherapy, radiotherapy (RT), or a combination of these three depending on tumor size and location [12]. In addition to these main procedures, other secondary methods such as photodynamic therapy, thermotherapy, sonodynamic therapy and gene therapy are used for the treatment of cancer. Among these methods, radiotherapy is a highly effective cancer treatment method that is also noninvasive. Four in ten of cancerous patients have received radiotherapy in the course of treatment. In radiotherapy, radiation treatment plans must be designed so that the damage imposed on the healthy tissue remains at a level tolerable for the patient, while an sufficient dose is delivered to the tumor [13]. Beam delivery methods are constantly evolving to improve the quality of confirming dose delivery to tumors and increase radiation efficacy. The methods of reducing normal tissue toxicity includes techniques such as irradiating the patient from multiple directions, conformal radiotherapy, intensity modulated radiotherapy (IMRT), volumetric arc therapy (VMAT), image-guided radiotherapy, proton radiotherapy, and the application of radiation modifiers (protectors and sensitizers) [14]. The new radiotherapy technologies help deliver precise doses, which will yield more favorable outcomes and benefit a larger number of patients [15, 16].

In recent decades, many studies have been undertaken on the application of organic and inorganic nanoparticles in all procedures associated with the diagnosis and treatment of cancers. In various fields of study, gold nanoparticles (GNPs) have received increasing attention due to their non-toxic nature, biological compatibility, and special properties. In this review, firs the properties of GNPs, synthesis, and their characterization are explained. Then, the applications of GNPs in various fields of cancer diagnosis and treatment are listed and finally the augmented radiation effect in the kilo and mega voltage energies in the presence of GNPs is discussed.

Gold nanoparticles (GNPs)

Using gold in medicine is not unprecedented. Gold-based materials were used for the treatment of syphilis, epilepsy, rheumatic, tuberculosis and various inflammatory skin diseases, in the early 19th and 20th centuries [17-19]. Water-soluble gold complexes like sodium aurothiomalate (Myocrisin TM) and aurothioglucose (Solganol TM) used for rheumatoid and Auranofin (Ridauro TM) exhibited great outcomes for the treatment of arthritis in 1985 [20].

The physical and chemical properties of GNPs are different dependent on their size and shape. In brief, there are three ways to synthesize GNPs: (a) physical methods, (b) chemical methods, and (c) biological methods [20]. In the synthesized stage, GNPs structures can take the form of nanotubes, nanorods, nanowires, nanocages, nanoshells, nanodisks, and some other geometries [21]. With a size in the range of cellular organelles, they can interact with cellular structures, and therefore have various medical applications in disease diagnosis and treatment [22].

Given the unique properties of GNPs, they have been utilized in recent years for the diagnosis and treatment of cancer in different fields such as cancer cell imaging, photothermal, photodynamic,and sonodynamic therapies, drug delivery, and radiotherapy. Special properties of GNPS are listed below:

- Facile synthesis in different sizes and shapes [23].
- Surface properties of GNPs: Due to the reactivity tendency of GNPs with thiol and amino compounds, several biological ligands, such as DNA, peptides, proteins, antibodies, and viruses can be used for coating the surface of GNPs [20].
- Optical features of GNPs: There is a phenomenon related to the surface metal nanoparticles called Surface Plasmon Resonance (SPR), from which the unique optical properties of GNPs originate [24]. SPR occurs due to the oscillation of valence electrons in a solid when they are irradiated by light. After the absorption of light in nanoparticles, the photons have been emitted with the same frequency in all directions [25]. The SPR properties of GNPs allows them to absorb light in near-infrared (NIR) and visible regions. This property of GNPs can be used in photothermal therapy and some modalities of optical imaging.
- Good biocompatibility
- Nontoxic nature
- Comparative stability [26]
- Desirable uptake by mammalian cells via

endocytosis [27]

- Low osmolality, even at high concentrations [28, 29]
- Low viscosity, which allows convenient injection even into small vessels [29]
- High absorption coefficient, high density and high atomic number make them an ideal agent for the diagnostic and treatment stages of radiotherapy.

After GNPs are synthesized, they can be readily characterized by several methods including:

1. Take size distribution by Dynamic Light Scattering (DLS) instrument

2.Ultraviolet-visible (UV-Visible) spectrophotometry for assessing optical and electric properties of nanoparticles. The maximum absorbance wavelength and optical density are dependent on particles size and their concentration in a given solution [24]. The UV–visible spectroscopy is used for size verification and stability assessment of GNPs following their synthesis.

3.Direct imaging of GNPs to control features such as size, morphology and surface coating by Transmission Electron Microscopy (TEM) and Atomic Force Microscopy (AFM) [2].

4.X-ray Photoelectron Spectroscopy (XPS) for the surface characterization of GNPs [30].

In light of these unique properties, GNPs have been extensively studied in various fields of cancer diagnosis and treatment. The special properties of GNPs are listed in Fig 1.

