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Review Article

Recent Advancements in the Clinical Applications of Gold Nano-Particles

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Abstract

The rapid progress in the field of nanotechnology provides a variety of opportunities to improve the therapeutic strategies to fight against life-threatening diseases like cancer, HIV, COVID-19, etc. In general, higher atomic number metal nanoparticles are used for this purpose. Among a number of heavy metal nanoparticles, the gold nanoparticles of different particle sizes are more attractive due to their suitable physical and chemical properties along with excellent electromagnetic radiation absorption ability. Several disciplinary works are in progress for the last few decades to improve the applications of gold nanoparticles as biomedicine by reducing their toxicity and enhancing their efficacy.

Keywords: Gold Nanoparticle; Clinical Application; Radiotherapy; Cell Imaging; Drug Delivery; Photo Thermal Therapy

Abbreviations

GNP: Gold Nanoparticle; PTT: Photo Thermal Therapy

Introduction

The nanometric form of gold, known as gold nanoparticle (GNP) is a vital entity in biomedical application [1-6]. GNP serves vital remedial role in various diagnostic field such as several heart related problems, arthritis, venereal issues, hysteria, tumors, and also in the field of syphilis diagnoses. Several clinical processes such as, radiotherapy [7], photo thermal therapy [8], CT imaging [9], drug delivery [10], nano-enzyme delivery [11], targeting etc. are recently used for the treatment of these diseases. GNP is very good chemical which is used for different purpose of these clinical methods. In the present review, a brief description of these techniques will be delivered along with the importance and the use of GNP for these clinical processes.

Descriptions of clinical methods

- **Radiotherapy:** In the process of radiotherapy, a high intensity radiation beam (the radiation may provide externally or the source of radiation may also can implanted in the body) is freed to tumors until the ruin of intracellular components or the death of stem cells which induces the tumor. This type of treatment is very effective. More than half of the cancer patients could be cured by this method [12-17].

- **Photo thermal therapy:** The photo thermal therapy (PTT) is a clinical process in which the treatment was done by the help of light. In this process the light was absorbed by the plasmonic nanoparticles which generate heat to destroy the affected cells by the help of thermal ablation [18,19].

- **CT imaging:** The computed tomography (CT) imaging is the process in which the 3D imaging of tissue is done with high accuracy. It is generally noticed that the elements which have a high atomic number and also have a high density, is a good absorbent of x-rays. If consecutively the x-ray energy is equal to the targeted atom K-shell electron binding energy then a sudden increase of absorption noticed, which is identified as K-edge. For that reason, to access a good contrast images we have to tune x-ray source energy in between the range of targeted atoms K-edge contrast [20,21].

- **Drug delivery:** In the process of drug delivery, the required drugs send to the targeted area by the help of special carrier. When GNP is used as a drug carrier, there are several scope of modification of its surface area by appropriately changing the functional group over its surface. Presently, cationic polymer such as thiol, amine or carboxyl group are employed to enhance the surface area of GNP to attach more drug on its surface [22,23]. The surface engineered GNP provides a stable and efficient immobilization of the drug. It is superior to protect the drug from the effect of enzyme degradation by the help of encapsulation of the drug with GNP complexes and in that case the serum proteins present in the blood stream couldn't harm it. In the case of targeted drug delivery, we have to attach the target specific molecules with the drug-GNP complexes to deliver at cell specific zone [24].

Advantages of the use of GNP

The several uses of GNP in cancer treatments as well as radiotherapy, photo thermal therapy, CT imaging and drug delivery are explored in recent time. This is because, its physical, chemical, electronic and optical properties are far better in the direction of its application in the field of clinical and therapeutic use than other metals. It holds a good biocompatibility, strong absorption power and a high accumulation rates with a simplified surface chemistry property which help it to exhibit a better molecular attachment capacity. If we want to functionalize the GNP with small molecules, DNA as well as proteins then we have to use the surface coating technique of GNP with the help of the group of phosphate-containing agent like thiol or amine. By the help of surface modification, we can improve the efficiency, stability, toxicity and reduces the aggregation probability of GNP.

Rapid expansion of the use of gold nanoparticles (GNP) in the field of clinical and biomedical areas at present research avenue has inspired us to explore more usefulness of GNP in the similar and allied fields. Present review will help to catch up a glimpse of the present status in the research filed and clinical uses along with predicted future aspects.

