Austin Journal of Nanomedicine & Nanotechnology

Open Access

Austin Publishing Group

Review Article

Synthesis Strategies and Potential Applications of Gold Nanoparticles in Cancer Theranostics: Labelling and Visualizing, Targeted Drug Delivery, Photoablation Therapy and Sensing

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Received: October 05, 2018; **Accepted:** November 03, 2018; **Published:** November 10, 2018

Abstract

Nanotechnology has transformed into a champion amongst the furthermost exciting and cutting-edge areas of research in the field of biomedicine. Gold Nanoparticles (GNPs) exhibit exceptional advantages when compared to other nanoparticles, mainly because of its unique properties. GNPs have widely used in quite a lot of cancer theranostic applications due to their very small size, inert nature, biocompatibility, high dispersity, noncytotoxicity, stability, larger surface area, tunable physical, chemical, optical and electronic properties. Biocompatible polymers are being utilized for the surface modification of GNPs to increase the therapeutic payload and also the stability of the GNPs, leading to enhanced systemic circulation and efficient cellular uptake of the GNPs in the cancer theranostics. The main purpose of the present review is to illustrate different synthesis methods viz. chemical, physical, green methods and also the theranostic applications of GNPs. The fundamental ideas and the mechanism involved in each of these applications, the main features of the GNPs required for each of these applications and additionally, a few examples are portrayed.

Keywords: Cancer; Gold nanoparticles; Theranostic; Targeted drug delivery; Polymers

Introduction

Over the past half century, chemotherapy has extensively enhanced the cancer treatment. But sadly, lack of selectivity for the conventional chemotherapeutic agents, less than one percent of the drugs were taken up by the tumor cells and its microenvironment, the remaining drug was going to the surrounding healthy tissues [1]. As chemotherapeutic agents are usually intended for a specific site in the body, this conventional method of delivering the drug is devoid of efficiency and need a significant amount of drug thereby leading to adverse side effects to the surrounding healthy systems. Multi Drug Resistance (MDR) is another major problem that is associated with the failure of chemotherapy. MDR results in low intracellular drug concentration in the tumor cells due to restrainment of efficient drug accumulation thereby resulting in a low response. Another major problem associated with the failure of chemotherapy is due to the differences in the tumor cells' chemo sensitivity, resulting in the difference in the tumor cell's percentage of response. Hence developing drug delivery systems that are efficacious selectively is one of the ultimate challenges confronting chemotherapy at present and that can be possible by Gold Nanoparticles (GNPs) [2].

GNPs are available in different shapes and sizes, and their unique properties make them suitable for various applications as shown in (Figure 1). As GNPs have a large surface area, their surfaces can be accessible to further alteration with hydrophilic, hydrophobic, anionic, cationic and neutral moieties, so that their applications can be drawn out to a further extent. GNP's electronic properties facilitate their use as sensitizers in radiotherapy with 3-6 folds improved potential when compared to the substances usually used in clinical trials (e.g., gadolinium complexes) [3]. GNP's optical properties facilitate them to induce hyperthermia at the tumor site upon irradiation by NIR light and show enhanced potential in photothermal therapy [4].

GNPs turned out to be excellent drug nanocarriers for anti-cancer drugs as they can effectively carry a high therapeutic payload and selectively release the chemotherapeutic drug at the tumor microenvironment [5]. They are selectively delivered at the tumor micro environment by active or passive targeting methods. The former is accomplished by conjugation with ligands having an affinity for the receptors expressed on malignant cells or its microenvironment. Various ligands used for this purpose include antibodies, oligosaccharides, organic molecules, and peptides. GNPs adopt dual way approach to killing cancer cells by delivering the anti-cancer drugs effectively at the tumor site and exert photoablation therapy. The latter is accomplished by EPR (enhanced permeation and retention) effect in which GNPs reaches the interstitial space of the tumor through the leaky vasculatures and the impaired lymphatic drainage constrains the clearance of the GNPs [6]. GNPs tend to accumulate and interact with the cancer cells due to their distinctive enhanced permeability and retention property [7].