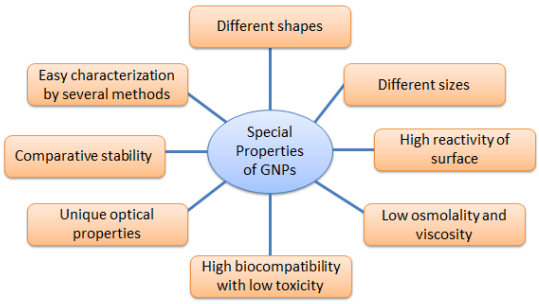

Fig 1. Unique properties of GNPs

Novel approaches to GNPs for cancer diagnosis and treatment

Application of GNPs in imaging as contrast agent

Recent studies have shown that GNPs can enhance the accuracy of diagnosis and stage of cancer by improving the quality of different imaging modalities such as X-ray imaging (mammography [31], CT scan [32, 33]), MRI, and cancer optical imaging [4, 5, 34-38].

X-ray Imaging

The X-ray imaging is founded upon tissue mass absorption coefficient. In kV energies used for X-ray imaging, there is a dominant photoelectric effect related to photon energy (E) and atomic number of materials (Z) via $(Z/E)^3$ [28]. One of the major X-ray imaging methods is Computed Tomography (CT) that is usually associated with a contrast agent.

For the tumor diagnosis, CT scan is performed with an contrast agent (commonly iodine) that increases tumor volumetric accuracy and stage determination by improving photoelectric effect [2]. The contrast agent in X-ray imaging is basically used to increase the attenuation coefficient, which is in turn dependent on the electron density and atomic number of the matter. The clinical CT contrast agent is iodine with an atomic number and electron density of 53 and 4.9 g/cm^3, respectively. In comparison, gold with an atomic number and electron density of 79 and 19.32 g/cm^3 has a higher absorption rate than iodine with improved contrast and lower dose. It has been shown that with 100 keV energy, gold can improve the image contrast up to three times in comparison to iodine [31]. Heinfeld et al. studied 1.9 nm GNPs under in vivo conditions, demonstrating the superior contrast of iodine with 22-kVp mammography unit. Further, gold nanorod with a size of 45×15 nm exhibited that the attenuation coefficient of targeted cells was five times higher than that of untargeted cancer cells or normal cells at 80 kVp energies. Hainfeld et al. demonstrated the positive effect of GNPs on in vivo vascular contrast enhancement [31]. Other studies have reported that 30 nm of polyethylene glycol (PEG) coated with GNPs can increase image contrast, while overcoming limitations of conventional CT contrast agent (Iodine compounds), such as low reactivity to bondage with most biological components or cancer markers, rapid clearance by kidneys that leads to an unsuitable short imaging time, renal toxicity, and vascular permeation [39]. PEG attachment to GNPS helps increase their passive targeting as PEGylation restricts interaction with cells and increases the circulation time of NPs, which offer more time for imaging [25]. Beik et al. reported decreased radiation dose and enhanced image contrast by using folic acid-modified GNPs in molecular CT imaging of nasopharyngeal KB cancer cells [40]. In another cellular study by

Khademi et al., the multifunctional cysteamine-folic acid conjugated with GNPs revealed greater X-ray attenuation coefficient compared to iodine-based contrast agent for the same concentration of tumor molecular CT imaging [41].

MRI

Several paramagnetic nanoparticles have been used for Magnetic Resonance (MR) imaging both in clinical practice and research. Recently, Au_3Cu1 nanoshells were proposed as magnetic resonance imaging (MRI) contrast agent for blood vessels in many in vivo studies, which suggests their potential use as blood contrast agents in MR angiography [5]. Hybrid NPs with super-paramagnetic iron oxide as the core of nanoparticles and gold as the shell of nanoparticles have been used as dual contrast agents for CT and MRI due to high attenuation of CT and good MR signals [42]. In other studies, the new GNP bonded with gadolinium (Gd) succeeded in increasing image contrast of CT due to the high-Z of gold and MRI by using Gd as a contrast agent for MR imaging [43].

Optical Imaging

There are several methods for using optical properties of GNPs in optical imaging of cells and tissues including two-photon luminescence, Raman spectroscopy, dark field light scattering, optical coherent tomography, and photoacostic imaging [44].

Loo et al. utilized near-infrared light scattering of gold nanoshells as a contrast agent to detect a molecular marker called human epidermal growth factor receptor 2 (HER2) inserted in the breast cancer cells using the dark-field microscopy [45]. Also, Bickford et al. showed that this structure is a suitable contrast agent for imaging liver HER2-overexpressing cancer cells using the two-photon microscopy [46].A special imaging modality that can provide sectional images of a biological sample with high resolution is the Optical Coherence Tomography (OCT). Gobin et al.showed that scattering is escalated in the present of Au-nanoshells, and it can provide an enhanced optical contrast image for accurate determination of tumor in mice [47].Photoacoustic imaging modality is another method that enables precise cancer diagnosis in early stages. This method integrates both optical and ultrasound imaging modalities [48-50]. It is based on irradiation of biological samples or tissues by short pulses of electromagnetic irradiation in its absorption range, leading to elevated temperature and local pressure, which can generate detectable acoustic waves [51-53].Motamedi et al. revealed that gold nanorods can enhance the diagnostic power of laser photoacoustic imaging system [54].