Use of GNP in different avenues of clinical and therapeutic area

Radio therapy for cancer treatments

Cancers is a big threat for our human society as well as health and standard of life. In this situation radiotherapy show a significant prosperity on cancer treatment. Mainly two types of radiotherapy are commonly used. These are named as externally placed beam radiotherapy and internally placed radioisotope therapy. These two methods are frequently implemented in present time cancer treatment. It is observed that there are positive effects on regional lymph node, early and terminal case of solid tumors and metastatic stage tumors also. A cellular damage takes place in this process when the biological tissues exposed in front of ionized radiation. However, till now, this clinical process has major limitations. There are toxic side effects and local discomforts of its use. Unwanted dose heterogeneity and a long-range exposure of healthy tissues are also the major concern. There has a strong evidence which suggests that if the radio resistance of a tumor cell is developed then it requires higher doses radiation treatment, which may cause of damage or death of normal cells and tissues.

There are several therapeutic methods presently have developed in radiotherapy field, such as inverse treatment planning with the help of improved computer assistance, radiation therapy with the help of intensity-modulation, image guidance, particle therapy and stereo-tactic radiation therapy to provide more accurate and efficient amount of drug dose delivery to the targeted zones [25]. Now a days, different proposal of strategies are coming out in a response to balance the tolerance level of the patient and reduce other harmful side effects. It may be highlighted such as an attempt to enhance the radiation tolerance quality of the normal tissues, reversing the resistance of radiations of tumour tissues, maintain the limit of the radiation deposition dose in tumour volume. Research activities are also going on to increase the radio sensitization percentage of tumour tissues [26]. The radio sensitizers are the chemical or biological compounds which can enhance the effective dose of radiation therapy in the case of cancer cells. For this reason, it gained a lot of attention in cancer treatment. The heavy metal nanoparticles, such as bismuth (Z = 83) [27], gold (Z = 79), tungsten (Z = 74) [28], tantalum (Z = 73) [29], hafnium (Z = 72)

[30] and silver (Z = 47) [31] are normally used for dose enhancers in the case of radiotherapy for their strong ability of attenuation of photons, and a strong ability to maintain the deposition rate of radiation. These elements are also identified as “nanoenhancers” and have much more mass energy absorption coefficients than other normal soft tissues [32]. The absorption advantage may even increase ~100 times. After a several investigations on various kinds of nanoparticle for the use of radio therapy applications, it is identified that the gold nanoparticle has better efficiency for the clinical applications and treatment of various kind of cancers.

The factors that helps gold nanoparticle as a better radiotherapy sensitizer are as follows:

1. The GNP has a high Z number which helps it to hold a high coefficient of photoelectric absorption.
2. GNP has large surface area to volume ratio.
3. GNP is inert material which has excellent biocompatibility and low level of biological toxicity compared to other traditional agents such as cyclooxygenase-2 inhibitor, cisplatin, iodinated DNA-targeting agents, dazone.
4. GNP is high contrast agent for cell imaging and thus, very useful for clinical diagnosis.
5. GNP has enhanced permeability and retention (EPR) effect and a very low systemic clearance at the affected site. It can preferentially deposit at tumour cells. On the other hand, It has very low permeability in the blood vessels and normal capillaries in different tissues such as lungs tissues, skin and heart.
6. The GNP has a good controlled size distribution as well as unique electro-chemical and optical properties in between the range of 1 to 150 nm.

The review of Yao Chen., *et al*. [33] summarize the various applications and role of gold nanoparticle in several types of localized radiations includings X-rays, gamma rays and proton therapy. This paper also tries to discuss on the strong mechanism of radio-sensitization to give a basic theoretical knowledge for future generation to develop the nanoparticle assisted radiotherapy.

Gold nanoparticle as a multi-functional agents

Due to the difficulties of *in vivo* drug delivery by the first generation nanoparticle, the second and third generations of nanoparticle are appropriately designed in taking the focus on the modifications of surface. The modifications may help it to make more efficient in enabling and targeting. Taking all concerns into our account we can say that the fictionalized gold nanoparticle can exhibit a large range of application advantages:

1. It enhances the blood circulation period and the uptake capacity of cells in tumour, and also with developed clearance, targeted at the inhibiting tumour metastasis and invasions.
2. Its coupling sites may offer to help biomarkers in the case of efficacy predictions and disease diagnosis.
3. Specified targeting sites in the case of targeting drug delivery, we can reduce the toxicity, take back the clearance and surveillance by the help of immune system and try to inhibit multidrug resistance (MDR).
4. It can deliver the drugs at the targeted zones in control formats and also helps to reduce the side effects.

