REVIEW ARTICLE e-ISSN: 2349-0659 p-ISSN; 2350-0964

Metallic Nanoparticles as Antimicrobials and Radiosensitizers: A Review

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Abstract

Nanoparticles have shown unique physical and chemical properties that have opened new era for chemotherapy, cancer therapy, and radiotherapy. As an improved technology for targeting tumors, it is suggested that nanoparticles can become clinically useful for radio sensitization and as an antimicrobials can be utilized in topical formulations such as ointments, gels, and creams. There are different types of nanoparticles involved in the treatment of cancer radiotherapy and tumor selective radiosensitizer which have been classified into different groups. One of the widest applications of nanoparticles is assigned to noble metal nanoparticles (MNPs) or metal-based radiosensitizers. MNPs are the entities of pure metals smaller than the scale of microns, that is, between 1 and 100 nm in size. These include gold, silver, zinc, platinum, iron, gadolinium, cerium, titanium, tantalum, Bismuth, Hafnium, and copper and their oxides, sulfides, phosphates, and chlorides. MNPs due to their unique physical and chemical characteristics such as large surface energy, larger surface-area-to-volume ratio, quantum confinement, and plasmon excitation have emerged as a powerful tool for bioimaging and diagnostic of cancer and other clinical applications. Therefore, this paper discusses the wider applications of metal-based nanoparticles in enhancing radiosensitivity in debt. Improving mechanistic approach and understanding in nanoparticles, the outcome of this study will be of enormous benefit in radiotherapy.

Keywords: Antimicrobial activity, Clinical applications, Metallic-nanoparticles, Radiosensitizers, Radiotherapy

Asian Pac. J. Health Sci., (2022); DOI: 10.21276/apjhs.2022.9.4S.34

Introduction

Nanotechnology is a novel approach and a promising tool in the field of medicine, especially pharmaceuticals for treatment of dermatological disorders and safe and targeted drug delivery. Metallic nanoparticles such as gold, silver, and zinc are widely used in topical and cosmetic formulations. Parameters, such as rigidity, hydrophobicity, and lipophilicity, size, and charge determine the skin permeation and penetration of a pharmaceutical topical formulation. Lipid nanoparticles and nanoemulsions have been widely used in skin care cosmetic formulations, whereas some like carbon nanotubes and fullerenes, nanorobots, and polymerases still need further exploration to be used for targeted delivery in pharmaceutical formulations. Nanoparticles, although, offer several advantages but also associated with certain disadvantages such as risks of nanopollution (remain stoked in environment), increased surface volume ratio, lung granuloma, allergens, cross reactants, and cytotoxicity.[1,2]

Clinical Applications of Metal-Based Nanoparticles

Enlisted below are some of the clinical applications of metallic nanoparticles.

Metallic Nanoparticles as Promising Tool for Targeted Drug Delivery

Gold (Au-NPs) and silver nanoparticles (Ag-NPs) serve satisfactory tool for targeted delivery of drugs, which are not achieved by conventional methods of drug admiration. A larger proportion of the drug may undergo first pass metabolism in the liver and even may not be able to pass the blood brain barrier. Hence, sufficient amount of drug cannot reach at the site of action. Bhattacharya *et al*. reported the use of gold nanoparticles to enable delivery of medicines to tumor cells by binding with folic acid PEG-amine, as this complex gets attached to the folate receptors present on cancerous cells.[3] Metallic nano-particles also protects the genetic material, that is, DNA and RNA from degradation by enzyme nuclease. Oligonucleotides conjugated nanoparticles have unique properties of gene regulatory agents. These regulatory agents are categorized as covalent and non-covalent. The covalent metallic nanoparticles are functionalized with thiolate oligonucleotides. In addition, the covalent metallic nanoparticle activate the genes related to the immune system, which is present on the mononuclear cells.[4]

Antimicrobial Agents

Metallic nanoparticles have broad spectrum antimicrobial activity and are effective against both gram +ve and gram –ve bacteria. Ag-NPs are widely used in topical formulations such as ointments used to treat wounds, burns, and cuts. Solutions and salt form of

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How to cite this article: Sharma S, Sharma S, Vashist S, Kaur G, Arora S, Sucheta. Metallic Nanoparticles as Antimicrobials and Radiosensitizers: A Review. Asian Pac. J. Health Sci., 2022;9(4S):171-174.

Source of support: Nil

Conflicts of interest: None.

