Int. Res. J. of Science & Engineering, 2018; Vol. 6 (5): 181-198 http://www.irjse.in
ISSN: 2322-0015

ORIGINAL ARTICLE

Applications of gold nano particles in medical research and cosmetics

Gupta Swaroopa Rani N

Department of Chemistry, Brijlal Biyani Science College Amravati, Maharashtra, India
Email: swargupta@yahoo.com

Manuscript Details
Received : 15.07.2018
Accepted: 22.09.2018
Published: 30.09.2018

ISSN: 2322-0015

Editor: Dr. Arvind Chavhan

Cite this article as:
Gupta Swaroopa Rani N. Applications of gold nano particles in medical research and cosmetic. *Int. Res. Journal of Science & Engineering*, 2018, 6 (5): 181-198.

ABSTRACT

Over centuries, Gold nano particles have been used by artists due to the vibrant colors produced by their interaction with visible light. Optical property of Gold nano particles is utilized in various technological applications, such as sensory probes, organic photo voltaic, catalysis, electronic conductors, therapeutic agents, medical applications, and drug delivery. The electronic as well as optical properties of nano particles of gold such as surface chemistry, size, shape, etc. can be fine tuned and used accordingly. Colloidal gold is a sol or colloidal suspension of submicrometre-size nanoparticles of gold in a fluid, usually water. The liquid is usually either an intense red colour (for particles less than 100 nm) or blue/purple (for larger particles). Due to the unique optical, electronic, and molecular-recognition properties of gold nanoparticles, they are the subject of substantial research, with applications in a wide variety of areas, including electron microscopy, electronics, nanotechnology, and materials science. The properties of colloidal gold nanoparticles, and thus their applications, depend strongly upon their size and shape. For example, rod like particles have both transverse and longitudinal absorption peak, and anisotropy of the shape affects their self-assembly. The synthesis of colloidal gold was crucial to the 4th-century Lycurgus Cup, which changes color depending on the location of light source. Later it was used as a method of staining glass. During the Middle Ages, soluble gold, a solution containing gold salt, had a reputation for its curative property for various diseases. Modern scientific evaluation of colloidal gold did not begin until Michael Faraday's work in the 1850s. Faraday recognized that the color was actually due to the miniature size of the gold particles. He noted the light scattering properties of suspended gold microparticles, which is now called Faraday-Tyndall effect. With advances in various analytical technologies in the 20th century, studies on gold nanoparticles has accelerated. Advanced microscopy methods, such as atomic force microscopy and electron microscopy, have contributed the most to nanoparticle research. Due to their comparably easy synthesis and high stability, various gold particles have been studied for their practical uses. Different types of gold nanoparticle are already used in many industries, such as medicine and electronics. For example, several FDA-approved nanoparticles are currently used

in drug delivery. Generally, gold nanoparticles are produced in a liquid ("liquid chemical methods") by reduction of chloroauric acid ($H[AuCl_4]$). After dissolving $H[AuCl_4]$, the solution is rapidly stirred while a reducing agent is added. This causes Au^{3+} ions to be reduced to Au^{+}ions. Then a disproportionation reaction occurs whereby 3 Au^{+} ions give rise to Au^{3+} and 2 Au^{0} atoms. The Au^{0} atoms act as center of nucleation around which further Au^{+} ions gets reduced. To prevent the particles from aggregating, some sort of stabilizing agent that sticks to the nanoparticle surface is usually added. This paper focuses review on Applications of gold nanoparticles in medical research which includes in vitro assays, cancer therapy, drug delivery, tumor detection, gene therapy, photothermal agents, radiotherapy dose enhancer, detection of toxic gas, gold nanoparticle based biosensor, optical biosensor, electrochemical biosensor and applications of gold nanoparticles in cosmetics. Paper also deals with Scanning Electron Microscope (SEM) images, Transmission Electron Microscope (TEM) images and FTIR spectra of Gold Bhasma medicine. This research, along with better regulation and reporting, will enable consumers to choose products with confidence. This in turn will allow companies to benefit from these novel technologies in the long term while retaining customer confidence. There are a lot of cosmetics companies that have been using gold nanoparticles in different products such as Day and Night creams, eye serums, and facial masks. The cosmetics industry has discovered multiple positive effects of gold nanoparticles, and the gold infused products has gained popularity due to its luxury appeal and effective therapeutic effects. The nanoparticles can also aid the faster delivery of vitamins and minerals to the skin, as it is in the smallest and most perfect form to stimulate the blood circulation in the skin with a gentle massage in its application. Gold has always been known to aid in healthy skin cell regeneration, especially in its nanoparticle form. They can gently stimulate the skin cells for a better cell renewal, which in turn gives the skin better elasticity and also improves the skin tone. Morphological graphs of the Gold Bhasma medicine samples are provided by scanning electron microscopy (Digital Scanning Electron Microscope - JSM 6100 - JEOL) with a Link analytical system operating at 15 KV (acceleration voltage) and transmission electron microscope (Transmission Electron Microscope, Hitachi H-7500, 120 kV). Scanning Electron Microscope images of Gold Bhasma medicine shows that the material mainly consisted of spherical to dumbbell shaped particles with 5–10 μm in diameter, and has a smaller aggregated particle size. Although the majority of material consists of micrometer grains, smaller particles with nanoscale (10–20 nm) are also present in the TEM images. Transmission Electron Microscope images of Gold Bhasma medicine shows that the material mainly consisted of spherical to dumbbell sized particles with 10–20 nm in diameter, and has a smaller aggregated particle size. Investigations well confirm the presence of gold particles with nanometric size between 10 and 20 nm.