GNPs have a variety of applicability over conventional contrast agents as gold has a higher atomic number and high absorption coefficient because of its electron density, so it increases computed tomography contrast further and is used as molecular probes in

Citation: Adena SKR, Upadhyay M, Vardhan H and Mishra B. Synthesis Strategies and Potential Applications of Gold Nanoparticles in Cancer Theranostics: Labelling and Visualizing, Targeted Drug Delivery, Photoablation Therapy and Sensing. Austin J Nanomed Nanotechnol. 2018; 6(1): 1050.

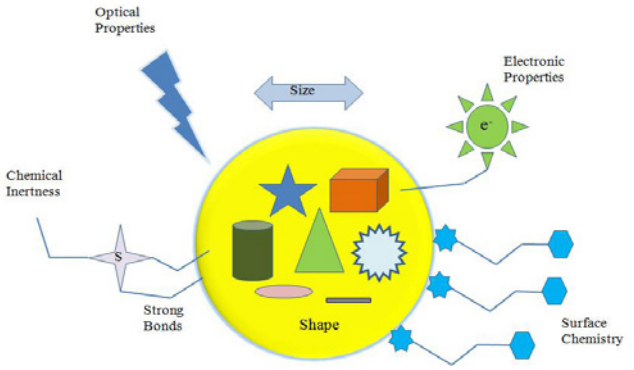

Figure 1: Graphical representation of main properties of GNPs.

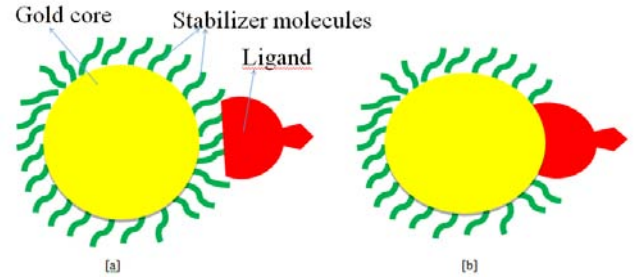

Figure 2: Schematic representation of ligand-conjugated GNPs. The colloidal stability is provided by the stabilizer molecules that are encompassed around the gold core. [a] ligand attached to the stabilizer molecules or [b] ligand attached to the gold core surface.

X-ray computed tomography imaging [8]. GNPs surfaces are readily accessible for adaptation with specific biomarkers or targeting molecules and are utilized in biomedical prospects [9,10]. They are widely used as contrast agents in molecular imaging such as MRI, CT, PET, ultrasound and optical imaging [11,12]. GNPs can get tunable absorption due to their unique anisotropic geometry and can be potentially used in the fields of photothermal therapy and biosensing [13]. Due to its Surface Plasmon Resonance (SPR), GNPs are widely used in tumor imaging, photoablation therapy, drug delivery and immune chromatographic detection of pathogens [14]. GNPs have a wide variety of applications in in-vivo imaging due to its SPR and scattering properties [15]. Surface modification of GNPs with a thermolabile polymer is utilized as a drug carrier which upon interaction with near infrared radiation releases their effectors. Because of their distinctive electronic and optical properties, GNPs have been extensively used in color indicating probes for the sensing of various analytes [16].

The purpose of the present review is to layout various applied properties of GNPs, their synthesis methods and to outline the applications and their utilization in distinctive areas of biomedicine. The theranostic applications of GNPs are catalogued into labelling and visualizing, targeted drug delivery, photoablation therapy, and sensing.

Synthesis Strategies of Gnps

GNPs of different nanoshapes are reported based on the synthesis method employed and the experimental conditions

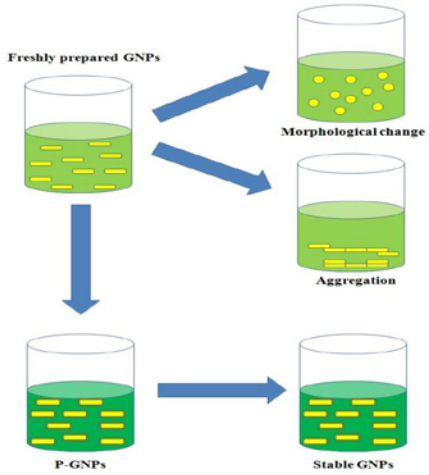

Figure 3: Schematic representation of distinction between GNPs and polymer stabilized GNPs upon storage.

involved, including gold nanospheres, nanoshells, nanocages, nanorods, nanoclusters, nanoboxes, nanocrystals, nanocubes, and nanostars [17,18]. However, when compared to other nanoshapes gold nanospheres, nanoshells, nanocages, and nanorods are widely investigated for various theranostic applications. Various synthesis methods, including chemical, physical and green methods have so far been introduced.

