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GOLD NANOPARTICLES: THE GLITTER OF ONCOMEDICINE.

[1]*Dr. Shaikh Firdous, [2]Dr. Sonia Sodhi and [3]Dr. Aamena Farooqui

[1]*Post-Graduate Student, MDS Oral Medicine and Radiology, CSMSS Dental College and Hospital, Aurangabad.
[2]Reader, Department of Oral Medicine and Radiology, CSMSS Dental College and Hospital, Aurangabad.
[3]Head, Department of Biotechnology, Dr. Rafiq Zakaria Centre for Higher Learning and Advanced Research, Aurangabad.

***Corresponding Author: Dr. Shaikh Firdous**

Post-Graduate Student, MDS Oral Medicine and Radiology, CSMSS Dental College and Hospital, Aurangabad.

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ABSTRACT

Nanotechnology is the branch of technology that deals with dimensions and tolerances of less than 100 nanometers. Nanomedicine is the medical application of nanotechnology. Nanoparticles have been making their way in biomedical applications and personalized medicine, allowing for the coupling of diagnostics and therapeutics into a single nanomaterial- Nanotheranostics. Gold Nanoparticles (AuNPs), in particular, have unique features that make them excellent nanomaterials for theranostics, enabling the integration of targeting, imaging and therapeutics in a single platform, with proven applicability in the management of heterogeneous diseases, such as cancer. Oral cancer is a prevalent cancer on a global scale. Nanoparticles can be used to detect / monitor cancer &/or alternative to traditional therapy.

KEYWORDS: Nanomedicine, gold nanoparticles, oncology, Nanotheranostics, Oncomedicine.

INTRODUCTION

Little things make big difference. An exciting revolution in health care and medical technology looms large on the horizon. Yet the agents of change will be microscopically small, future products of a new discipline known as nanotechnology.[1] Nanotechnology is the science and technology of small things – in particular, things that are less than 100nm in size. There are many natural nanoscale materials, such as catalysts, porous materials, certain minerals, soot particles, etc., that have unique properties particularly because of the nanoscale features.[2]

This review article mainly focuses on gold Nanoparticles & the revolution brought in the field of oral medicine and radiology focusing primarily on oncodiagnosis and treatment of malignancy.

Nanomedicine

Nanomedicine has been defined by the European Science Foundation's forward Look Nanomedicine as follows: "Nanomedicine uses nano-sized tools for the diagnosis, prevention and treatment of disease and to gain increased understanding of the complex underlying patho-physiology of disease. The ultimate goal is to improve quality of life." A relevant more recent terminology is that of "theranostics" involving both diagnostics and therapy with the same nanopharmaceutics.[3] Present-day nanomedicine exploits carefully structured nanoparticles such as dendrimers, carbon fullerenes (buckyballs) and nanoshells to target specific tissues and organs. Nanotherapeutics help to overcome the lack of selectivity, multidrug resistance and lack of aqueous solubility of conventional cancer chemotherapy.[4] This spectrum of nanotechnology is supposedly the fastest developing arena of medicine.

History of Nanomedicine

Nanotechnology was envisioned by the physicist and Nobel laureate Richard Feynman in his seminal lecture "There is plenty of room at the bottom" in 1959. After discussing his ideas with a colleague, Feynman offered the first known proposal for a nanomedical procedure to cure heart disease: "A friend of mine [Albert R. Hibbs] suggests an interesting possibility for relatively small machines"[5] Nanomedicine can be traced back to the use of colloidal gold in ancient times but Metchnikov and Ehrlich (Nobel Prize for Medicine in 1908) are the modern pioneers of nanomedicine for their works on phagocytosis, respiration, cell-specific diagnostic and therapy. Mentions of nanoparticles in relation to biomedicine appeared in the late 1970s but the term "Nanomedicine" only appeared at the turn of this century, and less than 30 papers term were published up to 2005. Ten years later, Web of Science indicates the publication of more than 1000 Nanomedicine article in 2015.[3]

The Nanoparticles of Aurum(Au)