FTIR can be routinely used to identify the functional groups and identification/quality control of raw material/finished products. FTIR spectra of Gold Bhasma medicine is obtained at room temperature by using an FTIR SPECTROPHOTOMETER - Perkin

Elmer - Spectrum RX-IFTIR. The spectra is collected in a range from 450 to 4000 cm^{-1}. Interpretation of FTIR Spectra of Gold Bhasma medicine shows presence of various functional groups such as Alkane - Ethyl, n - propyl, tertiary butyl; Alcohols - Secondary CH–OH; Aromatic – Monosustituted Benzene  , Ortho disustituted Benzene  , Meta disustituted Benzene  , Vicinal trisustituted Benzene  .

Key Words : Gold nano particles, Cancer therapy, Drug delivery, Tumor detection, Gene therapy, Photothermal agents, Radiotherapy dose enhancer, Gold nanoparticle based biosensor, Optical biosensor, Electrochemical biosensor, Gold Bhasma medicine.

INTRODUCTION

Over centuries, Gold nano particles have been used by artists due to the vibrant colors produced by their interaction with visible light. Optical property of Gold nano particles is utilized in various technological applications, such as sensory probes, organic photo voltaic, catalysis, electronic conductors, therapeutic agents, medical applications, and drug delivery. The electronic as well as optical properties of nano particles of gold such as surface chemistry, size, shape, etc. can be fine-tuned and used accordingly.

Colloidal gold is a sol or colloidal suspension of submicrometre size nanoparticles of gold in a fluid, usually water. The liquid is usually either an intense red colour (for particles less than 100 nm) or blue/purple (for larger particles) [1, 2]. Due to the unique optical, electronic, and molecular-recognition properties of gold nanoparticles, they are the subject of substantial research, with applications in a wide variety of areas, including electron microscopy, electronics, nanotechnology [3, 4], and materials science. The properties of colloidal gold nanoparticles, and thus their applications, depend strongly upon their size and shape [5]. For example, rod like particles have both transverse and longitudinal absorption peak, and anisotropy of the shape affects their self-assembly [6].

History

Cranberry glass bowl made by adding a gold salt to molten glass.

The synthesis of colloidal gold was crucial to the 4th-century Lycurgus Cup, which changes color depending on the location of light source [7]. Later it was used as a method of staining glass.

During the Middle Ages, soluble gold, a solution containing gold salt, had a reputation for its curative property for various diseases.

In 1618, Francisci Antonii, a philosopher and member of the medical profession, published a book called Panacea Aurea, sive tractatus duo de ipsius Auro Potabili [8] (Latin: gold potion, or two treatments of potable gold). The book introduces information on the formation of colloidal gold and its medical uses.

About half a century later, English botanist Nicholas Culpepper published book in 1656, Treatise of Aurum Potabile [9], solely discussing the medical uses of colloidal gold.

In 1676, Johann Kunckel, a German chemist, published a book on the manufacture of stained glass. In his book Valuable Observations or Remarks About the Fixed and Volatile Salts-Auro and Argento Potabile, Spiritu Mundi and the Like [10], Kunckel assumed that the slight pink color of Aurum Potabile came from small particles of metallic gold, not visible to human eyes.

In 1842, John Herschel invented a photographic process called chrysotype (from the Greek χρῡσός meaning "gold") that used colloidal gold to record images on paper.

Modern scientific evaluation of colloidal gold did not begin until Michael Faraday's work in the 1850s [11, 12]. In 1856, in a basement laboratory of Royal Institution, Faraday accidentally created a ruby red solution while mounting pieces of gold leaf onto microscope slides [13]. Since he was already interested in the properties of light and matter, Faraday further investigated the optical properties of the colloidal gold. He prepared the first pure sample of colloidal gold, which he called 'activated gold', in 1857. He used phosphorus to reduce a solution of gold chloride. The colloidal gold Faraday made 150 years ago is still optically active. For a long time, the composition of the 'ruby' gold was unclear. Several chemists suspected it to be a gold tin compound, due to its preparation [14, 15]. Faraday recognized that the color was actually due to the miniature size of the gold particles. He noted the light scattering properties of suspended gold microparticles, which is now called Faraday-Tyndall effect [16].

In 1898, Richard Adolf Zsigmondy prepared the first colloidal gold in diluted solution [17]. Apart from Zsigmondy, Theodor Svedberg, who invented ultracentrifugation, and Gustav Mie, who provided the theory for scattering and absorption by spherical particles, were also interested in the synthesis and properties of colloidal gold [6, 18].

With advances in various analytical technologies in the 20th century, studies on gold nanoparticles has accelerated. Advanced microscopy methods, such as atomic force microscopy and electron microscopy, have contributed the most to nanoparticle research. Due to their comparably easy synthesis and high stability, various gold particles have been studied for their practical uses. Different types of gold nanoparticle are already used in many industries, such as medicine and electronics. For example, several FDA-approved nanoparticles are currently used in drug delivery.[19]

Synthesis

Generally, gold nanoparticles are produced in a liquid by reduction of chloroauric acid ($H[AuCl_4]$). After dissolving $H[AuCl_4]$, the solution is rapidly stirred while a reducing agent is added. This causes Au^{3+} ions to be reduced to Au^{+}ions. Then a disproportionation reaction occurs whereby 3 Au^{+} ions give rise to Au^{3+} and 2 Au^{0} atoms. The Au^{0} atoms act as center of nucleation around which further Au^{+} ions gets reduced. To prevent the particles from aggregating, some sort of stabilizing agent that sticks to the nanoparticle surface is usually added.