Chemical Methods

In chemical method, the synthesis of GNPs involves the reduction by using reducing agents like citrate acid, borohydrides, oxalic acid, formaldehyde, hydrogen peroxide, acetylene, and stabilization by using stabilizing agents like oxygen, phosphorus and nitrogen based ligands, polymers and surfactants. Turkevich method is the well-known, and widely used method for the synthesis of GNPs in which tetrachloroauric acid in water is boiled and the reducing agent trisodium citrate dehydrate is rapidly added into it with vigorous stirring. The color of the resulting solution changes from light yellow to wine red after a few minutes. In this method, there is no need of adding a stabilizing agent as citrate ions play both the role of reducing and stabilizing agents [19]. Brust-Schiffrin method is an easy and simple method for the stable GNPs synthesis with controlled size and good colloidal dispersity. In this method, tetraoctyl ammonium bromide is used as a phase transfer agent which transfers the aqueous $AuCl_4$ solution to a toluene phase. The resultant is reduced by using sodium borohydride in the presence of dodecanethiol. The thiol stabilized GNPs results from a color change of orange to deep brown [20]. Schematic representation of ligand conjugated GNPs is shown in (Figure 2). Other nanoshapes can be synthesized besides growing of GNPs of spherical shape.

In general, non-spherical GNPs have the tendency to aggregate. High curvature of GNPs and the nature of ligands on their surface are the main factors that influence the flocculation. Smaller GNPs due to a less number of ligands capping while larger GNPs due to interparticular interaction *via* weak hydrogen bonds shows a low affinity towards flocculation [21,22]. Flocculation is the main limitation that poses a challenge for the synthesis of a stable GNPs

Table 1: Polymers used in the synthesis of P-GNPs.

Polymer	Nature	Reference
Cellulose derivatives	β linked D-glucose units	[24]
Chitosan	Linear polysaccharide, hydrophilic, cationic	[25]
Dextran	Branched polysaccharide, hydrophilic, cationic	[26]
Gelatin	From porcine skin, thermostable	[27]
Guar gum	Galactomannan, cationic	[28]
Heparin	Sulfated glycosaminoglycan, UV sensitive, anionic	[29]
Hyaluronic acid	Nonsulfated glycosaminoglycan, water soluble	[30]
Maltose	Disaccharide	[31]
Polycaprolactone	Film formation by thermal pressing	[32]
Polydiallyl dimethyl ammonium	Polyelectrolyte, Layer by layer assembly forming, Cationic	[33]
Polyethylene glycol	Biocompatible, non-toxic	[34]
Polyethylene imine	Cationic	[35]
Polystyrene sulfonate	Ion exchange resin, anionic	[36]
Polyvinyl caprolactam	Thermoresponsive	[37]
Polyvinyl pyrrolidone	pH- responsive	[38]
Pullulan	Amphiphilic, maltotriose units, hydrophilic, cationic	[39]
Xanthan gum	Repeated pentasaccharide, hydrophilic, anionic	[40]

colloidal solution. So, to avoid this limitation and to synthesize a stable GNPs colloidal solution, polymers are employed in the formulation. With the advancement in nanotechnology, Polymeric Gold Nanoparticles (P-GNPs) are extensively employed as drug nanocarriers for the targeted drug delivery. Direct, grafting to and grafting from methods are mainly followed in the synthesis of P-GNPs [23]. Polymers generally used in the synthesis of P-GNPs are cellulose derivatives, chitosan, dextran, gelatin, guar gum, heparin, hyaluronic acid, maltose, polycaprolactone, polydiallyl dimethyl ammonium, polyethylene glycol, polyethylene imine, polystyrene sulfonate, polyvinyl caprolactam, polyvinyl pyrrolidone, pullulan, and xanthan gum are illustrated in (Table 1) [24-40]. Graphical illustration of the distinction between GNPs and polymer stabilized GNPs are shown in (Figure 3).