Active targeting and passive targeting are the two types of targeted drug delivery methods that are normally used to ensure the adequate concentrations of the gold nanoparticle into the tumour cells. In a case of passive targeting, it is observed that a high amount of endocytic uptake by the cancer cells and the tumour vascular leakage around it was used to organize large levels of accumulation of the nanoparticle into the tumour cells. On the other hand, in the case of the active targeting the gold nanoparticle was quoted as per requirement with the specific molecules to target the receptors of the cancer cell. Its function is similar to the function of antibodies.

Use of enveloped GNP

In very recent age, the use of enveloped GNP is increasing due to several advantages of its modeling. It is very easy to decorate the envelope of GNP having the desired property according to the choice of its use. So far a variant of organic and inorganic compounds are used for the coating of GNP. A few of them are described here.

PEG coated GNP

Polyethylene glycol (PEG) is a well-known surface modifier. We can hide the gold nanoparticle by the help of polyethylene glycol surface coating. This kind of characteristics helps us to reduce the gold nanoparticle identification capacity by the help of RES and the gold nanoparticle surveillance, to enlarge the efficacy of blood circulation time. The polyethylene glycol can culture by the covalent linking, where the covalent bond helps to absorb or encapsulate the polyethylene glycol chain above the surface of the gold nanoparticle.

The core shape and size of gold nanoparticle can be modified by the help of biocompatible and non-immunogenic bifunctional polyethylene glycol and it also helps to regulate the surface charge of the gold nanoparticle which can positively affect the bio distribution of it. Kumar., *et al*. [34] provided a good demonstration on the biocompatibility and the low cytotoxicity of the polyethylene gylated gold nanoparticles (pGNPS) in the Hela cells. When we try to couple it in case of *in vitro* x-ray irradiation, it provides 1.3 - 2.8 times higher cell death after completing the treatment with the several concentrations of polyethylene gylated gold nanoparticle compared with the control group cells which is present without the polyethylene gylated gold nanoparticle. From another study of Yasui., *et al*. [35] it is found that poly ethylene gylated nanogel and gold nanoparticle combination can radiosensitized by the help of X-Ray irradiation with 220 kVp of Chinese hamster lung fibroblasts V79 and murine squamous cell carcinoma SCCVII. This kind of radiosensitization helps to slain DNA repair capacity and raises apoptosis by the help of stress related proteins over expressing endoplasmic reticulum. We also found from another study that for the case of B16F10 murine melanoma cells a cellular uptake enhancement was done by the help of polyethylene gylated gold nanoparticle which arrange the radio sensitization effects at the presents of irradiation with 6MeV.

From the above discussion, it can be conclude that the gold nanoparticle is applicable in the field of radiotherapy as a theragnostic agents. In the case of *in vivo* application, it is observed that around the blood vessels a large amount of polyethylene gylated gold nanoparticle aggregates but in the case of cellular uptake it shown a limited efficacy. So, it can be stated that we need further development of the surface of gold nanoparticles to sensitize the tumor cells by the help of irradiation effect.

Chitosan coated GNP

It is found that Chitosan is a pseudo natural cationic polymer with some special properties. For these unique properties researchers have tried to use it in several fields such as depollution and flocculants for protein recovery. It also has some other characteristics such as biodegradability, biocompatibility, sensitivity with the help of chemical modification, and a governed drug release. Depending on these pharmaceutical characteristics it is used frequently in the field of medical use.

BSA coated GNP

The bovine serum albumin (BSA) is an effective efficient surface modifier having the characteristics of excellent biodegradability, biocompatibility, flexibility in surface modification and bio-safety. When BSA-coated nanoparticle is delivered, at the time of its delivery it is apparently invisible in the blood circulation cycle. These characteristics stretch its existence in the blood circulation and help the nanoparticle to exhibit better therapeutic efficacy. In addition to this, the BSA-coated gold nanoparticle are used in several fields of application such as bioimaging, gene carriers, biosensing, drug carriers and cancer therapy.

Conclusion

In this review, the use of gold nanoparticle in clinical and medical area is discussed. The advantages and disadvantages of its use is also highlighted. From this study it can be concluded that GNP has excellent contrast properties, efficient drug delivery properties and superior therapeutic efficiency. Still, this field of research is emerging and there are huge vacant areas of its application which is not explored yet. We are hopeful that more and more researches will be carried out in this regard which will help to develop our clinical and medical aids.

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Conflict of Interest

Authors declare that there is no conflict of interest.

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