This paper focuses review on Applications of gold nanoparticles in medical research which includes in vitro assays, cancer therapy, drug delivery, tumor detection, gene therapy, photothermal agents, radiotherapy dose enhancer, detection of toxic gas, gold nanoparticle based biosensor, optical biosensor, electrochemical biosensor and applications of gold nanoparticles in cosmetics. Paper also deals with Scanning Electron Microscope (SEM) images, Transmission Electron Microscope (TEM) images and FTIR spectra of Gold Bhasma medicine. This research, along with better regulation and reporting, will enable consumers to choose products with confidence. This in turn will allow companies to benefit from these novel technologies in the long term while retaining customer confidence.

APPLICATIONS OF GOLD NANOPARTICLES IN MEDICAL RESEARCH

In vitro assays

Gold nanoparticles have been employed for many applications such as immunoassay [20-22], protein assay [23], time-of-flight secondary ion mass spectrometry [24], capillary electrophoresis [25], and detection of cancer cells [26, 27]. In one report, dynamic light scattering (DLS) enabled quantitative estimation of the concentration of intravenously injected gold nanoshells in mouse blood [28]. This technique may also be applicable towards estimating the circulation life time of other solid nanoparticles. Gold nanoshells functionalized with a pH-sensitive SERS reporter molecule, 4-mercaptopyridine, were shown to be responsive to the pH of the surrounding media within the range of 3 to 7

[29]. Another study has evaluated the use of gold nanoshells as optical biosensors for real-time detection of streptavidin-biotin interactions in diluted human blood [30]. However, both the sensitivity (~3 μg/mL) and the dynamic range (3–50 μg/mL) were very poor.

Cancer therapy

Conventional strategies for cancer intervention include surgery, chemotherapy, and radiation therapy. Taking advantage of their unique properties, most studies of gold nanoparticle-based cancer therapy have used photothermal therapy for the destruction of cancer cells or tumor tissue, which may be potentially useful in the clinical setting. When irradiated with focused laser pulses of suitable wavelength, targeted gold nanospheres, nanorods, nanoshells, and nanocages can kill bacteria [31] and cancer cells [32-37]. It was estimated that 70–80 °C was achieved through light absorption by the gold nanoparticles [34] and up to 150 antibodies can be conjugated to a nanoshell through a bifunctional PEG linker [38].

Drug delivery

Several studies have reported the use of gold nanoparticle as drug delivery vehicles. Tumor necrosis factor-alpha (TNF-α), a cytokine with excellent anticancer efficacy, is systemically toxic which severely limited its therapeutic applications [39, 40]. A nanoparticle delivery system, consisting of PEG coated gold nanoparticle loaded with TNF-α, was constructed to maximize the tumor damage and minimize the systemic toxicity of TNF-α [41]. Combination of local heating and nanoparticle-based delivery of TNF-α resulted in enhanced therapeutic efficacy than either treatment alone. Thermally-induced tumor growth delay was enhanced by pretreatment with the nanoparticle, when given intravenously at the proper dosage and timing. Tumor blood flow suppression, as well as tumor perfusion defects, suggested vascular damage-mediated tumor cell killing. Surprisingly, following intravenous administration, little to no accumulation in the RES (eg, liver and spleen) or other healthy organs of the animals was observed [42]. Subsequently, this nanoparticle conjugate has also been used to destroy the tumor within an iceball, again without significant systemic toxicity [43]. Phase I clinical trials of this conjugate, subsequently termed "CYT-6091" [44], are currently ongoing to evaluate its safety, pharmacokinetics, and clinical efficacy.

Gold nanoparticles can be used to optimize the biodistribution of drugs to diseased organs, tissues or cells, in order to improve and target drug delivery [45, 46]. It is important to realize that the nanoparticle-mediated drug delivery is feasible only if the drug distribution is otherwise inadequate. These cases include drug targeting of difficult, unstable molecules (proteins, siRNA, DNA), delivery to the difficult sites (brain, retina, tumors, intracellular organelles) and drugs with serious side effects (e.g. anti-cancer agents). The performance of the nanoparticles depends on the size and surface functionalities in the particles. Also, the drug release and particle disintegration can vary depending on the system (e.g. biodegradable polymers sensitive to pH). An optimal nanodrug delivery system ensures that the active drug is available at the site of action for the correct time and duration, and their concentration should be above the minimal effective concentration (MEC) and below the minimal toxic concentration (MTC) [47].

Gold nanoparticles are being investigated as carriers for drugs such as Paclitaxel [48]. The administration of hydrophobic drugs require molecular encapsulation and it is found that nanosized particles are particularly efficient in evading the reticuloendothelial system.

Gold nanoparticles are also used to circumvent multidrug resistance (MDR) mechanisms [49]. Mechanisms of MDR include decreased uptake of drugs, reduced intracellular drug concentration by activation of the efflux transporters, modifications in cellular pathways by altering cell cycle checkpoints, increased metabolism of drugs, induced emergency response genes to impair apoptotic pathways and altered DNA repair mechanisms.

Gold nanoparticles (AuNPs) provide non-toxic carriers for drug and gene delivery applications. With these systems, the gold core imparts stability to the assembly, while the monolayer allows tuning of surface properties such as charge and hydrophobicity. An additional attractive feature of AuNPs is their interaction with thiols, providing an effective and selective means of controlled intracellular release [50].

Recent advances in the use of gold nanoparticles in drug and gene delivery systems has been reviewed. The topics of surface modification, site-specificity and drugs and gene and gene delivery are discussed [51].