These polymers show a variety of advantages in cancer therapyviz. improving biocompatibility, imparting non-immunogenicity, improving the stability of GNPs, tuning of surface density, tuning of solubility and increasing the hydrophilicity of the outer surface [41]. In the direct synthesis method, tetrachloroauric acid is subjected to reduction in the presence of sulphur-terminated polymers to form P-GNPs in a single step [42]. In grafting to method, functionalized polymers are attached to the surface of GNPs by polymers containing thiol or amine group. In grafting from method, GNP's surface is subjected to polymerization in the presence of a chain transfer agent like thiocarbonyl compounds [43,44].

Synthesis of controllable size P-GNPs is the prerequisite for its potential theranostic applications in the treatment of cancer, which could be possible by controlling the proportions of the polymers used in the formulation. Some polymers have both reducing and stabilizing properties,e.g., xanthan gum, polystyrene and polyethylene imine, therefore, using these polymers as capping agents possibly will circumvent the use of reducing agents [45]. The advantages of

Figure 4: Advantages of P-GNPs to enhance the efficacy of chemotherapeutic agent for the treatment of cancer.

P-GNPs to enhance the efficacy of the chemotherapeutic agent for the treatment of cancer are illustrated in (Figure 4).

Physical Methods

Gamma irradiation method is one of the best method used for the GNPs synthesis with high purity and controlled size, where alginate solution which is a natural polysaccharide is used as a stabilizing agent [46]. Bovine serum albumin protein is employed as a stabilizing agent for the synthesis of very small GNPs in gamma irradiation method [47]. By adopting heating or photochemical reduction method, GNPs are synthesized in which malate, citrate and tartrate ligands are used to reduce tetrachloroauric acid [48]. In the photochemical method, redox and polymerization reactions are used to synthesize gold-polyethylene glycol nanoparticles. In this method, glycine and tetrachloroauric acid solution were exposed to UV radiation wherein amino acid functionalized with glycine is used as photochemical initiator [49]. In microwave method, Cissus quadrangularis aqueous

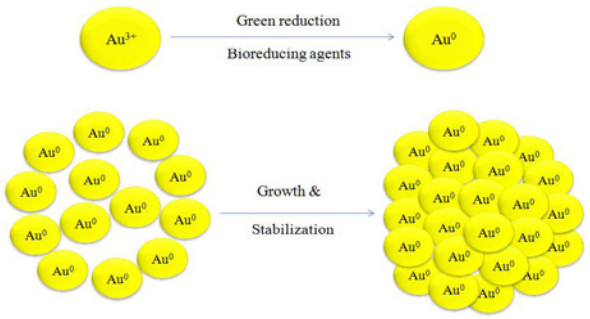

Figure 5: Schematic representation of bioreduction and stabilization of gold into GNPs.

extract is used as a reducing agent [50]. In seed approach method, synthesis of stable GNPs is done by Co-60 irradiation using chitosan as a reducing agent. Synthesis of porous GNPs is done by using alloys of gold and silver where firstly micro emulsion of nanoparticles are prepared by using tetrachloroauric acid and silver nitrate and then reduced with sodium borohydride followed by de-alloying with nitric acid [51].

Green Methods

Chemical and physical synthesis strategies were proved to be harmful and may be injurious to humans as well as the environment due to the use of toxic chemical and elevated temperature in the synthesis process [52]. The green synthesis of GNPs is getting prevailing due to its non-toxicity and natural reduction at room temperature. This method emerges to be safe for clinical research as it is biocompatible, rapid, simple, suitable for large scale production, cost-efficient and eco-friendly [53]. There is a growing need to develop eco-friendly technologies in the field of nanotechnology to synthesize GNPs using micro-organisms and plants. A schematic illustration of the mechanism of bioreduction and stabilization of GNPs is shown in (Figure 5).

Table 2: Green synthesis of GNPs using different bioreducing agents.

