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Review Article

Gold nanoparticles in cancer therapy: Overview and perspectives

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ABSTRACT

Nanoparticles can improve cancer diagnosis, imaging and therapy at the cellular and molecular levels. Gold as a drug and medicinal agent have been used for disease treatment since long time ago. Primitive application of gold for medicinal purposes returned to Alexandria, Egypt, Over 5000 years ago. It was used for mental, bodily and spiritual purification. Gold is a transition metal which is known to possess many intriguing properties. Its lustrous attributes has lead to avalanche of applications. Soluble and stable colored gold that appeared around 4th century B.C. in Egypt and China led to its use as a pigment for coating glasses, enamel and chinaware among others. Based on the concepts and the methodologies, various chemical methods of syntheses of GNPs evolved. The most important attributes of GNPs is their size tunability, easy absorption by body fluids and passage through the body circulation without rejection. GNPs can pass through leaky capillaries and directly reach tumor surfaces. The anticancer drugs either kill cancer cells or modify their growth. However, selectivity of majority of drugs is limited and they are one of the most toxic drugs used in therapy.

Keywords: Nanoparticles, Medicinal Purposes, Anticancer drugs.

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INTRODUCTION

Gold is a transition metal which is known to possess many intriguing properties. Its lustrous attributes has lead to avalanche of applications. "Soluble" and stable colored gold that appeared around 4th century B.C. in Egypt and China led to its use as a pigment for coating glasses, enamel and chinaware among others. The emergence of Nanoscience is a versatile branch of material science, which deals with the properties of material at nano-metric dimensions of 1-100 nm. Nano science has given enough evidence to show that at macro-scale and micro-scale levels the objects behave differently than that at Nano scale. During the reduction the size of a solid from micro-level to Nano-level, the appearance gets completely altered, especially with metals. Gold appears lustrous yellow at macro-scale, but when brought to nano-level its colour turns to various shades of red, depending on the size and shape of the nanoparticles.[1] Nanoparticles can improve cancer diagnosis, imaging and therapy at the cellular and molecular levels[2]. Gold as a drug and medicinal agent have been used for disease treatment since long time ago[3]. Primitive application of gold for medicinal purposes returned to Alexandria, Egypt, Over 5000 years ago. It was used for mental, bodily and spiritual purification.[4]

Development of Contemporary Concept of Gold NanoParticles (GNPs): For nearly forty years, Faraday's work remained unnoticed, even the scientists who worked on the ruby glass and Purple of Cassius were not aware of it. Zsigmondy[5] began his investigations into the color of ruby glass and formulated a method for preparing colloidal gold by reducing dilute, slightly alkaline solution of gold chloride with boiling formaldehyde. After becoming aware of Faraday's methods, especially reduction using phosphorus, he combined both the synthesis techniques to arrive at a two-step synthesis method. This method is referred to as the seed-mediated method in the contemporary literature and was called 'nuclear method' in the early days. Also the nanoparticles were typically described as ultramicroscopic particles and the in place of nanometers (nm) as a unit, the equivalent unit used was ultra-microns (μμ). gmondy invented the ultra-microscope which allowed Siedentopf and Zsigmondy to visualize the colloidal gold particles (i.e. nanoparticles), showing that colloidal matter consisted of dispersion of particles of measurable size. Zsigmondy was able to make some of the first particle tracking studies to determine the diffusion behaviour of the nanoparticles. Zsigmondy was awarded Nobel Prize in 1925 for his demonstration of the heterogeneous nature of colloidal solutions and for the methods he used, which have since become fundamental in modern colloid chemistry.[6]

Types of Gold Nanoparticles: Au-NPs could be categorized depending on the shape, size, and physical properties. The first achievement in the field of Au-NPs was Au nanospheres, although they were not exactly spherical. Later, various other forms were obtained, such as nanorods, nanoshells, and nanocages as shown in Fig.1. Another types of Au (gold) Nano Particles were also produced with great surface enhanced Raman scattering properties named as SERS Nanoparticles.

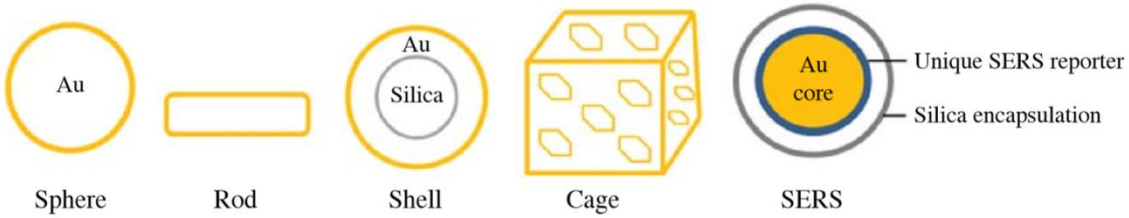

Fig.1: Schematic representation of various types of Gold Nanoparticles.