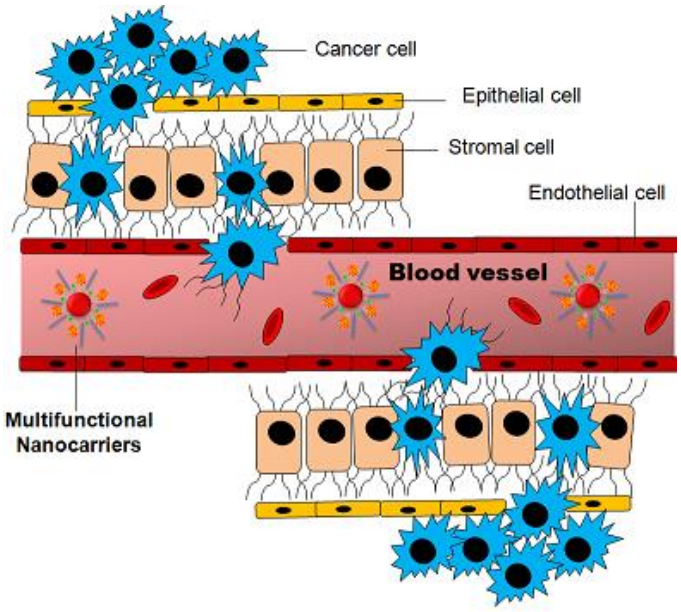
Tumor detection

The current state-of-the-art of gold nanoparticles in biomedical applications targeting cancer is summarized. Gold nanospheres, nanorods, nanoshells, nanocages, and surface enhanced Raman scattering nanoparticles discussed in detail regarding their uses in in vitro assays, ex vivo and in vivo imaging, cancer therapy, and drug delivery. A multifunctional platform based on gold nanoparticles, with multiple receptor targeting, multimodality imaging, and multiple therapeutic entities, holds the promise for a "magic gold bullet" against cancer [52].

In cancer research, colloidal gold can be used to target tumors and provide detection using SERS (Surface Enhanced Raman Spectroscopy) in vivo. These gold nanoparticles are surrounded with Raman reporters, which provide light emission that is over 200 times brighter than quantum dots. It was found that the Raman reporters were stabilized when the nanoparticles were encapsulated with a thiol-modified polyethylene glycol coat. This allows for compatibility and circulation in vivo. To specifically target tumor cells, the pegylated gold particles are conjugated with an antibody (or an antibody fragment such as scFv), against, e.g. Epidermal growth factor receptor, which is sometimes overexpressed in cells of certain cancer types. Using SERS, these pegylated gold nanoparticles can then detect the location of the tumor [53].

Gold nanoparticles accumulate in tumors, due to the leakiness of tumor vasculature, and can be used as contrast agents for enhanced imaging in a time-resolved optical tomography system using short-pulse lasers for skin cancer detection in mouse model. It is found that intravenously administrated spherical gold nanoparticles broadened the temporal profile of reflected optical signals and enhanced the contrast between surrounding normal tissue and tumors [54].

Cancer cells reduce adhesion to neighboring cells and migrate into the vasculature-rich stroma. Once at the vasculature, cells can freely enter the bloodstream. Once the tumor is directly connected to the main blood circulation system, multifunctional nanocarriers can interact directly with cancer cells and effectively target tumors.



Tumor targeting via multifunctional nanocarriers

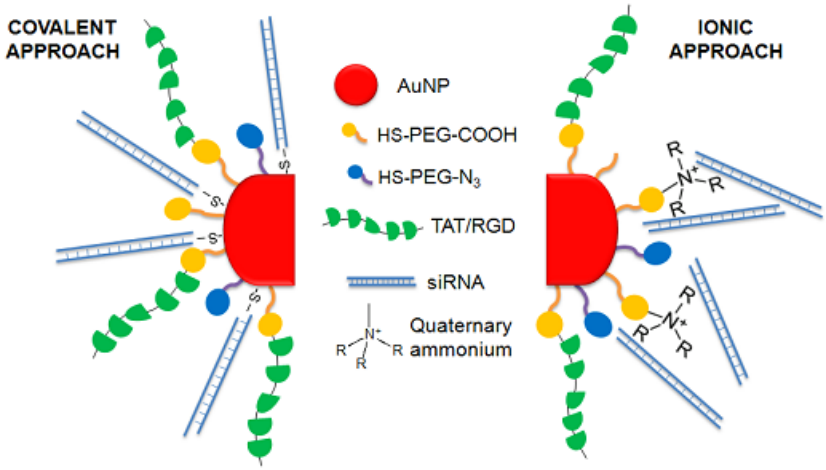
Therefore, gold nanoparticles have the potential to join numerous therapeutic functions into a single platform, by targeting specific tumor cells, tissues and organs. The evaluation of the inflammatory response and therapeutic siRNA silencing via RGD-nanoparticles in a lung cancer mouse model has been reported. This study reported the use of siRNA/RGD gold nanoparticles capable of targeting tumor cells in two lung cancer xenograft mouse models, resulting in successful and significant c-Myc oncogene downregula-

tion followed by tumor growth inhibition and prolonged survival of the animals. This delivery system can achieve translocation of siRNA duplexes directly into the tumour cell cytoplasm and accomplish successful silencing of an oncogene expression. Actually, RGD/siRNA-AuNPs can target preferentially and be taken up by tumor cells via integrin αvβ3-receptor-mediated endocytosis with no cytotoxicity, showing that can accumulate in tumor tissues overexpressing αvβ3 integrins and selectively delivered c-Myc siRNA to suppress tumor growth and angiogenesis [55].

Gene therapy

Gene therapy is receiving increasing attention and, in particular, small-interference RNA (siRNA) shows importance in novel molecular approaches in the knockdown of specific gene expression in cancerous cells. The major obstacle to clinical application is the uncertainty about how to deliver therapeutic siRNAs with maximal therapeutic impact. Gold nanoparticles have shown potential as intracellular delivery vehicles for siRNA oligonucleotides with maximal therapeutic impact.