Bioreducing agent	Size	Shape	Reference
Azadirachta indica	11 nm	Spherical	[56]
Bacillus cereus	10-30 nm	Spherical	[57]
Butea monosperma	70-75 nm	Spherical	[58]
Micrococcus luteus	6-50 nm	Spherical	[59]
Streptomyces sp.	40 nm	Spherical	[60]
Brevibacterium casei	10-50 nm	Spherical	[61]
Mentha piperita	90 nm	Spherical	[62]
Bacillus stearothermophilus	5-30 nm	Triangular, spherical	[63]
Trichoderma viride	20-30 nm	Spherical	[64]
Zingiber officinale	5-15 nm	Spherical	[65]
Volvariella volvacea	20-150 nm	Triangular, spherical, hexagonal	[67]
Natural honey	15 nm	Spherical	[68]
Anacardium occidentale	36 nm	Hexagonal	[69]
Olive	50-100 nm	Triangular	[70]
Hibiscus cannabinus	13 nm	Spherical	[71]
Mango peel	6-18 nm	Spherical	[72]
Coriander	6-57 nm	Spherical	[73]
Nerium oleander	2-10 nm	Spherical	[74]
Solanum nigrum	50 nm	Spherical	[75]
Botrytis cinerea	1-100 nm	Triangular, spherical, hexagonal, decahedral and pyramidal	[76]

The biocompatibility is vital for GNPs for their theranostic applications. In GNPs green synthesis the addition of external stabilizing agents is not necessary as the biogenic components of micro-organisms and plants act themselves as stabilizing as well as capping agents.

An easy biosynthesis method for the preparation of GNPs is by using eggshell membrane. In this method eggshell membrane is immersed in tetrachloroauric acid solution, to form stable GNPs. In another method, chitosan is used as a natural reducing and stabilizing agent to synthesize GNPs in aqueous sodium chloride solution [54]. GNPs are also synthesized by using sunlight irradiation method in the reduction of gold salt is done by using solar energy. By using citrus fruits juice extracts which are obtained from Citrus reticulate, Citrus sinensis and Citrus limon [55] tetrachloroauric acid is reduced to produce GNPs. Green synthesis of GNPs using different bioreducing agents are illustrated in (Table 2) [56-75].

Applications of Gnps in Cancer Theranostics

Labelling and visualizing

GNPs are mainly used for labelling applications, where they provide contrast for the examination and visualization by directing and enriching them at the region of interest. GNPs can be visualized with a wide variety of techniques, which makes them exceptionally appealing contrast agent. GNPs substantially tend to absorb and scatter visible light. A surface plasmon is observed in which the free electrons present in the GNPs get excited by the light energy and upon light absorption, the electrons show collective oscillation in the GNPs [76]. Transfer of energy to the gold lattice results in relaxation of the excited electrons and the light absorption leads to heating of GNPs.

The visualization of the particles in numerous ways is possible mainly due to the interaction of GNPs with the light. GNPs of diameter more than 25nm are directly imaged by using Differential Interference Contrast (DIC) or optical microscopy in phase contrast mode [77]. GNPs can be used for labelling with different colors, which depends on their particle's size and shape [78]. In the case of small GNPs, the cross section for absorption decreases slowly whereas for scattering it decreases rapidly. Absorption of the light results in heating of the GNPs which subsequently leads to heating of the GNP's environment. This is observed by photothermal imaging and photoacoustic imaging. The density fluctuations of the GNPs are recorded by DIC microscopy in the former and expansion of the liquid environment due to the absorption of heat is recorded in the latter [79].

Due to light absorption, a local heat pulse is generated, resulting in the expansion of the GNP's environment which ultimately leads to the generation of a sound wave that can be detected with the help of a microphone. Small GNPs tends to emit fluorescence

Table 3: Summary of GNPs imaging applications.

Imaging	Property Required	Shape suitable	Reference
X-ray	X-ray absorption, no morphology/ shape relationship	Spherical	[86-88]
Optical	Strong light scattering	Spherical	[89,90]
Fluorescence	Strong inherent fluorescence	Spherical, rod, shell	[91-92]
Photoacoustic	Strong absorption in the NIR window	Spherical, rod, cage	[93-94]
SERS	Strong electromagnetic field	Spherical, star	[95-96]

NIR- Near-infrared; SERS-Surface-enhanced raman spectroscopy.

upon photoexcitation which can be visualized by using fluorescence microscopy [80]. Apart from the visible light interaction, the electron waves and X-rays interaction is used as a valuable tool for the visualization of GNPs. Due to high atomic weight of GNPs, they give high contrast in Transmission Electron Microscopy (TEM). GNPs are used as X-ray contrast agents as they can efficiently scatter X-rays. With the help of neutron activation, GNPs can be radioactively labelled and can be detected by gamma radiation [81].