Received: 11/03/2022 **Revised:** 12/04/2022 **Accepted:** 15/05/2022

ointments containing silver have been widely commercialized. Ag-NPs are also utilized in targeted delivery of chemotherapeutic drugs and in cosmetic and textile industries. Green synthesis, chemical reduction, evaporation, and condensation are some of the methods used for the synthesis of Ag-NPs.[5]

Metallic Nanoparticle as Catheter Modifiers

Central Venous Catheters are extensively used for intravenous administration of nutrients in malnutritional patients and for replacement therapy. However, they are very much prone to hospital acquired infections. *Staphylococcus aureus* is the main bacteria responsible for such infections and majority of them are methicillin resistant *S. aureus*. Ag-NPs are used to induce antimicrobial effects in such medical devices.[6]

Metal-Based Nanoparticles as Radiosensitizer

Metal-based nanoparticles are extensively used and analyzed radiosensitizers with a curative intent. Characteristically, the much smaller size of gold nanoparticles compared to others and outstanding biocompatibility has led to an increase in strong photoelectric photon absorption to differentiate between tumor and non-tumor cells. This factor is called therapeutic ratio which is introduced by high atomic number (Z) material into the target. Where, gold can play significant role as potent radiosensitizer possessing Z=79 on the edge of simple and easy synthesis.[7]

Mode of Action

Physical Mechanism

When a metallic nanoparticle interacts with the incident photon, it can be partially or completely absorbed by an electron of a metal atom. This absorption causes an ejection from the inner atomic orbital leaving behind a vacant site which is occupied by outer shell electrons releasing low energy. This phenomenon is called a photoelectric effect, followed by the cascade release of secondary electrons as a result of emitted low energy by the photon. The cascade release is termed as the Auger cascade plays a significant role in low-energy electrons production which is a key factor in highly targeted ionizing events.[8]

Biological Mechanism

Inside the cell, metallic nanoparticles interaction results in the production of oxidative stress and reactive oxygen species (ROS). This is carried by DNA damage and bystander effect. As the metal particles such as gold and silver are chemically inert and electronically active surface, they can catalyze the chemical reactions involved in increasing ROS. This is basically catalyzed by the transfer of electrons from metallic nanoparticles to oxygen present inside the cell which stimulates the production of superoxide. This leads to loss of function in mitochondria due to superoxides and H_2O_2 thus released in the cytosol as a result of membrane potential further damaging DNA and causes necrotic cell death. The mode of action of Au-NPs coated with drug have been illustrated in Fig.1 showing the mitochondrial damage and clinical applications.

Gold Nanoparticles (Au-NPs) (GNPs)

Plenty of studies on GNPs has attributed successful interaction and significant binding with targeted cancer cells at subcellular levels.

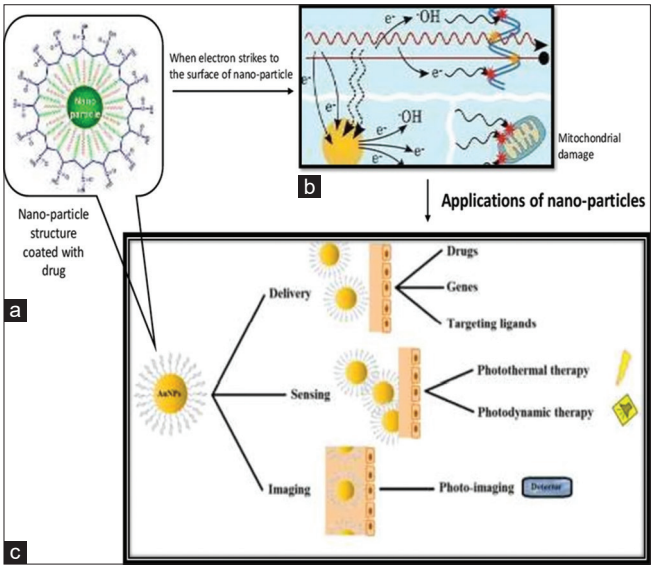

Figure 1: (a) Structural view of nanoparticle coated with drug (functional groups attached). (b) Excitation of electrons and energy when incident light strikes the surface of the nanoparticle and mitochondrial damage. (c) Wider application of gold nanoparticle in different parameters including drug delivery, bioimaging, and photothermal therapy

Exposure of cells to radiation causes certain biological effects such as cell cycle disruption and apoptosis which are dependent on different cell cycle phases. The late Synthesis phase (S-phase) is highly radioresistant, whereas the G2 phase and Mitotic phase is highly sensitive to radiations. Therefore, the checkpoints in G1, G2, and S phase have been activated by the cell as a defense mechanism. Gold nanoparticles increase in the sub G1 phase causes disturbance in the G1-S transition inside the cancerous cell and signals apoptosis leading to death of the cell. Radiation damages DNA by causing double-stranded breaks but gold nanoparticles combined with radiation increases residual damage. This residual damage causes delay or inhibition of DNA damage and further delay in repair mechanism of the cancerous cell, thus increasing radiosensitivity and enhanced radio sensitization.[9]