Au Nanospheres: The diameters could vary from 2nm to100nm, which could be synthesized by reducing aqueous $HAuCl_4$ solution with addition of various reducing agents under different parameters and conditions. The reducing agent, where most commonly used was the citrate, produced monodisperse Au nanospheres. Lesser the amount of citrate would yield the greater amount of nanospheres. Hence, many diverse methods for nanosphere synthesis were experimented using other reducing agents or ligands. Interestingly, dendrimers could be used as stabilizers or templates for synthesis of Au nanosphere preparation.[7-11] The shape and size of Au nanospheres would depend on controlling the synthesis parameter, such as, concentrations of the reactants, $HAuCl_4$, and blocked co-polymers. The absorption peak of Au nanosphere ranged from 510nm to 550nm. As the particle size increased, the absorption peak shifted to a longer wavelength, and the width of the peak indicated the range of size distribution. Interestingly, several investigators tried to grow Au nanospheres in human cells.[12]

Au Nanorods: Synthesis of Au nanorods was performed using the template method, based on the electrochemical deposition of Au within the pores of nanoporous polycarbonate or alumina template

membranes.[13,14] The diameter of Au nanorod could be pre-determined by the diameter of the pores of the template membrane. The length of Au nanorod could be controlled by the amount of deposited Au within the pores of the membrane. The most common way of synthesis of Au nanorod would be the "Seed-mediated synthesis", as it resulted higher aspect ratios in comparison to other methods.[15,16] Au seed solution was generally made in the presence of a strong reducing agent, like $NaBH_4$, for reducing the Au chloride. These seeds would act as the site of nucleation for nanorods. If they were would continue to grow in the presence of Au chloride growth solution along with a weak reducing agent, like ascorbic acid and hexadecyltrimethylammonium bromide1. By regulating the Au seed solution with respect to Au precursor, the aspect ratio of Au nanorods could be controlled.[17,18]

Au Nanoshells: Nanoshell referred as a type of spherical nanoparticle with a dielectric core, which was covered by a thin metallic shell (usually Au) [19]. These nanoshells involved a quasi-particle, called plasmon, produced from collective excitation or quantum plasma oscillation, where the electrons could simultaneously oscillate with respect to all ions. The simultaneous oscillation was also known, as Plasmon hybridization, which was associated with the hybridization of outer and inner shells to produce higher or lower energy levels. The lower energy level strongly would combine with the incident light, whereas the higher energy would not bind and could combine rather weakly with the incident light. Hence, the interaction of plasmon hybridization on thin shell layers would be stronger, and the shell thickness and overall particle radius, as coupled together, could determine the wavelength of the light emitted.[20] Au nanoshells could also be synthesized by changing the composition and dimensions of layers, which could be fabricated with Surface Plasmon Resonance (SPR) with peaks between visible and NIR regions.[21] By changing the core size ratio to its shell thickness, SPR peak of Au nanoshell could be tuned for a given composition. By coating Au nanoshells with silica or polymer beads, Au nanoshells could be prepared with SPR peaks in the NIR region.[22] The growth of silica cores was carried out by reducing Tetra-ethyl Ortho Silicate in Ethanol, using the Stober process. Silica NPs were coated with Au solution by using the seed mediated method1. Other approaches exhibited the attachment process of small Au nanospheres to the silica core with diameter of 2-4nm. The diameter of the silica core would determine the diameter of the Au nanoshell. The shell thickness could be controlled by the amount of deposited Au on the core surface.[23]