Au-nanocages have been reported to produce more detailed images of vascular structures as it enhances the contrast between blood and the surrounding tissues up to 81%.

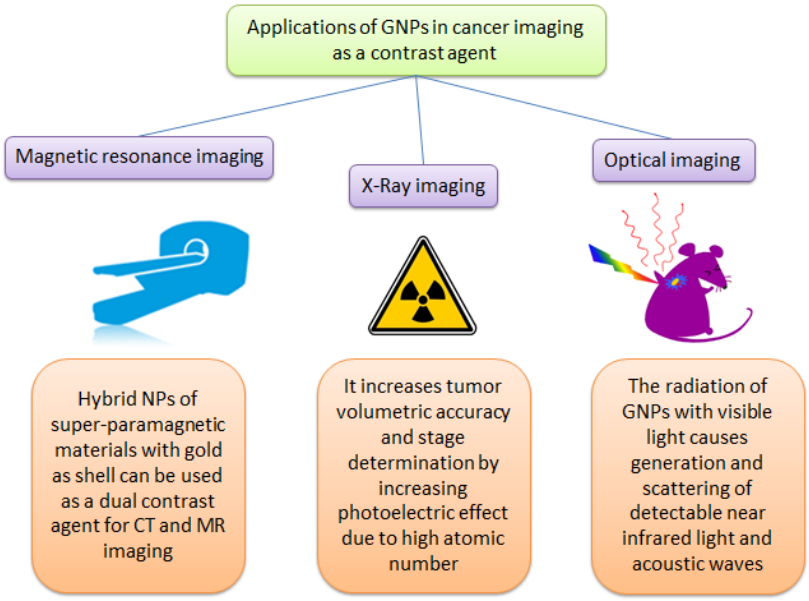

Fig 2. Applications of GNPs in cancer imaging

Additionally, it has been reported that nanocage-shaped GNPs have larger optical absorption cross-sections than gold nanosells and are more suited for in vivo applications [55].

Application of GNPs in cancer treatment

Drug delivery

The ability of NPs as drug delivery systems in carrying drugs is 10 to 100 times higher than molecular administration of drugs to the vicinity of tumors to improve diagnostic and therapeutic applications [11]. In addition, the drug circulation time within NPs can be increased due to fewer uptakes by the reticula-endothelial system (RES), and it can augment the uptake of drugs by tumor cells [56, 57]. Due to features such as biocompatibility, nontoxicity nature and strong affinity, GNPs surface can be used for active targeting of tumors using ligands, antibodies, and biomarkers that are capable of specific binding to tumors. Site-specific delivery of cytotoxic drugs can improve diagnosis and treatment while diminishing adverse side effects [20, 58]. Some studies have reported the use of GNPs to deliver anti-cancer drugs including methotrexate [59], tamoxifen [60], paclitaxel [61], as well as platinum-based drugs such as cisplatin, and oxaliplatin to improve therapeutic efficiency [62, 63].

Photodynamic therapy

Photodynamic therapy (PDT) is a novel method for cancer therapy [13, 57]. The PDT is based on using a type of photosensitizer that becomes excited after light irradiation. Reactive Oxygen Species (ROS) is generated after light irradiation due to the transfer of energy to surroundings [20]. Conventionally, clinical photosensitizing agents (porphyrins and phthalocyanines) are hydrophobic, unable to enter cells duo to the lipid membranes. Therefore, they need a proper carrier that can enter cancer cells without changing the agent. In fact, in photodynamic therapy studies, nanoparticles function as a carrier for the delivery of photosensitizer drugs [64]. In addition, the binding of nanoparticles to photosensitizing molecules can elevate ROS generation [65-67].

Some studies have shown that GNPs conjugated to photosensitizer agents can improve the efficiency of PDT [57, 65, 68]. Khaing et al. reported that the use of 5-aminolevulinic acid (5-ALA) bonded with GNPs can enhance the uptake rate of 5-ALA in comparison with free 5- ALA by fibrosarcoma cells. It was reported to induce a two-fold increase in the ROS production [65]. Also, Mohammadi et al. reported that the presence of GNPs (34nm) bonded with 5-ALA leads to further uptake of 5-ALA photosensitizer drug by melanoma cells in comparison to 5-ALA alone in PDT. The results of an in vivo study suggested that the use of a designed gold nanoconjugate with 5-ALA would increase the efficiency of PDT compared to free 5-ALA [68]. In different delivery systems, GNPs covered by the PEG layer exhibit the highest efficiency for PDT drug delivery [64].