Major classes of biologically relevant nanostructures include semiconductor quantum dots, magnetic nanoparticles, polymeric particles, carbon-based nanostructures and metallic nanoparticles.[6] Nanoparticle multifunctionality is accomplished by combining different properties for imaging, targeting, or therapeutic delivery into one single platform.[7] Compared with other nanostructures, metallic nanoparticles have proven to be the most flexible nanostructures

owing to the synthetic control of their size, shape, composition, structure, assembly and encapsulation, as well as the resulting tunability of their optical properties.gold nanoparicles are the leading ones in the world of Nanomedicine in today's scenario. Ranging in diameter from small clusters of 2–5 nm up to 100 nm, AuNPs can be synthesized in different shapes such as spheres, hollow, rods, diamonds, prisms, cages, either single solid bodies or in a core shell format.[8] The most widely applied and simplest methods to produce AuNPs use chemical reduction of gold salt to metallic gold in the presence of a capping ligand, with the Turkevich and Brust-Schiffrin methods being the standards for aqueous and organic-based synthesis, respectively.[7] GNPs exhibit unique physicochemical properties including surface Plasmon resonance (SPR) and the ability to bind amine and thiol groups, allowing surface modification and use in biomedical applications.[9] It is demonstrated that gold Nanoparticles have an immense potential to enhance the efficiency of cancer treatment.[10]

AuNPs in photodiagnosis:

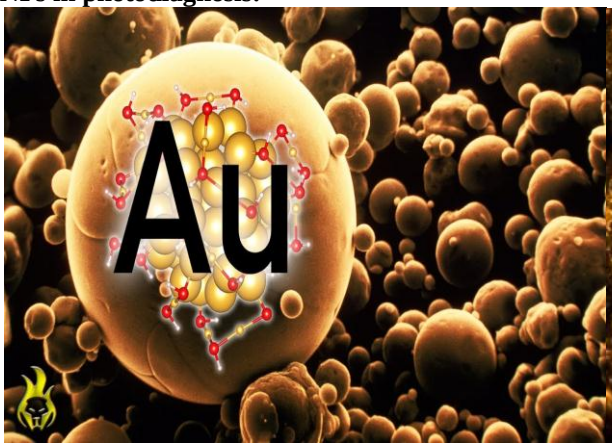

Fig 1: The 3-D Structure of Gold.

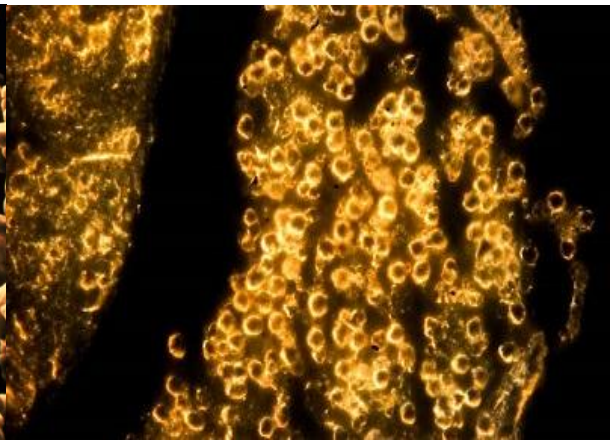

Fig 2: Gold Nanoparticles

Oral squamous cell carcinoma is the sixth most common cancer for both sexes worldwide.[11] today biopsy is considered as a gold standard for the diagnosis of oral squamous cell carcinoma but this procedure possesses greater risk of infection and psychological trauma being an invasive technique.

Recently, an increased amount of effort has been made to develop less invasive early diagnostic modalities for oral cancer, of which the *in vivo* high-resolution imaging of oral epithelial tissues using novel optical systems and the chemical analysis of saliva show great promise as valuable tools.[12] Metallic nanoparticles have recently been investigated to overcome the limitations of these imaging and chemical-based diagnostic techniques.[5] metallic nanoparticles exhibit unique optical response to light which allow them to resonantly scatter light when excited at their surface plasmon resonance frequency[13] Gold nanoparticles also possess other favourable physicochemical properties for use as optical probes for early detection of oral cancer. They can provide an optical contrast to discriminate between cancerous and normal cells.[14] They can be easily conjugated to antibodies or peptides through electrostatic charge interaction or coordinate bonding to probe for specific cellular biomarkers with high specificity and affinity. When coupled with appropriate biomarkers, these gold nanoparticles bioconjugates may provide useful optical signal for molecular specific information to assist clinicians in diagnosis of pre-cancers.[15] The studies by Sokolov *et al.* showed that gold nanoparticles can be targeted molecularly to cancer cells and tissue by conjugation with anti-epidermal growth factor receptor (anti-EGFR) antibodies.[16] Metal nanoparticles, especially gold nanorods, also exhibit enhanced two-photon and multiphoton luminescence. Sensor test chips containing thousands of nanowires, able to detect proteins and other biomarkers left behind by cancer cells, could enable the detection and diagnosis of cancer in the early stages from a few drops of a patient's blood.[17] Swift detection of oral malignant and premalignant lesions has been made possible by the development of this nano-bio-chip, which is able to detect oral cancer via an immediate, noninvasive technique.[18]