Au Nanocages: In 2006, Au nanocages, consisted controllable pores on the surface, were synthesized by the galvanic replacement reaction of truncated silver nanocubes and aqueous HAuCl4. Furthermore, it was observed that the generated morphologies of the Silver nanostructures could be controlled through Pylol reduction. Here, ethylene glycol reduced AgNO3 to generate silver atoms, and further reduction yielded nanocrystals or seeds. Desired nanostructures were produced through addition of extra silver atoms and by simultaneously controlling the silver seed crystalline structures with addition of polyvinylpyrrolidone, which posed a potential of selective binding to the surface.[24] By adjusting the molar ratio of silver to $HAuCl_4$, the dimension and wall thickness of the resultant Au nanocages could be precisely controlled. Au nanocages could provide some major advantages, such as: (i) their surface Plasmon resonance peaks could be tuned by changing the ratio between the Ag nanocubes and $HAuC_{l4}$. This could also cover the entire spectral region from 500 to 1200nm; (ii) by controlling the number of truncated corners and void sizes, their absorption coefficients could be varied; (iii) the Au nanocages could still exhibit resonance peaks in the near-IR region with extremely small size of about (50 nm); and (iv) surface modifications could be performed and applied in various biomedical applications.[25]

METHODOLOGY

Synthesis of Gold NanoParticles: Based on the concepts and the methodologies, various chemical methods of syntheses of GNPs evolved. Some of the common chemical syntheses methods of colloidal GNPs are mentioned are hereby briefly discussed. All these methods are based on reducing the gold ions to nanoparticles using chemical reducing agents.

Turkevich Method: The synthesis of colloidal gold nanoparticles by reduction of chloroauric acid with sodium citrate. The citrate ion acts as a reducing agent as well as a capping agent thereby producing monodispersed gold nanospheres. Turkevich and his co-workers explored the properties of color, coagulation, adhesion, alloying and other catalytic properties of colloidal gold.[26]

Brust Method: This is a method for synthesizing GNPs from $HAuC_{l4}$ in non-aqueous solution using tetraoctylammonium bromide as a phase-transfer catalyst and sodium borohydride to reduce Au(III) to Au(0) shown in Fig.2. There is no doubt to say the Brust process of gold nanoparticle synthesis is a valuable technique for preparing thiolstabilized nanoparticles, but the functional groups are limited by the compatibility of thiols, the identification of a

unique set of reaction conditions is often required for the preparation of each functionalized target, and most of the method in these reports are always accompanied with hazardous synthesis process.[27]

$NaBH_4$ Reduction Method: In $NaBH_4$ reduction process, $NaBH_4$ is the reducing agent and the citrate acts only as a stabilizing agent. The reaction rate in the single aqueous system is controlled by the reaction conditions. Different reaction parameters (e.g. reaction temperature, reactant concentration, addition rate for $NaBH_4$) are studied to get GNPs with uniform size distribution.[28]