Photothermal therapy

The absorption of light in the visible and NIR region by GNPs renders them an excellent candidate for photothermal therapy (PTT). In the PTT method, the temperature rises due to the heat generation by GNPs, which can lead to cell death at temperatures above 50 °C [26]. The temperature rise and absorption of light in NIR region is more than the visible region. Irradiation with NIR light excites electrons at different atomic levels, at come back to stable state; they emit the energy as heat, which can raise the temperature of its surrounding. Scattering and absorption in the NIR region are a function of the shape of GNPs. Photothermal studies with GNPs have demonstrated that GNPs shaped as nanorode, nanocages, and nanoshells have absorption peaks in NIR region, but spherical GNPs peak in the visible region at 530 nm [25]. The results of several studies have shown that gold nanospheres are not as efficient as other shapes in terms of photothermia because absorbance peak is in the visible rather than NIR region [26]. Different cancer cell lines of epithelial, breast, and colon have been successfully treated by the PTT method in the presence of GNPs, both under in vitro and in vivo conditions [69-71]. Hirsch et al. reported the use of silica nanoparticles coated with gold nanoshell under in vitro and in vivo conditions for the treatment of human breast cancer cells by NIR PTT [72]. In the study of Ghahremani et al. Saos-2 cells death soared in the presence of GNPs due to microwave exposure. They reported the size and concentration increase of GNPs were key factors responsible for improved efficiency of thermal therapy by microwave radiation [73]. In another study undertaken by Mehdizade et al., the mouth epidermal carcinoma cells (KB cells) was treated with laser irradiation in combination with folate-

conjugated gold nanorods [74]. Salem et al. utilized the 5-FU-loaded chitosan-wrapped GNPs with laser irradiation for human hepatocellular carcinoma cells (HepG2). After 20 min laser exposure, the 5-FU-GNPs showed enhanced light absorption with highly efficient photothermal conversion, which led to a seven-fold decrease in the IC50 value [75].

Sonodynamic therapy

Sonodynamic Therapy (SDT) is a noninvasive method of cancer treatment that uses ultrasound [76, 77]. In SDT, the accumulation of sonosensitizing agents in tumors followed by ultrasonic exposure can trigger cavitation phenomenon [27, 78]. There are two stable and transient modes for acoustic cavitation. As a result of acoustic cavitation phenomenon, ultrasound waves with high intensity and low frequency possess great curative potentials [79]. In the course of transient cavitation, bubbles grow several times larger than their initial size and suddenly collapse. Therefore, high mechanical and physiological stresses applied to the surrounding area can be exploited to destroy cancer cells [80, 81].

Several studies have investigated SDT in the presence of GNPs. Sazgarnia et al. reported that ultrasound irradiation had an insignificant effect on tumor, but the effect was enhanced with GNPs in an in vivo study with CT26 cell line.

A significant difference was observed between SDT+GNPs group and other groups 13 days after treatment in terms of tumor volumes [27].

In another study, the cavitation potential of GNPs was investigated in the terephthalic acid solution, with the results suggesting that GNPs can function as a cavitation site and elevate the cavitation rate [82].

Radio-Sensitizer in radiotherapy

Almost 60% of cancer patients go through radiotherapy during their treatment [83]. An important clinical method to reduce the effect of radiation on normal tissues and improve cell killing in tumors involves the application of radiation modifiers agents (protectors and sensitizers) prior to or shortly after radiation exposure [14].

From a physical perspective, high atomic number compounds containing elements such as iodine, which are used as contrast agents, can also act as a radio-sensitizer. Unfortunately, they cannot be absorb selectively by cancer cells. Furthermore, they may produce numerous side effects such as anaphylactic shock, hypersensitivity, kidney failure, and selective iodine uptake within the thyroid gland [84]. A variety of inorganic nanoparticles such as platinum, silver, gadolinium and gold have been studied as radio sensitizers in recent years. Unique properties of GNPs, particularly their nontoxic nature and high atomic number, have