Evidence of in vitro and in vivo RNAi triggering via the synthesis of a library of novel multifunctional gold nanoparticles, using a hierarchical approach including three biological systems of increasing complexity: in vitro cultured human cells, in vivofreshwater polyp (Hydra vulgaris), and in vivo mice models has been privided. Effective conjugation strategies has been developed to combine, in a highly controlled way, specific biomolecules to the surface of gold nanoparticles such as: (a) biofunctional spacers: Poly(ethylene glycol) (PEG) spacers used to increase solubility and biocompatibility; (b) cell penetrating peptides such as TAT and RGD peptides: A novel class of membrane translocating agents named cell penetrating peptides (CPPs) that exploit more than one mechanism of endocytosis to overcome the lipophilic barrier of the cellular membranes and deliver large molecules and even small particles inside the cell for their biological actions; and (c) siRNA complementary to a master regulator gene, the protooncogene c-myc, were bond covalently (thiol-siRNA) and ionically (naked/ unmodified siRNA) to gold nanoparticles [56].



Multifunctional siRNA-gold nanoparticles with several biomolecules: PEG, cell penetration and cell adhesion peptides and siRNA

Two different approaches were employed to conjugate the siRNA to the gold nanoparticle: (1) Covalent approach: use of thiolated siRNA for gold-thiol binding to the nanoparticle; (2) Ionic approach: interaction of the negatively charged siRNA to the modified surface of the AuNP through ionic interactions.

Gold nanoparticles have also shown potential as intracellular delivery vehicles for antisense oligonucleotides (ssDNA,dsDNA) by providing protection against intracellular nucleases and ease of functionalization for selective targeting [57, 58]. A new theranostic system capable of intersecting all RNA pathways: from gene specific downregulation to silencing the silencers, i.e. siRNA and miRNA pathways have been developed. The development gold nanoparticles functionalized with a fluorophore labeled hairpin-DNA, i.e. gold nanobeacons, capable of

efficiently silencing single gene expression, exogenous siRNA and endogenous miRNAs while yielding a quantifiable fluorescence signal directly proportional to the level of silencing [59]. This method describes a gold nanoparticle-based nanobeacon as an innovative theranostic approach for detection and inhibition of sequence-specific DNA and RNA for in vitro and ex vivo applications. Under hairpin configuration, proximity to gold nanoparticles leads to fluorescence quenching; hybridization to a complementary target restores fluorescence emission due to the gold nanobeacons' conformational reorganization that causes the fluorophore and the gold nanoparticle to part from each other [60]. This concept can easily be extended and adapted to assist the in vitro evaluation of silencing potential of a given sequence to be later used for ex vivo gene silencing and RNAi approaches, with the ability to monitor real-time gene delivery action [61].

Photothermal agents

Photothermal cell damage is a promising direction in both tumor therapy [62] and the therapy of infectious diseases, which has been intensively developing. The essence of this technique is that gold nanoparticles reach their absorption maximum in the visible or near-infrared region and become hot when irradiated at the corresponding light wavelength. If they are located inside or around the target cells (which can be achieved by conjugation of gold particles with antibodies or other molecules), these cells die.

A number of studies have been published in which the application of gold nanorods [63, 64], nanoshells [65, 66], and a relatively new class of particles – gold-silver nanocages [67, 68] – for plasmonic photothermal therapy (PPTT) is described. The results of a comparison of the efficiency of heating nanorods, nanoshells, and nanocages are provided in [69, 70].

Gold nanorods are being investigated as photothermal agents for in-vivo applications. Gold nanorods are rod-shaped gold nanoparticles whose aspect ratios tune the surface plasmon resonance (SPR) band from the visible to near-infrared wavelength. The total extinction of light at the SPR is made up of both absorption and scattering. For the smaller axial diameter nanorods (~10 nm), absorption dominates, whereas for the larger axial diameter nanorods (>35 nm) scattering can dominate. As a consequence, for in-vivo applications, small diameter gold nanorods are being used as photothermal converters of near-infrared light due to their high absorption cross-sections. Since near-infrared light transmits readily through human skin and tissue, these nanorods can be used as ablation components for cancer, and other targets. When coated with polymers, gold nanorods have been known to circulate in-vivo for greater than 15 hours half-life. Apart from rod-like gold nanoparticles, also spherical colloidal gold nanoparticles are recently used as markers in combination with photothermal single particle microscopy.

Radiotherapy dose enhancer

Following work by Hainfield et al. [71] there has been considerable interest in the use of gold and other heavy-atom containing nanoparticles to enhance the dose delivered to tumors. Since the gold nanoparticles are taken up by the tumors more than the nearby healthy tissue, the dose is selectively enhanced. The biological effectiveness of this type of therapy seems to be due to the local deposition of the radiation dose near the nanoparticles [72]. This mechanism is the same as occurs in heavy ion therapy.

Detection of toxic gas

Researchers have developed simple inexpensive methods for on-site detection of hydrogen sulfide H_2S present in air based on the antiaggregation of gold nanoparticles (AuNPs). Dissolving H2S into a weak alkaline buff solution leads to the formation of HS-, which can stabilize AuNPs and ensure they maintain their red color allowing for visual detection of toxic levels of H_2S [73].

Gold nanoparticle based biosensor

Gold nanoparticles are incorporated into biosensors to enhance its stability, sensitivity, and selectivity [74]. Nanoparticle properties such as small size, high surface-to-volume ratio, and high surface energy allow immobilization of large range of biomolecules. Gold nanoparticle, in particular, could also act as "electron wire" to transport electrons and its amplification effect on electromagnetic light allows it to function as signal amplifiers [75, 76]. Main types of gold nanoparticle based biosensors are optical and electrochemical biosensor.

The situation of infectious diseases and biothreats all over the world remains serious. The effective identification of such diseases plays a very important role. In recent years, gold nanoparticles have been

widely used in biosensor design to improve the performance for the detection of infectious diseases and biothreats. Recent advances of gold-nanoparticle-based biosensors in this field are summarized [77].