Immunostaining

From a long back GNPs have been used in biology for immunostaining wherein by using antibodies the specific targeted components of outside and inside of the cells can be labelled. They can't be visualized without labelling as they lack contrast. GNPs conjugated with antibodies that are specific to the components of interest are added to the fixed and permeabilized cells. The GNPs provide brilliant contrast for TEM imaging and with optical microscopy [82], larger structures can also be imaged. Even without fixing and permeabilizing the cells immunostaining is possible, but only labelling of the structures on the cell's surface can be done. In this case, photoacoustic imaging provides an additional feature in contrasting besides the abovementioned imaging techniques. When GNPs approach together, the plasmon resonance frequency tends to shift to higher wavelengths. When compared to freely scattered single GNPs, small aggregates of GNPs absorb light at wavelengths above the plasmon resonance. GNPs generate a photoacoustic signal when GNPs conjugated with antibodies binds to the receptors on the cell surface, unlike the GNPs which arbitrarily distributed on the surface of the cells [83].

X-rays contrast agents

The concept used in immunostaining for visualizing the components of cells is also used for providing in-vivo contrast to the organs in animals and human beings. When GNPs conjugated with antibodies or ligands are administered into the circulation system, they will bind to the specific organ through ligand-receptor interaction. They eventually provide contrast and resolve the structure of the desired organ through imaging. The main problem associated with GNPs as contrast agents is that their short circulation time in the body, only a small amount of GNPs get the opportunity to bind to the specific organ while the significant amount of GNPs is eliminated through the eliminating organs of the body.

By using CT, GNPs are imaged with a significant signal to voice ratio [84] so that the exposure times can be reduced leading to a reduction in the radiation harm to the surrounding healthy tissues (Table 3) [86-96]. The organs of the body are imaged for the treatment by the penetration of X-rays through the skin. Moreover, X-ray computed tomography setups are readily available in many hospitals and diagnostic centres. GNPs causes less damage when compared to the quantum dots that are used as fluorescent semiconductor detecting and imaging agents [85].

Targeted Drug Delivery

GNPs are used as drug nanocarriers for the delivery of therapeutic agents into the tumor cells from quite a long time. Therapeutic agents are adsorbed on the GNP's surface and the entire conjugate by means gene guns or particle ingestion is introduced into the tumor cells. Therapeutic agents will detach from the GNPs inside the tumor cells eventually after its introduction. DNA is adsorbed on the GNP's surface and these nanobullets are introduced into the tumor cells for the ballistic influx of DNA [97,98]. GNPs ingestion into the tumor cells is either nonspecific or specific through receptor-ligand interaction and the main objective involved in this is to transfer and deliver the therapeutic agents adsorbed on the GNP's surface into the cells [99]. To deliver the therapeutic agents from the GNPs into the cytosol, GNP's surface is encapsulated with membrane disruptive peptides [100,101].

The delivery of therapeutic agents into tumor cells through particle ingestion is mainly useful in gene therapy and drug targeting. In gene therapy, for the expression of corresponding proteins, DNA adsorbed on the GNP's surface is introduced into the tumor cells [102]. In drug targeting, for the delivery of anticancer drug specifically to the target tumor cells or its microenvironment, GNPs are conjugated with specific ligands. To facilitate these applications, there is no need to exploit any of the unique properties of GNPs and their characteristics like inertness, stable, small and relatively easy to conjugate with ligands make them be used as a biocompatible and reliable means for targeted drug delivery [103,104].

Photoablation Therapy (PAT)

PAT is mainly grouped into Photothermal Therapy (PTT) and

Table 4: Shapes of various GNPs and their applications in the field of medicine.