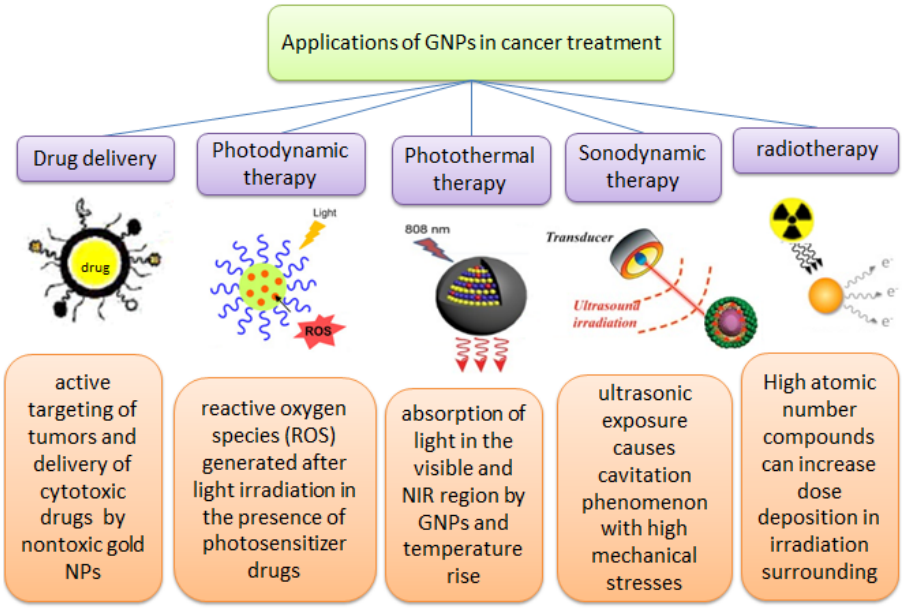

Fig 3. Different applications of GNPs in cancer treatment

made them an appropriate candidate for radiosensitizers. The effect of GNPs as radiosensitizer has been investigated through simulation under in vitro and in vivo conditions at low and high energies in several studies. We will further elaborate on this subject in the following sections.

In all GNPs applications, prior to their application in clinical settings as drug, their toxicity and health impact on targeted and normal tissues must be investigated. It is essential to study toxicity and uptake of GNPs because GNPs are extensively used in different medical applications. We reviewed cellular and animal studies on the toxicity and uptake of GNPs in a recent article. Different in vitro and in vivo studies have shown that the uptake of GNPs by cells and their toxicity depend on several factors such as size, shape, surface properties of GNPs, and cell types. For more information about the factors affecting the uptake and toxicity of GNPs, refer to the last reviewed article. [85]

Diverse applications of GNPs in cancer treatment have been summarized in Fig 3.The following sections describe the application of GNPs as a radiosensitizer in radiotherapy.

Effect of GNP as a radiosensitizer in radiotherapy

The size, shape, concentration, and surface coating of GNPs are important factors that influence their application as a radiosensitizer. Understanding GNPs interaction with ionizing radiation with different energies coupled with the type and energy of secondary particles released after interaction (e.g. secondary electrons, Auger electrons, photoelectrons, and the secondary low energy photons) enables the development of GNPs that are well suited for radiotherapy.Many studies have investigated and optimized parameters affecting the radiosensitivity of GNPs in different routes including Monte Carlo simulation, cellular research and animal studies.

Simulation studies

Following the interaction of photons with GNPs, a series of secondary electrons including photoelectrons, Compton electrons and a shower of Auger electrons are produced. This can increase absorbed dose in the surrounding of GNPs. In the Monte Carlo studies, the effects of different parameters are explored to find optimal physical characteristics of GNPs. In other simulation studies, the size of GNPs and its effect on dose enhancement has been investigated at different energies.

McMahon et al. evaluated dose enhancement in the presence of a single GNP (at different sizes ranging from 2 to 50 nm) in water after irradiation by monoenergetic X-rays of 20 to 150 keV. They reported that smaller GNPs can deposit at a higher dose in the vicinity of particle due to their greater surface to volume ratio, so that the energy deposited by GNPs of 2 nm in their vicinity is two times greater. The results of this study suggested that low energy Auger electrons are responsible for increased dose enhancement in the presence of GNPs [86].

According to Chow et al., the distribution of low energy electrons produced after interaction with photon beams at 35, 73, and 660 keV energies does not change significantly; however, the share of high energy electrons with higher penetration power increases at higher photon energies. The results of this simulation study exhibited that the range of low energy electrons is dependent on the energy of first photon beam, and for photons of 660 keV, the secondary electrons can spread 100 times more than photons of 35 keV. In conclusion, the interaction of higher photon energies takes place at a larger volume [87]. In other words, dose deposition in the vicinity of GNPs is not dependent on the energy of photon beams due to the same low energy distribution, but at greater distances, it depends on the energy generated by secondary electrons with higher energy.

In another study, different brachytherapy sources of ^{103} Pd, ^{125} I, ^{169} Yb, ^{192} Ir and external radiations of 300 kVp and 6 MV were evaluated in combination with GNPs at sizes of 1.9, 5, 30, and 100 nm. Results of the Monte Carlo simulation illustrated escalated photoelectric interactions in GNPs for lower energy radiations and larger GNPs. However, smaller particles induced a greater deposited dose in the simulated tumor, which could be attributed to the escape of more low-energy electrons into the surrounding medium containing GNPs [88]. In the study of Chow et al., dose deposition via mono-energetic electrons of 50 keV, 250 keV, 1 MeV and 4 MeV was evaluated in the presence of spherical GNPs that were 2, 50 and 100 nm in diameter in the water. The results showed that the mean range of secondary electrons increased with an increase in electron beam energy and GNP size [87].