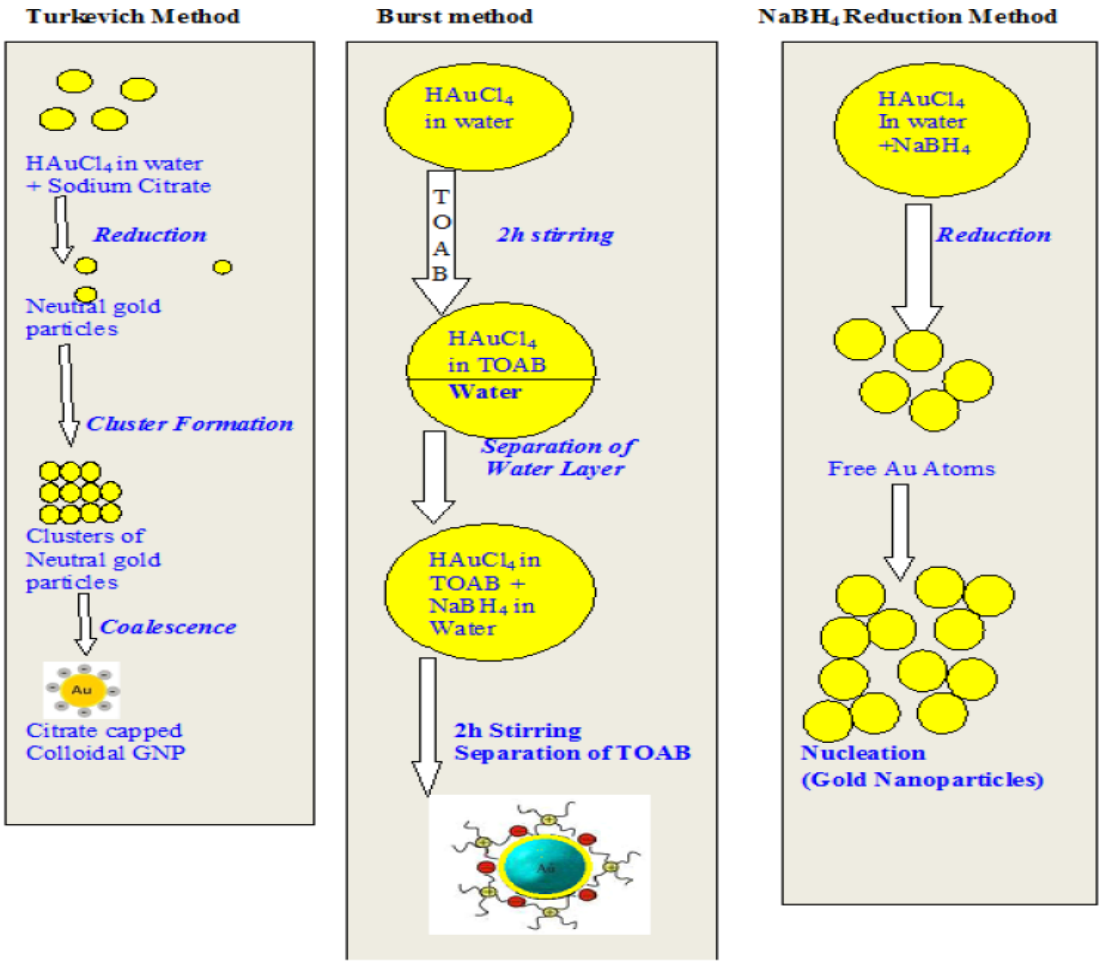

Fig. 2: Schematic diagram of various gold nanoparticales synthesis methods.

Martin Method: Martin Method was brought to light much later in 2010 by the Eah's group[29], this technique generates "naked" GNPs in water by reducing $HAuC_{14}$ with $NaBH_4$. Even without any other stabilizer like citrate, these GNPs are stably dispersed. The size distribution is nearly monodispersed and the diameter can be precisely and reproducibly tuneable from 3.2 to 5.2 nm. The key is to stabilize $HAuC_{l4}$ and $NaBH_4$ in the aqueous stock solutions with HCl and NaOH for >3 months and >3 hours respectively. In addition, the ratio of $NaBH_4$-NaOH ions to $HAuC_{l4}$-HCl ions has to be precisely controlled in the "sweet zone".

Treatment of Cancer: Advanced cancer that can't be cured, often still can be treated. The physical symptoms it causes almost always can be managed. At any stage of cancer, the treatment goal should be clear. You should know if the goal is to cure the cancer, slow its growth and help you live longer, or relieve symptoms. This can sometimes be confusing because some treatments used to cure cancer are also used to slow its growth or relieve symptoms.[30] The anticancer drugs either kill cancer cells or modify their growth. However, selectivity of majority of drugs is limited and they are one of the most toxic drugs used in therapy.[31]

Treatment of Cancer Using Metals: Among many chemotherapy drugs that are widely used for cancer, Cisplatin is one of the most compelling ones. It was the first FDA approved platinum compound for cancer treatment in 1978.[32]

Treatment Using Gold Nanoparticles: Gold nanoparticles in chemotherapy and radiotherapy are

the use of colloidal gold in therapeutic treatments, often for cancer or arthritis. Gold nanoparticle technology shows promise in the advancement of cancer treatments. Some of the properties that gold nanoparticles possess, such as small size, non-toxicity and non-immunogenicity make these molecules useful candidates for targeted drug delivery systems. With tumor-targeting delivery vectors becoming smaller, the ability to by-pass the natural barriers and obstacles of the body becomes more probable. To increase specificity and likelihood of drug delivery, tumor specific ligands may be grafted onto the particles along with the chemotherapeutic drug molecules, to allow these molecules to circulate throughout the tumor without being redistributed into the body.[33]Nanotechnology has shown tremendous promising potential in cancer diagnostics and treatment which can revolutionize this field in near future. The solubility of nanoparticles in water, ease of functionalization, biocompatibility to normal cells is important factors which make these nanomaterials effective agent for cancer therapy. The effectiveness of cancer therapeutic device is measured by its ability to reduce and eliminate tumors without damaging the surrounding healthy tissues. Therefore, targeting tumors becomes essential for efficient working of therapeutic device. An increased site specificity and internalization can improve the efficacy of treatment and decrease the possibility of serious side effects that cancer patients often experience in conventional therapy protocol. The most important attributes of GNPs is their size tunability, easy absorption by body fluids and passage through the body circulation without rejection. GNPs can pass through leaky capillaries and directly reach tumor surfaces. Also, GNPs display negligible toxicity owing to its biological precursors. These properties can be exploited for designing molecular armadas for ferrying therapeutic moieties to solid tumors. GNPs can be targeted passively through the capillary or the surface of the nanoparticle can be modified using antibodies or receptor proteins to target tumor cells and enter the cell via receptor mediated endocytosis, i.e. active targeting. [34]