Shape	Applications
Branched particle	Substrates for surface enhanced raman spectroscopy which could be utilized for imaging at the single molecule level [135].
Hollow particle	Photothermal cancer therapy, drug delivery, optical imaging, and catalysis [136].
Faceted particle	Catalytic activity, effective and reproducible substrates for SERS [137].
Nanocage	Contrast agent for optical coherence tomography [138] and endomicroscopy imaging [139].
Nanocube	Catalysis and field enhancement applications [140].
Nanorod	Selective biomarkers in diagnostics and selective targeting in photothermal therapeutics [141].
Triangular particle	Optical sensor application and filed enhancement [142].

Photodynamic Therapy (PDT) [105]. In order to accomplish the penetration in the blood and the tissue, NIR light is usually used. In PTT the absorbed light is converted into local heat i.e., hyperthermia which shows a significant cytotoxic effect on the tumor cells and its microenvironment [106]. In PDT the photon energy is converted to generate ROS (reactive oxygen species) by the stimulation of photosensitizers to kill tumor cells and its microenvironment. The absorption of light by the GNPs results in the excitation of the free electrons and this excitation at the SPR eventually leads to the cumulative oscillation of the energized free electrons. The GNP's crystal lattice and the electrons interaction lead to the relaxation of the electrons and the heat energy is exchanged to the lattice and subsequently scattered to the surrounding environment [107]. Apart from its various imaging methods, heating of GNPs in a controlled manner leads to manipulation of the surrounding tissues in various ways [108].

Intracellular delivery and the molecular uptake which mainly depends on phagocytosis and endocytosis can be potentiated by inducing hyperthermia at the tumor site [109]. Due to extreme sensitivity, even a small increase in the temperature by a few degrees leads to the cells death. Temperature above 38°C results in fever and above 42°C results in cell damage in humans and by making use of hyperthermia in a controlled way cancer can be treated. This is possible by coordinating the GNPs whose surface is conjugated with ligands that are specific to the receptors that are over-expressed on tumor cells. When the locally enriched GNPs in the tumor cells are heated with the help of external stimuli, the tumor cells which are in the vicinity of the GNPs can be killed selectively [110]. In this way, we can enrich malignant tissues with GNPs and illuminate the tissue. Tumor cells can be destroyed locally by GNPs mediated heat [111] without exposing the whole organism to higher temperatures.

PDT is a light sensitizer stimulation therapy which comprises of a particular wavelength of drug activating light, a photosensitizer drug and oxygen [112]. The stimulation of photosensitizer leads to energy transfer and eventually yields highly reactive oxygen species which imparts apoptosis and necrosis by inducing microvasculature damage [113]. Unlike radiotherapy, PDT does not have any harmful impact on cells and tissues that are devoid of photosensitizer drug as the light used for the stimulation is nonionizing. So it can be used safely without causing any harm to the neighbouring healthy tissue after taking a multi-dosage regimen [114,115]. By using fluorescence resonance energy transfer mechanism, the self-quenching capacity of GNPs plays a major role in image guided PDT in annihilating the tumor.

Sensing

Besides using GNPs in labelling, visualizing and targeted drug delivery, they are also used in active sensor applications. GNPs acts as sensors and explicitly register the existence of analyte molecules to give a readout which specifies the amount of analyte.GNP based sensors have a significant impact in diagnostics because of its small size.

Quenching

When the fluorophores are in close vicinity to the gold surface, their fluorescence can be quenched and this can be used for competitive displacement sensor strategy [116]. For quantitative identification of an individual analyte molecule, ligands are conjugated with the GNPs that distinctively bind to the analyte molecule. By saturating with the analyte molecules, the binding sites of the ligands get jammed and then these analyte molecules are customized with fluorophores. Their fluorescence can be quenched as they are firmly connected to the GNPs. The free analyte molecules dislocate the analyte molecules that are bound to the ligands in a constant dynamic equilibrium. When the concentration of the free analyte molecules is more, the fluorophore labelled molecules discharges from the GNP's surface and there will be no quenching. This strategy can be changed by using GNPs as quenchers for quantum dots which are substituted by analyte molecules [117].