The impact of nanoparticles on dose

enhancement has been evaluated with 30 mg/ml gadolinium and GNPs in the simulated tumors. The simulation was performed with sources of ^{60}Co, ^{198}Au, ^{192}Ir, ^{169}Yb. Accordingly, a dose enhancement in the range of 0.5–106.1 % and 0.4–153.1 % was reported for gadolinium and gold nanoparticles, respectively. In other simulation parameters (photon energy of the beam, concentration of nanoparticles in the simulated tumor, and tumor distance from the center of water phantom), the effect of GNPs on elevating absorbed dose in the surrounding medium was higher than gadolinium nanoparticles [89].

In the study of Mesbahi et al., the effect of GNPs of different sizes (30, 50, and 100 nm) on energy deposition was investigated as a macroscopic dose enhancement factor (DEF). They simulated mono-energetic X-ray beams (50-120 keV), Cobalt^{60} beam, and 6 & 18 MV photonic beams. For kilo-voltage beams, DEF was reported in the range of 1.4 to 3.7, but for the megavoltage energies, it was significantly lower than kilo-voltage beams for all GNP sizes and concentrations. highest most DEF was found in 90 keV X-ray beam [90]. Cho et al. demonstrated the dose enhancement in a tumor with 140 kVp X-ray radiation can increase by a factor of 2. The dose enhancement in tumor region was in the range of 1 to 7% for 4 and 6 MV photon beams and 5 to 31% for the ^{192}Ir source [91].

In the study of Roeske et al., 0.5 - 0.8% DEF was reported for 18 MV in comparison with 6 MV beams, which can be attributed to the presence of pair-production interaction [92]. Jones et al. showed that the microscopic deposition dose around GNPs was increased by factors of 10-1000 at a distance of 30 µm from GNP surface for low energy photon compared to a factor of 10 for 6 MV photons [93]. Pakravan et al. observed a weak relationship between nanoparticle size and dose enhancement for high energy photons. They reported that it was mainly affected by the concentration rather than size of nanoparticles. They also analyzed the impact of flattening filter on radiosensitization effect of GNPs, reporting that tumor dose enhancement with and without the flattening filter was 1–5 and 3–10%, respectively. The beam-related DEF without flattening filter was larger than the flattened beam. This can be explained by the fact that the beam without flattening filter contains more low energy photons than the flattened beam, which increases the probability of photoelectric interactions [93].

According to Anijdan et al., the maximum DEF obtained in the presence of GNPs (50 nm) with 18 megavoltage (MV) beams is about 12%. It seems that DEF value is strongly correlated with size, concentration, position, and geometry of GNPs distribution in terms of tumor volume [94].

In vitro studies

As suggested by the vast majority of studies in this field, it seems that the impact of radiation on cells in the presence of GNPs is variable. It depends on several parameters such as size, shape, concentration, surface properties of GNPs, cell type, and beam energy.

For GNPs that are 14, 50, and 74 nm in size, the Radiosensitization Enhancement Factor (REF) was estimated at 1.20, 1.43, and 1.26, respectively at 220 kVp X-ray. In the presence of 50-nm GNPs with 105 kVp and 6-MV photons, the lowest and highest REF were 1.66 and 1.17, respectively [95].

Kong et al. explored various parameters including surface properties of GNPs, cell type and photon energy in their study. The radiation treatment of MCF-7 cells by 200-kVp photon beams in the presence of glucose-coated GNPs (Glu-GNPs) and cysteamine-coated GNPs (AET-GNPs) boosted radiation cytotoxicity by 63.5% and 31.7% for Glu-GNP and AET-GNP respectively in comparison with irradiation alone. It appears that dose enhancement is dependent on surface coating of GNPs. The cell type is an important factor that should be taken into account. After irradiation in the presence of Glu-GNP under similar conditions, the cell viability of MCF-7 cells dropped to 40%, while no significant changes occurred in normal MCF-10A cells ($p>0.05$). The results of this study showed the GNPs wielded influence only on radio sensitivity of cancer cells, but normal breast cells were unaffected. In the evaluation of photon energy, 200- kVp X-rays radiations improve radiation sensitivity up to 30% for AET-GNPs and 60% for Glu-GNPs, ^{137}Cs g-rays with ^{60}Co g-rays demonstrating smaller enhancement (12.7 and 13.1%, respectively) [96].

The radiosensitivity enhancement of bovine aortic endothelial cells has been investigated by superficial X-ray and megavoltage electron radiation beams at 1 mM concentration of GNPs. The results have been shown to be a function of radiation type and energy as well as GNP concentration. The effect of radiation increases by 25 times for superficial X-ray beam, though it

is not significant for 6-MeV electron beam in the presence of GNPs [17].