AuNPs in imaging

The implementation of imaging techniques for diagnostic purposes enables the non-invasive assessment of anatomical, functional and molecular information, with image-guided drug delivery gaining much attention nowadays.[19] The imaging modalities most often used in the clinics are computed tomography (CT), ultrasound

(US), magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), photoacoustic tomography (PAT) and fluorescence imaging. CT is a commonly used diagnostic imaging tool offering broad availability at a relatively modest cost. This modality usually provides image contrast to visualize tissue density differences and may be tuned to distinguish between normal and cancerous tissue.[20]

The properties of AuNPs that has resulted in the exploration of AuNPs as contrast agents for X-ray based imaging techniques such as computed tomography (CT) are listed below,[7]

1. The high atomic number and electron density of Au leads to efficient absorption of X-ray irradiation, superior to conventional iodine-based contrast agents currently used in the clinic.
2. AuNPs can offer longer circulation times than conventional agents, enabling prolonged imaging, targeting to specific cell types or other ligands and cell tracking.
3. The payloads of AuNPs in biocompatible carriers can be precisely controlled
4. The biocompatibility of gold compared with other elements that also strongly attenuate X-rays.

Fluorescence imaging is highly suitable for high-throughput screening with high sensitivity, providing detailed molecular profiling with subcellular resolution, enabling multicolor imaging and being relatively inexpensive, but has low tissue penetration and spatial resolution, thus limiting its applications in clinical settings.[20] The fluorescence of bulk gold, first observed by Mooradian in 1969, is very weak with a quantum yield in the order of 10−10. Strikingly, strong fluorescence with a quantum yield of up to 10−3 is observed in AuNPs such as rods or shells.[7] Another common class of nanostructure contrast agents includes the magnetic nanoparticles, which are used to improve the imaging contrast in MRI.[21] Park et al. were able to image the 3D distribution of luminescent gold nanoshells (AuNS) in murine tumors using two-photon induced photoluminescence.[22] The SERS mechanism is a result of two major enhancements that result in an increase in the Raman scattering cross-section of the adsorbed molecules. First, there is the long-range electromagnetic (EM) enhancement, Second, there also exists a short-range chemical enhancement.[23] Colloidal gold nanoparticles have been used widely as SERS substrates to probe components in living cells, especially to study the interaction of various antitumor drugs with their pharmacological targets, such as DNA, within living cancer cells.[23][24] In photo acoustic imaging, the subject is irradiated with light, which results in localized heating, and a small expansion of tissue, causing a sound wave. Use of short laser pulses generates sound waves in the ultrasonic frequency range.[25] Agarwal et al. published one of the earliest examples of gold nanoparticles used as contrast agents for photo acoustic imaging.[26]

Availability of a highly advanced contrast enhanced diagnostic imaging modality provides a helping hand to the physician in overcoming the challenges in identifying & treating diseases like pre-cancers as well as malignancy.

AuNPs in therapeutics

The current line of treatment for malignant lesions is considered to be radiotherapy along with chemotherapeutic agents as an adjunct with or without surgical intervention. Chemotherapeutic drugs target rapidly dividing cells, and thus not only kill cancer cells, but also destroy normal cells like bone marrow cells and immune cells. This gives rise to widespread "collateral damage" in the patient's body. Radiation therapy involves the use of high energy radiation like X-rays and gamma rays to destroy tumor cells, and inevitably causes deleterious effects to healthy tissues along the radiation path.[27] Nanotechnology is probably the only method that can be used for site-specific action without causing side effects by killing the normal cells.[5] The use of AuNPs is gaining popularity in these areas of research for several reasons. Firstly, AuNPs are considered to be relatively biologically non-reactive and therefore suitable for *in vivo* applications compared to the very toxic cadmium and silver NPs, although various groups are challenging this view. Other advantageous qualities include the strong optical properties of AuNPs due to localized surface plasmon resonance (LSPR), easily controllable surface chemistry which enables versatility in adding surface functional groups, and lastly, the ease in control over particle size and shape during synthesis. AuNPs may be considered to be fully multifunctional, with the possibility of combining different desired functionalities in one molecular-sized package. All these factors contribute to the strong interest and preference for the use of AuNPs over other NPs.[27]

The therapeutics modalities discussed in this article are;

- 1} AuNPs in Drug Delivery.
- 2} AuNPs in Phototherapy.
- 3} AuNPs as Radio sensitizers.
- 4} AuNPs in Gene delivery.