Surface Plasmon Resonance

GNPs are used in sensing mainly because of its most reliable intrinsic feature, plasmon resonance frequency [118] that can be altered directly by coupling the molecules to the GNP's surface [119]. When the GNPs are closely arranged, the plasmon resonance frequency drastically changes and they form minute aggregates which can be used for colorimetric identification of the analyte molecules. This technique was developed by Mirkin and his associates and is considered as one of the most distinguished illustrations of the gold based sensor [120,121]. To find the DNA, this innovative assay was developed. Oligonucleotides correlated to the target sequence that was supposed to be identified was conjugated with GNPs. When the target sequence does not exist then the GNPs freely scatters and the colloidal solution seems red. When it exists, the GNPs bind to it by hybridization of DNA complimentary strands. The hybridization leads to the development of GNPs aggregates, resulting in the adjustment in the plasmon resonance and the solution shows up a blue/ violet color. At the point when the sample is subjected to heat, mismatch in even a single sequence result in an altered melting temperature which causes a change in the color. The quantitative identification of DNA sequences is feasible with this idea, even at a very low concentration [122].

Apart from DNA assays, the same idea is also used for the quantitative identification of the metals or proteins [123]. The enzymatic action can also be checked with the same idea [124]. Other than the analytes detection, such color changes can furthermore be utilized to measure the lengths. Discrete areas of analytes can be linked to GNPs and the conformation changes in the analytes can be examined [125].

Surface-Enhanced Raman Scattering

With the help of raman scattering, many analyte molecules are distinguished, owing to their characteristic spectra [126]. In raman scattering, the scattering is inelastic and the scattered light show lower or higher energy than the incident light. When the scattered light has lower energy, the energy is stored in the analyte molecules and when it has higher energy, the energy is attained from the analyte molecules. This shift in the energy is characteristic for the entities in the analyte molecules and they possess a characteristic raman spectrum which is used for their identification and detection. The scattering efficiency mainly depends on the incident light's wavelength. Characteristically raman signals are relatively weak and for that reason, an adequate

concentration of the analyte molecules is required to provide signals that are relatively enough. In surface enhanced raman spectroscopy, the raman scattering can be significantly enhanced by guiding the analyte molecules close to the surface of GNP's having a high curvature [127,128]. Because of the GNP's plasmon resonance, the electric field near the GNPs will be stronger than the field strength of the incident light.

Binding of the ligands to the GNP's surface significantly enhances the raman signal of the analyte molecules and helps in its identification [129,130]. Recent advancements comprise of GNPs customized with raman active analyte molecules for the identification of proteins [131,132] or DNA [133] and two photon excitation [134]. Various shapes of GNPs and their respective applications in the field of medicine are illustrated in (Table 4) [135-142].

Conclusion

GNPs have brought a change in the field of biomedicine by virtue of its applications in labelling and visualization, targeted drug delivery, photoablation therapy and sensing due to their exceptional stability, inert nature, biocompatibility, non-cytotoxicity, very small size, large surface area, and tunable physical, chemical, optical and electronic properties. The remarkable properties of the GNPs make them as a most valuable means in numerous applications. Almost all the comparative applications can be performed by using diverse material nanoparticles like quantum dots, the numerous properties and features possessed by GNPs make them unique. GNPs are inert and biocompatible and till now there is no evidence of gold corrosion. The synthesis of GNPs and its conjugation with the biomolecules can be done in a simple way. The unique optical properties of GNPs make them be visualized with distinctive strategies specifically because of its SPR and they are used as sensors in view of any changes in SPR.

GNPs enhance the quality life of patients due to the fact that the side effects of conventional drugs are reduced by conjugation with GNPs. By using GNPs, targeted drug delivery of therapeutic drugs can be achieved as the drug gets released at a specific site and can interact with the tumorous cell. GNPs can be used in various *invitro* assays and standard kits and there is a lot of scope for them in new research to widespread its usage by using its unique properties. They can also be used in a number of commercial sensor assays for the identification of analyte molecules.

The use of GNPs in the cancer treatment for the development of stable systems with consistent reproducibility is a future challenge GNPs are facing today. To accomplish an effective cancer response, the development of GNPs of 10nm size for their delivery to the cytosol is a prerequisite to be fulfilled by GNPs.

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Citation: Adena SKR, Upadhyay M, Vardhan H and Mishra B. Synthesis Strategies and Potential Applications of Gold Nanoparticles in Cancer Theranostics: Labelling and Visualizing, Targeted Drug Delivery, Photoablation Therapy and Sensing. Austin J Nanomed Nanotechnol. 2018; 6(1): 1050.