Jain et al. investigated the effect of radiation on breast cancer cells of MDA-MB-231, prostate cancer DU145 cells, and normal L132 in combination with 1.9 nm GNPs. Their findings exhibited the sensitization enhancement is cell specific, as observed in MDA-MB-231 cells by radiation sensitizer enhancement ratios (SERs) of 1.41, 1.29, and 1.16 for photons of 160 kVp, 6 MV, and 15 MV, respectively. Despite the uptake of GNPs in all cell lines, there was no significant change in DU145 and L132 cells at kV or MV energies (SER 0.97–1.08) [97]. In another study, Hela cells were exposed to 105 kVp, 220 kVp, and 6 MV X rays after incubation with 50 nm GNPs for 24 h and DEFs of 1.66, 1.43, and 1.17 were achieved respectively [11]. The radiation of CT26 murine cancer cells in high concentrations of 6.1 nm GNPs covered with PEG layer was the subject of another research. Accordingly, they estimated DEFs of ~ 1.44, 1.1, and 1.32 for 8 keV, 160 kVp, and 6 MV X-ray beams, respectively. In this research the sensitizing improvement was higher than the previous two studies. It revealed that the concentration of GNPs was an important factor [98].

In the study Zhang et al., the intracellular uptake of simple GNPs and Glu-GNPs by prostate cancer cells induced a growth inhibition of 30.57 and 45.97%, respectively, as compared to a growth inhibition of 15.88% in the group with radiation alone. The evaluation of GNPs properties indicated that Glu-GNPs induced1.5 to 2-fold irradiation cytotoxicity enhancement compared to simple GNPs [99].

Based on preliminary clonogenic survival results, Sim et al. reported that GNPs (50nm), with a PEG layer used to increase their biocompatibility and stability, can induce DEFs that are approximately two times greater than LNCaP human prostate cancer cells with 6 MV irradiation [100]. Wang et al. observed the uptake of 13 nm Glu-GNPs by lung-cancer cells (A549) can induce an SER of 1.49 in cells after irradiation with 6 MV X-rays [12]. Another evaluation of Glu-GNPs radiosensitization effect on MDA-MB-231 cells showed that 49-nm Glu-GNPs produced an SER of 1.86, which was stronger than the effect of 16-nm Glu-GNPs with an SER of 1.49 [101].

Jain et al. compared the radiosensitivity of 1.9 nm GNPs on prostate cancer (DU145), breast cancer (MDA), and normal lung (L132) cell lines after irradiation with 160 kVp and 6-15 MV megavoltage photons. They demonstrated that GNPs could provoke significant sensitization at 160 kVp and 6 MV just in MDA cells. The DEFs for this cell line were estimated at 1.41, 1.29 and 1.16 for 160 kVp, 6 and 15 MV, respectively [102]. It has been shown that GNPs coated with thioglucose can be used as a radiosensitizer to enhance the radiotherapy efficiency of human ovarian cancer cells (SK-OV-3). The presence of 14.37 nm Glu-GNPs in SK-OV-3 cells enhanced cell proliferation inhibition by 30.48% for 90 kVp and 26.88% for 6 MV irradiation [30].

Neshastehrize et al. reported the folate conjugated GNPs radiosensitization in MV energies even at low concentrations (103). In the study of Soleymanifard et al, the radiosensitivity of two human lung (QU-DB) and breast (MCF7) cancer cell lines was improved in the presence of thioglucose GNPs for both 100 KV and 6MV X-rays radiations [104].

In vivo studies

In one of the pioneering studies, Heinfeld et al. utilized 1.9 nm GNPs that was injected intravenously into mammary tumor-bearing mice 5 min before irradiation with 250 kVp X-ray. The investigation of pharmacokinetics illustrated that gold concentrations reached its maximum in tumor 7 min after injection. They reported that GNPs alone had no effect on tumor growth. On the other hand, they did not induce any toxicity in the tumor tissue. However, the presence of GNPs led to a significant reduction in tumor growth and a one-year survival of 86% compared to 20% for X-rays alone [105]. Chang et al. investigated the effect of 13-nm GNPs (intravenously 24 h after injection) on melanoma tumor-bearing mice (B16F10) in conjunction with a single dose of 25Gy of 6MeV electron beam. The result suggested that the number of apoptotic cells in the animals receiving GNP plus radiation was twice greater than that of animals receiving radiation alone [106].

In another in vivo study, 50 nm GNPs was applied to a growing melanoma tumor before 6 and 18 MV X-ray radiations. The average tumor volume after various treatment modalities was significantly different between control and treatment groups. Contrary to the above studies, this difference was not significant between groups receiving radiation only and radiation with GNPs

[107]. Hainfeld et al. used murine squamous cell carcinoma (SCCVII), which is a high radio-resistant cell line, for in vivo evaluation of mice irradiated by 1.9 nm GNPs with filtered photons produced in a synchrotron. For the same radiation doses, the tumor growth delay and long-term tumor control in 68 keV was more effective than that of 157 keV when GNPs were combined with radiation, as compared with radiation alone. They concluded that GNPs impacted the radiation therapy of radioresistant cancer cells [23].

Hebret et al. reported a maximum tumor uptake of 5-nm in MRI detectable gadolinium-coated GNPs obtained 10 min after injection with a tumor-to-surrounding ratio of 3:1. In this study, the mice bearing MC7-L1 murine breast cancer cells were exposed to 150 kVp X-rays beam. They did not observed any significant difference between the survival time of the groups receiving GNPs-radiation (of 17 days) and radiation alone (14 days) [108].