1] AuNPs in Drug Delivery.

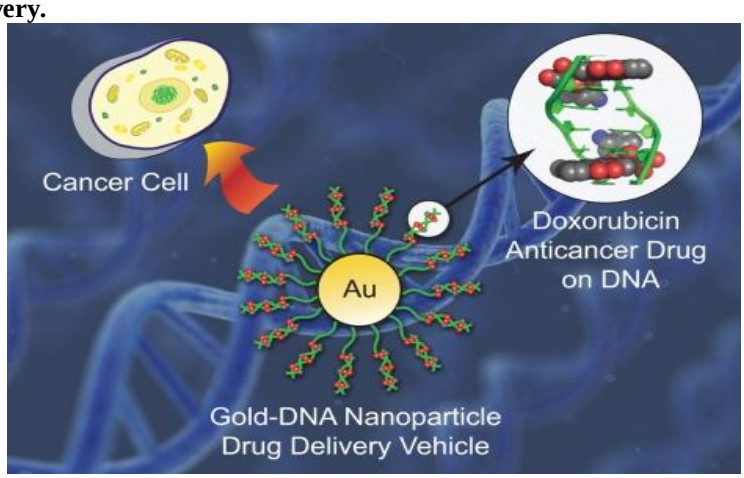

Fig 3: AuNPs in Drug Delivery.

Delivery of molecules into cells, AuNPs have been described as "promising nanocarriers for therapeutics" owing to their ease of synthesis and functionalization, relative biocompatibility as well as low toxicity in preliminary assays.[27] There is intense interest in modifying existing drugs to improve pharmacokinetics, thereby reducing non-specific side effects and enabling higher dose

delivery to target tissues.[28] AuNPs have a range of properties that make them suitable for drug delivery. Additionally, high surface area and a choice of surface chemistries facilitate the loading of not only a large therapeutic cargo but also other entities such as targeting molecules, linkers, additional contrast media and so on.[7] Spivak and co-workers developed and tested a gold nanoformulation for drug delivery and treatment of heart failure by demonstrating that levosimendan functionalized AuNPs (Simdax) were able to accumulate in the endothelial cells of infarcted arterioles and capillaries. The nanoformulation showed significant cardioprotective effects in doxorubicin-induced heart failure rats, higher than that of Simdax alone.[29] While the ease of surface modification is what makes AuNP attractive for drug delivery, the strength of drug attachment and timing of the release needs to be suitably controlled to produce the highest therapeutic efficacy. Foremost, the method of release at the tumor site is dependent on how the drug is attached to the AuNP, whether covalently or through non-covalent binding. Generally, drugs in the active form are loaded non-covalently while the covalent-conjugation of the drug to AuNP is in the pro-drug form, thereby requiring a second reaction to release the drug from the attachment as well as to activate it.[27] Similarly in the field of cancer therapy, AuNPs are currently being explored as potential drug delivery agents for the introduction of drugs into tumor cells.[30] Huang *et al* (2008) have described two methods for tumor targeting: the first involved conjugation of AuNPs to PEG, and the second involved conjugation of AuNPs with specific antibodies which bind unique biomarkers expressed on tumor cells.[31] Jiang et al synthesized citrate-coated GNPs of controlled sizes ranging from 2 to 100nm bound with multiple trastuzumab antibodies to enable targeting and cross-linking of human epidermal growth factor receptor (HER)-2 in human SK-BR-3 breast cancer cells.. This important work demonstrated that GNPs may not simply act as passive drug carriers, but may also influence drug–cell interactions and enhance therapeutic effects.[32] The development of polymersomes offers a novel way to deliver therapy directly into tumour cells. Use of PMPC-PDPA (poly 2- (methacryloyloxy)ethyl phosphorylcholine) polymersomes may enhance polymersome-mediated antitumor therapy.[33]