Optical biosensor

Gold nanoparticles improve the sensitivity of optical sensor by response to the change in local refractive index. The angle of the incidence light for Surface Plasmon resonance, an interaction between light wave and conducting electrons in metal, changes when other substances are bounded to the metal surface [78, 79]. Because gold is very sensitive to its surroundings' dielectric constant [80, 81], binding of an analyte would significantly shift gold nanoparticle's SPR and therefore allow more sensitive detection. Gold nanoparticle could also amplify the SPR signal [82]. When the Plasmon wave pass through the gold nanoparticle, the charge density in the wave and the electron I the gold interacted and resulted in higher energy response, so called electron coupling. Since the analyte and bio-receptor now bind to the gold, it increases the apparent mass of the analyte and therefore amplified the signal [74]. These properties had been used to build DNA sensor with 1000-fold sensitive than without the Au NP [83]. Humidity senor was also built by altering the atom interspacing between molecules with humidity change, the interspacing change would also result in a change of the Au NP's LSPR [84].

Electrochemical Biosensor

Electrochemical sensor covert biological information into electrical signals that could be detected. The conductivity and biocompatibility of Au NP allow it to act as "electron wire" [74]. It transfers electron between the electrode and the active site of the enzyme [85]. It could be accomplished in two ways: attach the Au NP to either the enzyme or the electrode. GNP-glucose oxidase monolayer electrode was constructed use these two methods [86]. The Au NP allowed more freedom in the enzyme's orientation and therefore more sensitive and stable detection. Au NP also acts as immobilization platform for the enzyme. Most biomolecules denatures or lose its activity when interacted with the electrode [74]. The biocompatibility and high surface energy of Au allow it to bind to a large amount of protein without altering its activity and results in a more sensitive sensor [87, 88]. Moreover, Au NP also catalyzes biological reactions [89, 90]. Gold nanoparticle under 2 nm has shown catalytic activity to the oxidation of styrene [91].

Other Applications of gold nanoparticles

Gold nanoparticles are used in resonance scattering dark-field microscopy for the detection of microbial cells and their metabolites [92], the bio-imaging of tumor cells [93], and for the detection of receptors on their surface [94], and for the study of endocytosis [95].

Gold nanoparticles are increasingly actively being used not only in diagnostics and cell photothermolysis experiments, but also for therapeutic purposes. In 1997, the successful application of colloidal gold in a patient with rheumatoid arthritis was first reported [96].

Antibiotics and other antibacterial agents are also considered as objects that can be delivered by gold nanoparticles. The possibility of producing a stable complex of vancomycin and colloidal gold and the efficacy of such a complex against various enteropathogenic strains of Escherichia coli, Enterococcus faecium, Enterococcus faecalis (including vancomycin-resistant strains) have also been demonstrated [97]. Similar results were obtained in [98]: a complex of ciprofloxacin with gold nanoshells showed high antibacterial activity towards*E. coli* . The anti-leukemia drug 5-fluorouracil, conjugated with colloidal gold, has a noticeable antibacterial and antifungal effect against Micrococcus luteus, Staphylococcus aureus, Pseudomonas aeruginosa, E. coli, Aspergillus fumigates, and A. niger [99]. It should be noted that in all of the listed cases, the complexes of drugs with gold nanoparticles were stable, which could be attested by the optical spectra of conjugates.

An overview of the recent advances and current challenges facing the biomedical application of gold nanoparticles of various sizes, shapes, and structures is provided. The review is focused on the application of gold nanoparticle conjugates in biomedical diagnostics and analytics, photothermal and photodynamic therapies, as a carrier for delivering target molecules, and on the immunological and toxicological properties [100].

APPLICATIONS OF GOLD NANOPARTICLES IN COSMETICS

There are a lot of cosmetics companies that have been using gold nanoparticles in different products such as Day and Night creams, eye serums, and facial masks. The cosmetics industry has discovered multiple positive effects of gold nanoparticles, and the gold infused

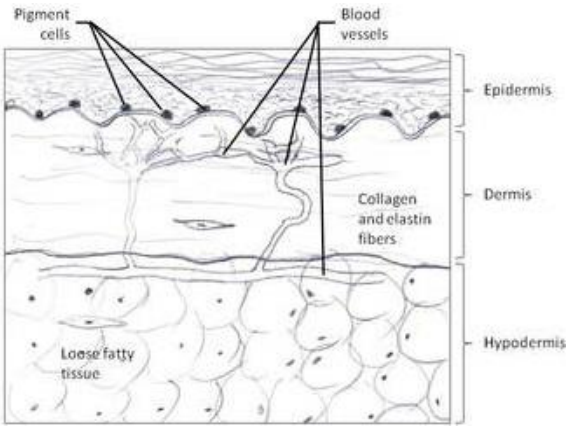
products has gained popularity due to its luxury appeal and effective therapeutic effects. The nanoparticles can also aid the faster delivery of vitamins and minerals to the skin, as it is in the smallest and most perfect form to stimulate the blood circulation in the skin with a gentle massage in its application. Gold has always been known to aid in healthy skin cell regeneration, especially in its nanoparticle form. They can gently stimulate the skin cells for a better cell renewal, which in turn gives the skin better elasticity and also improves the skin tone.

Incorporation of engineered nanomaterials into cosmetic products including sunscreens, makeups, soaps, moisturizers and shampoos is becoming increasingly more commonplace. Manufacturers incorporate nanomaterials into their products to improve product stability, improve the delivery of vitamins and antioxidants and make products more aesthetically appealing [101].