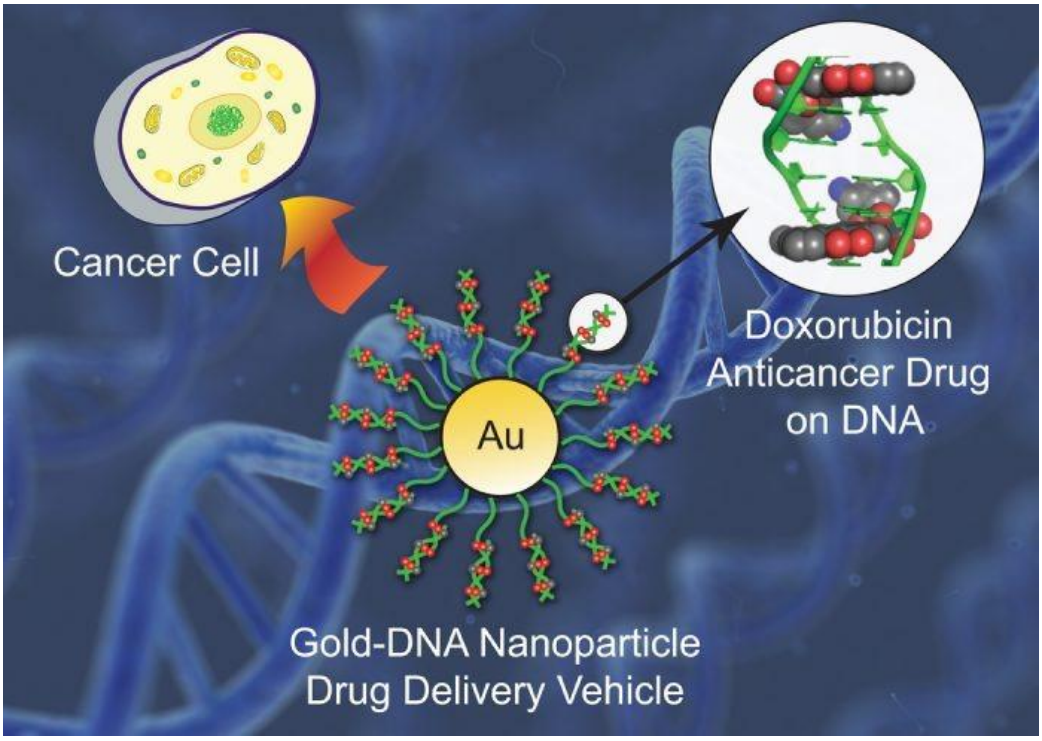

Fig.3: Schematic diagram of combining GNPs with Doxorubicin.

Azadirachtaindica acts as a biological sink for fabrication of gold nanoparticles (GNPs) and its applications in efficient delivery of anticancer drug doxorubicin (DOX) shown in Fig.3. Sucrose density gradient centrifugation used to isolate the spherical GNPs of <50 nm from the mixture (containing both spherical and nonspherical) of nanoparticles synthesized using leaves of Azadiracta indica at inherent Ph.[35] The stability of GNPs due to the biological capping agents can be scrutinized by measuring the flocculation parameter which was found to be in the range of 0–0.65. On the surface of these capped GNPs, doxorubicin attached along with activated Folic Acid (FA) as navigational molecules for targeted drug delivery. The GNPs-FA-DOX complex was found be non-toxic for normal cells and considerably toxic for HeLa cells. The drug loading

capacity of the GNPs was found to 93%. Doxorubicin release kinetics using GNPs followed 1st order at pH 5.3 which is ideal for solid tumor targeting.[35]

Conclusion

The main application of Gold particles are currently limited to the treatment in rheumatoid arthritis like the gold drug Auranofin and used as theranostic agent. But by using the gold nano particles we can able to treat the cancer very effectively. The main drawback of gold nano particles are that they are very expensive and release hazardous chemicals and having biological risks. But as they having effective action against tumor cells led to synthesize newer methods on larger scale with different morphology. By using these types of newer methods we can able to make most effective gold nanoparticles for treating cancer with less harmful effects and lower costs.

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