Gold Nanoparticles in Imaging

In the presence of nanoparticles, radiation absorption is dependent on the amount and size of nanoparticles inside the cell. Cellular uptake of nanoparticles can influence the radiosensitization, optimum range of gold nanoparticles significantly increases uptake, and hence increases radiosensitization and extensive imaging capacity. Additionally, higher atomic number and long circulation time of gold atom makes it suitable for CT scan imaging and electronic microscopy in detecting small tumors. Reports suggested that telomerase target cancerous cells except the healthy tissues, oligonucleotides which are potent inhibitors of telomerase serves as a promising method for anticancer approach. Due to inappropriate cellular uptake, limitations to this technology are resolved by utilizing gold nanoparticles (Au-NPs). These were combined with a mono-functional layer of oligonucleotides and cell penetrating amino acid chains which enhanced the radioactive oligonucleotides with beneficial ability to inhibit function of telomerase.[10] An increase in the formation of energy

cluster deposition while radiation therapy, gold nanoparticles combined with ionization radiations have been evaluated as a successful therapeutic approach. Gold nanoparticles uptake by cellular means increased differentiation potential between cancerous and non-cancerous cells.[11] Talking about effectiveness and efficacy of radiation therapy, it prevents the progression of tumors and further decreases growth of systematic metastasis. Thus, gold nanomaterials in radiation dose enhancer combined with local radiosensitizing agents such as cisplatin and docetaxel have a significant impact in future radiotherapy.[12] This study demonstrated that gold nanoparticles when involved in radiation therapy-induced cytotoxic effects in MCF7 cancer cells and DNA damage. In addition, the effects of gold nanoparticles were dependent on the size of the particles used for the study, where 4 nm particles damaged cytoplasm and 14nm were found in the nucleus. Not restricted to *in vitro*, *in vivo* studies also suggested the delay in tumor growth of the human triple negative breast cancer xenograft mouse model (TNBC). The authors, further, underlined the importance of size-dependent gold nanoparticles for immunological mechanisms and future capabilities of radiotherapy treating cancer.[12] From radiotherapy to optical imaging agents and photothermal therapies, gold nanoparticles have evolved as an effective tool in cancer detection. The ability of gold nanoparticles to function as multiple clinical radionuclides further illustrated their utilization in single-photon emission computed tomography and positron emission tomography in targeted therapeutics.[13]

Zinc Nanoparticles

Nanoparticles doped with Zinc hydroxyapatite were synthesized and combined with ionization radiation to inhibit the growth of breast cancer cells. When the quantity of zinc metal was increased an elevated percentage of β-tricalcium phosphate and phases were discovered. Whereas, low percentage resulted in anti-growth agent for developing cancer cells and also induced apoptosis cleaving caspase-7 and other beneficiary proteins. They also suggested the use of low dose of Zinc MNPs irradiation therapy of breast cancer cells.[14]

The ability of pure Zinc oxide nanoparticles in radiosensitizing breast cancer lines MDA-MB-231 has also been demonstrated alone and in comparison, with chitosan Zinc Oxides bio-nanocomposites (CS-ZnO BNCs). The authors also tested for the Toxicity by MTT assay indicating CS-ZnO as least toxic at various parameters. However, size dependability of these nanoparticles was also given importance in tracking radiobiological characteristics and induction of apoptosis. They were also able to delay the DNA repair mechanism, hence, can be used as potential radiosensitizers when studied both *in vitro* and *in vivo*.[15] Radiosensitization efficacy and *in vitro* antitumor properties of nanoparticle Zinc Oxide Caffeic acid (ZnO-CA) were evaluated by assessing cell viability in the human breast (MCF-7), elaborating it further by *in vivo* assay. It was observed that ZnO-CA nanoparticles resulted in a decline in tumor growth and its overall weight. B-cell lymphoma-2 was down-regulated, a decrease in the level of vascular cell adhesion molecule 1 and protein depression of 2 (p-ERK1/2) was hindered by applying nanoparticles during ionization radiation, whereas DNA fragmentation and cyclic phase sub-G_0/G_1 indicated the cell death by absorbing maximum radiation and showing absorbance peaks in cancerous cells. Thus, supporting the role of using zinc oxide nanoparticles in cancer therapy and highlighting the future advancement in nanoparticle-based therapeutics.[16] Reported the application of synthesized superparamagnetic nanoparticles of Zinc oxide combined with cobalt and ferrous Zn0.4Co0.6Fe2O4 in radiotherapy against HT-29 colorectal cancer. The ability of these nanoparticles in radiosensitization and anti-tumor was assayed by colony formation method which estimated that 43% of cancerous cells were prevented during the cell growth. Furthermore, the author suggested that synthesis of Zinc-oxide coated with other nano-particles or in combination can improve efficacy of radiotherapy in response to colorectal cancer.[17] After effects and regrowth of cancer cells were the two major challenges in treating with radiations which are densely connected to induced therapy cellular senescence. Therefore, an investigation of cancerous cell properties treated with gamma-irradiation revealed the signs of senescence among the cell cluster after eradication. Furthermore, the ability of cells to regrow within 10–20 days was seen but was reduced after treatment with Zinc-Oxide nanoparticles assumed to attract more therapeutic options for residual senescent cancer cells or oncogenes.[18]

Discussion

Metallic nanoparticles have wide clinical applications such as antimicrobial agents, drug targeting activity, prevention of hospital acquired infections by use of medical devices, etc. Gold and Silver nanoparticles are also extensively used in cosmetic and textile industries. Research activities are going on coencapsulation of bacteriocins isolated from probiotic microorganisms with metallic nano-particles such as zinc and silver. Bacteriocins or the natural antibiotics along with metallic nanoparticles increases the antimicrobial activity manifolds.

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