Brands like Lancome (L'Oreal), Dior and Olay (Procter and Gamble) employ a variety of nanomaterials into their products including niosomes, liposomes and nanoemulsions. Niosomes and liposomes are amphiphilic, which means they have both hydrophobic ("water-fearing") and hydrophilic ("water-loving") parts. This nature is what allows them to carry vitamins and drugs across the skin [102].

Skin is composed of three main layers: the epidermis, dermis and hypodermis. The epidermis is the outermost skin layer and it mainly comprises dead cells that we continuously shed. There is a constant generation of new cells, with the newest cell found in the deeper layers and the older cells found on the outermost layer. It is the dermis that supports the epidermis and contains our hair follicles, oil, sweat glands, muscles, nerves and blood vessels. The dermis also contains connective tissues, mostly made of collagen and elastin.Collagen is a group of proteins that serve as one of the main structural components of skin and connective tissue. It, along with other proteins like keratin and elastin, is responsible for the structural integrity and elasticity of the skin. As we age, collagen and elastin break down and as a result skin loses its elasticity and its ability to retain its shape.

Over time, the collagen in skin becomes degraded and contributes to the signs of aging (i.e. wrinkles). In addition to time, other things that contribute to the aging process include pollution, eating and sleeping habits, smoking, exercise, UV radiation, and genetics. One process that is known to lead to visible signs of aging, like wrinkles, is the formation of advanced glycation end products (AGEs). AGEs are the products of a chain of reactions that initially kick off with a reaction between carbohydrates (sugars) and proteins, like collagen. Carbohydrates are one of main fuel sources for your body and are found in fruits, vegetables, bread and many other foods. The accumulation of AGEs in the skin causes the skin to lose some of its elasticity.



Epidermis and dermis

Collagen molecule from RCSB Protein Data Bank

Understanding how the accumulation of AGEs affects skin elasticity leads us to the role of gold in cosmetics. Gold nanoparticles are able to compete with carbohydrates to bind to amino acids like lysine and arginine. With gold particles taking up the place where carbohydrates would otherwise bind, the formation of AGEs should therefore be inhibited, and fewer wrinkles should form on the skin [103, 104].
Gold nanoparticles have a wealth of pharmaceutical and medical uses. Notably, the ability of these nanoparticles

to absorb light and turn this light into heat has put them at the center of ongoing cancer studies exploring their efficacy in destroying malignant cells. They have even been used as contrast agents in electron microscopy, but their ability to deliver other materials has made them candidates for drug and gene delivery and interesting to explore for inclusion in skin care [105].

OROGOLD exclusive 24K Nano Day Recovery
This is extremely light yet very rich. It is gel-like cream and is infused with Gold flakes, Vitamin A (Retinyl Palmitrate), Seaweed Extract (Liminaria Japonica Extract), Sodium Hyaluronate and Caffeine. This nourishing day cream was formulated to reduce the appearance of fine lines and wrinkles, leaving skin feeling soft and looking radiantly younger. [106]

OROGOLD exclusive 24K Nano Night Recovery
It is truly ground-breaking with its potent formula which delivers nutrients, essential oils, and gold for skin that looks youthful and radiant. [107]

OROGOLD exclusive 24K Nano Hydra Silk Mask
This unique leave-on mask is infused with flecks of Gold and an exclusive blend to transform the mask from a silky cream to water. This nourishing mask is formulated with Sodium Hyaluronate and Caprylyl Methicone and PEG-12 Dimethicone/PPG-20 Crosspolymer, a unique blend to keep skin soft and looking hydrated. Also, it infused with Vitamin E (Tocopheryl Acetate), flower and fruit extracts such as Acai fruit extract (Euterpe Oleracea Fruit Extract) to offer skin a boost of hydration and exceptional care. [108].

OROGOLD exclusive 24K Nano Ultra Silk Serum
Packed with fruit and plant extracts, this waterless nano gold serum helps restore loss of moisture while significantly improving the appearance of wrinkles and expression lines. This nourishing serum provides skin with the variety of components it needs to look younger and healthier. [109]

METHODOLOGY

The Electron Microscope is an essential component for scientific analysis of a variety of materials. Scanning Electron Microscope (SEM) and Transmission Electron Microscope (TEM) together comprises a powerful tool in studying (cell and molecular biology, anatomy, microbiology, pathology and forensic science) biological specimens, food stuffs and several other areas of material sciences (electronics, metallurgy, polymer and surface science).

Morphological graphs of the Gold Bhasma medicine samples are provided by scanning electron microscopy (Digital Scanning Electron Microscope - JSM 6100 - JEOL) with a Link analytical system operating at 15 KV (acceleration voltage) and transmission electron microscope (Transmission Electron Microscope, Hitachi H-7500, 120 kV)

Scanning Electron Microscope (SEM) - Digital Scanning Electron Microscope - JSM 6100 (JEOL)
SEM facilitates the observation of very fine details (high resolution) of biological materials and good focus over a wide range of specimen surface (large depth of field). It also produces clear image of specimen ranging from object visible to the naked eye to a structure spanning few nanometers. Besides its use in studying soils, sedimentary particles and rock materials, it also helps to elucidate the architecture and evolution of microfossils. The JSM-6100 is used with a digital image processor. It has a large specimen chamber that allows observation of the entire surface of a specimen upto 150 mm and a tilt of -5 to 90^{o}. A special feature of this SEM is a cryostage attached to it to study the low melting point specimens. The image processing function permits image averaging and storage, filling of acquired still images and comparison of two/four images displayed simultaneously on the 12 inch CRT. This function makes it possible to observe specimens without causing damage to them.