Mechanism of GNPs radiosensitization

According to the above studies, the impact mechanism of GNPs as a radiosensitizer can be investigated from a physical or biological aspect.

Physical Mechanisms

- ***Photoelectric Effect:*** The interaction of a matter with radiation is highly dependent on photon beam energy. For low-energy superficial photons (< 50 keV), the photoelectric effect is dominant for soft tissues that deposited the highest energy in interaction surroundings. By using heavy NPs like GNPs, it is possible to boost photoelectric effect, which consequently results in dose enhancement.
- ***Compton Interaction:*** For energies in the range of 50 keV–10 MeV, the Compton interaction is dominant, as it can produce low-energy secondary electrons. The cross-section of Compton interactions is not dependent on atomic number, and the contribution of this interaction type is not promoted in the presence of heavy NPs. Since the Compton scattering is not dependent on atomic number for high-energy photons of > 50keV, the GNPs accumulated in tumor do not exert any effect on dose enhancement based on physical interactions [109].
- ***Production of Auger Electrons:*** Several Auger emissions may occur simultaneously from inner shell ionization in a process called Auger cascade. The electrons produced by Auger cascade usually possess energies in the range of a few keV or less, with penetrations that typically range from 10 to 100 nm [110]. As a result, electrons deposit their energy locally. This highly localized deposition of energy is comparable to that of ion therapy. The biological effect was first described using the local effect model developed to link the ion-induced radiation track structure to the biological effect [86, 111]. This highly localized deposition of energy is one of the main features of heavy nanoparticles [102]. The simulation studies showed that the share of Auger electrons in dose deposition is strongly dependent to the size of NPs with smaller NPs having higher efficacy due to larger surface-area-to-volume ratio.

Dose enhancement in the presence of GNPs in MV energies can be attributed to greater production of low-energy Auger electrons. However, dose enhancement in experimental studies was higher than that of simulation studies, which could be due to incorporation of the biological impact of GNPs in their physical effects.

Biological Effects

In almost all studies, enhancement factors at MV energies were lower than kV photon beams, but still far greater than MC simulations, which is due to the biological effect of GNPs. The biological effects of GNPs can be considered from different aspects. Here, we have summarized them in four categories.

- ***Cell Phase Arrest:*** Several studies have shown that GNPs can influence cell cycle by activation of CDK kinase, leading to the acceleration of cell cycle in the G0/G1 phase and the arrest of cells in the G2/M phase. Accumulation of cell population in G2/M phase which is the most radiosensitive phase of cell cycle, incurs more extensive DNA damage [9, 12, 30, 101].
- ***Gene Expression:*** It has been reported that GNPs may wield influence on the expression of critical proteins, which encompass factors in apoptosis pathway such as Bcl-2, Bax and caspase 3. Irradiation in the presence of GNPs disrupts balance between Bcl-2 and Bax by the deregulation of Bcl-2 gene family and upregulation of Bax gene family, which play anti-apoptotic and pro-apoptotic roles, respectively. Moreover, the caspase 3 is the most important factor in the death receptor pathway of apoptosis in the caspase family, and the presence of GNPs can influence its

activation [12].

➢ ***Increase of the Reactive Oxygen Species (ROS) Production:*** The irradiation of GNPs is followed by the production of free radicals from gold atoms. Free radicals have high reactivity power that can generate ROS molecules [112, 113]. Geng et al. reported the enhancement of intracellular RO generation for both 90 kVp and 6 MV X-ray radiations in human ovarian cancer cells (SKOV-3) in the presence of Glu-GNPs. They concluded that higher production of ROS in the interaction of radiation with GNP was a major mechanism underpinning GNPs radiosensitivity [30].

➢ ***Reduction of Angiogenesis in Animal Models:*** Angiogenesis is a physiological process through which new blood vessels are generated to supply nutrition and oxygen required by new cells. Angiogenesis is essential for the growth and progression of tumors [114, 115]. The in vivo model of nude mouse ear demonstrated a reduction in angiogenesis [114].

CONCLUSION

Thanks to their special properties, GNPs have received increasing attention in the field of cancer detection and treatment in recent years. In this review paper, we summarized different aspects of GNPs applications as a cancer theranostic agent in various diagnostic and treatment modalities. Studies have shown that GNPs can be helpful in different imaging modalities of X-ray, MRI, and optical imaging. On top of that, they can improve the efficiency of cancer treatment in drug delivery, photodynamic therapy, photothermal therapy, sonodynamic therapy, and radiotherapy.

GNPs act as a radiosensitizer by inducing several physical and biological effects. Under radiation with kV energies, they can increase the photoelectric effect, but their biological effect on dose enhancement is escalated in the presence of MV energies. The bulk of studies have demonstrated that GNPs can play an influential role in cancer theranostic applications.

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