2] AuNPs in Phototherapy

One of the major advances in minimally invasive therapies for cancer is photodynamic therapy PDT).[5] Gold nanoparticles have been used to harm bacteria, viruses, and cancer cells based on their heating effects under laser irradiation due to the enhanced absorption induced by localized surface plasmon resonance (LSPR); this is defined as photothermal therapy.[10] Photothermal therapy (PTT) is based on the selective sensitization of cells to thermal damage, or hyperthermia, near 45 °C.[20] The property of photon absorption and conversion into thermal energy by AuNPs quickly found use in photothermal therapies, especially for cancer applications.[7] Traditionally, heat has been used in the treatment of cancer via the induction of hyperthermia, a condition in which cells are subjected to high temperatures which kill them. While the sources of heat varies from microwaves, radiowaves, ultrasound waves to laser light in the past, such approaches to cancer therapy have not been widely used because of the consequential damage to normal tissues surrounding the targeted tumor. With the advent of nanotechnology, diverse nanostructures have been manufactured for the purpose of photothermal therapeutics. Noble metal NPs such as AuNPs (and including Au nanospheres, nanorods, and nanocages) attract particular interest because they possess enhanced absorption cross-sections. Their strong absorbance enables effective laser therapy with minimal "collateral damage" to the surrounding healthy tissue.[27] In addition to the strong Mie scattering,

gold nanoparticles absorb light strongly as a result of the SPR.[6] SPR is the mechanism by which AuNPs exhibit the photodynamic effect. Many researchers have focused on the photothermal therapy of gold nanoparticles with different size and morphology, such as gold nanorods (GNRs), gold nanostars, gold nanorings, gold nanocages, and hollow gold nanoshells.[10] This therapeutic approach can be highly targeted to cancer due to greater nanoparticle accumulation in tumors compared with normal tissue and selective irradiation of only the tumors. For example Chen et al. synthesized Au nanocages with tunable NIR absorption between 600–1200 nm.[7] Von Maltzahn et al used a theranostic approach to photothermal therapy using AuNRs to treat cancer in vivo.[34] Evaluation of this modality needs to be done by adapting this approach in clinical trials.

3] AuNPs as Radiosensitizers.

Another interesting feature of AuNPs is their radiosensitizing property.[7] Most researchers have attributed GNP radiosensitisation to increased photoelectric photon absorption by high-Z materials at kilovoltage photon energies.[28] Radiotherapy is widely used in cancer therapy since radiation (X-rays, γ-rays and fast-moving charged particles such as ions, electrons and protons) induces DNA damage, thus killing cancer cells. Gold is an excellent absorber of X-ray energy and can greatly elevate the dose of absorbed irradiation, once localized in the tumor site, thus increasing the therapeutic effects of the radiation dose.[7] The effectiveness of AuNPs as radiosensitizers seems to be closely related to their surface functionality.[27] Liu et al. tested different X-ray sources on cancer cell survival with and without the presence of PEG-coated AuNPs. They found that survival of cells that were exposed to Xrays in the presence of Au NPs decreased in an X-ray dose dependent fashion.[35] Hainfeld et al. evaluated 1.9 nm, PEGylated AuNPs for enhancement of radiotherapy in tumor bearing mice.[36] the discrepancy over the radiosensitizing effects of AuNPs may also be attributed to the different dimensions of AuNPs used as well as the type of tumor cells under study.[27]

Nanotoxicology:

Nanoparticles pose a separate problem within the area of toxicology, designated as nanotoxicology.[5] In applications where large doses are needed, such as CT, where doses as high 1.35 g Au/kg have been used, this is absolutely crucial. In applications where the dose of gold is much lower, such as photo acoustic imaging (as low as 22.7 μg Au/kg227), excretion may be less crucial, as small amounts of gold are typically present and tolerated in the body.[7] Bulk gold has generally been considered an inert metal valued for medicinal purposes and AuNPs have been thought to be likewise. In the literature, AuNPs have been reported to lack the ability to induce adverse and acute toxicity and are thus deemed to be biocompatible entities for use in biomedical applications.[27]

CONCLUSION

Medicine has come a long way from mere use of a torch to use of optical illumination for diagnosis of diseases. Invasive modalities are succeeded by the new less invasive and non invasive options available for trials as well as use. Acceptance of trending techniques guides towards doors of endless research. The ongoing study of gold nanoparticles has emerged as a new era of diagnostic and therapeutic medicine. Furthermore, experimentation is duly required for this branch to flourish.

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