Other features of this microscope are:

Resolution	=	4.0 nm at 8mm working distance
Working distance	=	6 to 48 mm
Accelerating Voltage	=	0.3 to 30 KV
Magnification	=	x10 to x300,000
Image Recording	=	on 120 B&W Roll Film (100 ASA) or 35mm B&W roll (25 ASA)
Instant Print	=	an instant print is also possible on a Thermal Video Printer (8x10.5)

Transmission Electron Microscope (TEM) - 120 kV Transmission Electron Microscope

TEM is analogous to the optical microscope. It provides very high resolution which can reach approximately 0.1 nm in the case of lattice images. Consequently very high magnification (Close to 1 million times) can be obtained. TEM is used to examine very thin sections (<60 nm in thickness) through the cells and tissues or through materials as well as replicas of the surfaces of the samples.

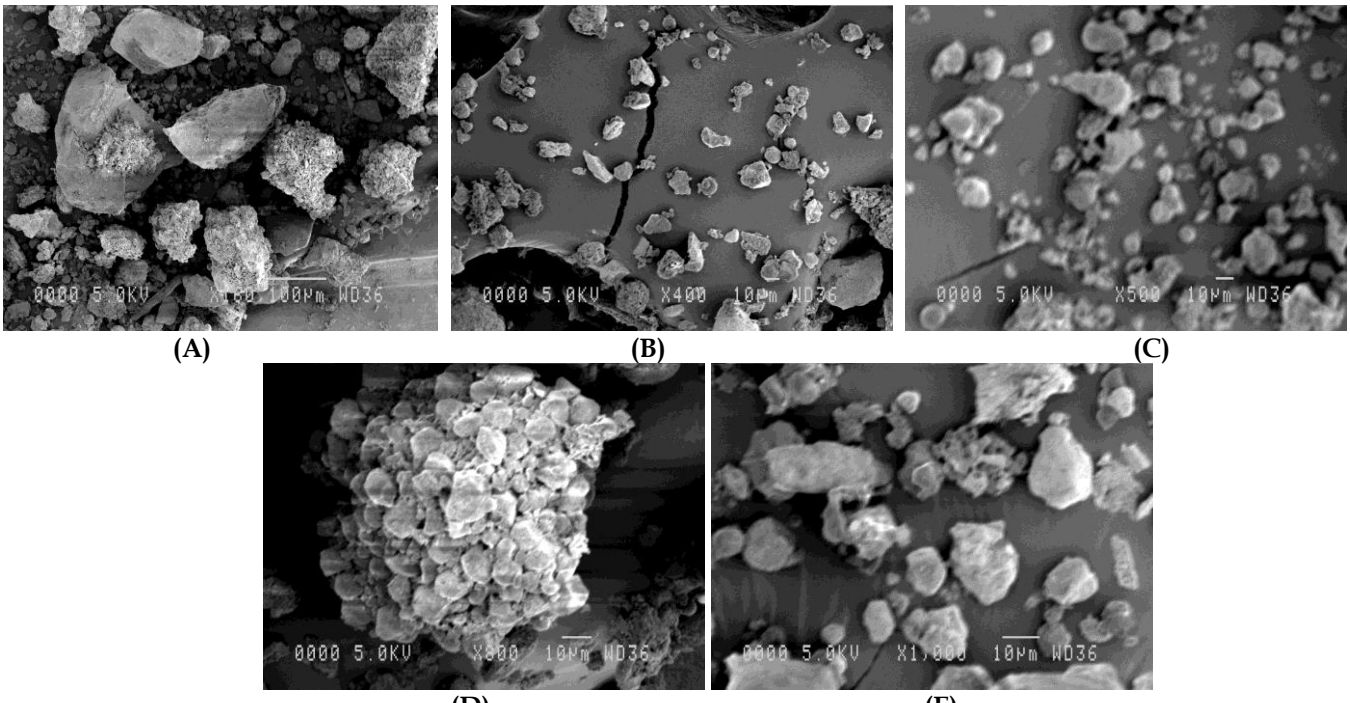
A Transmission Electron Microscope, Hitachi (H-7500) 120 kV is used with CCD Camera This instrument has the resolution of 0.36 nm (point to point) with 40-120 kV operating voltage and can magnify object up to 6 lakh times in High Resolution mode. It has Electron Diffraction, Tungsten Filament, Low Dose Function, High Contrast Mode with ergodynamic look. The specific features of the instrument are: maximum field of views at x700 with dual picture modes, Auto-navigation, Largest possible field with mose contrast, auto pre-irradiation mode (APIS). The equipment has provision for future up-gradation for an analytical system by adding EELS, EDS and STEM attachments.

FTIR Spectrophotometer - Perkin Elmer - Spectrum RX-IFTIR

FTIR can be routinely used to identify the functional groups and identification/quality control of raw material/finished products. Spectrum RX-I offers fast throughput and rapid access to reliable and dependable IR results. High signal to noise ratio makes FTIR more useful for difficult samples. It has resolution of 1 cm^{-1} and scan range of 4000 cm^{-1} to 250 cm^{-1}. In the normal mode around 10 mg sample is required in the form of fine powder. The sample can be analyzed in the form of liquid, solid and thin films also.

FTIR spectra of Gold Bhasma medicine is obtained at room temperature by using an FTIR Spectrophotometer - Perkin Elmer - Spectrum RX-IFTIR. The spectra is collected in a range from 450 to 4000 cm^{-1}.

RESULTS AND DISCUSSION



(A) **(B)** **(C)**

(D) **(E)**

Figure 1 (A) – (E) . Scanning Electron Microscope images of Gold Bhasma medicine

Figure 1 (A) – (E) shows Scanning Electron Microscope images of Gold Bhasma medicine. We can learn from Figure 1 (A) – (E) that the material mainly consisted of spherical to dumbbell shaped particles with 5–10 µm in diameter, and has a smaller aggregated particle size. Although the majority of material consists of micrometer grains, smaller particles with nanoscale (10–20 nm) are also present in the TEM images (Fig. 2 C to G).

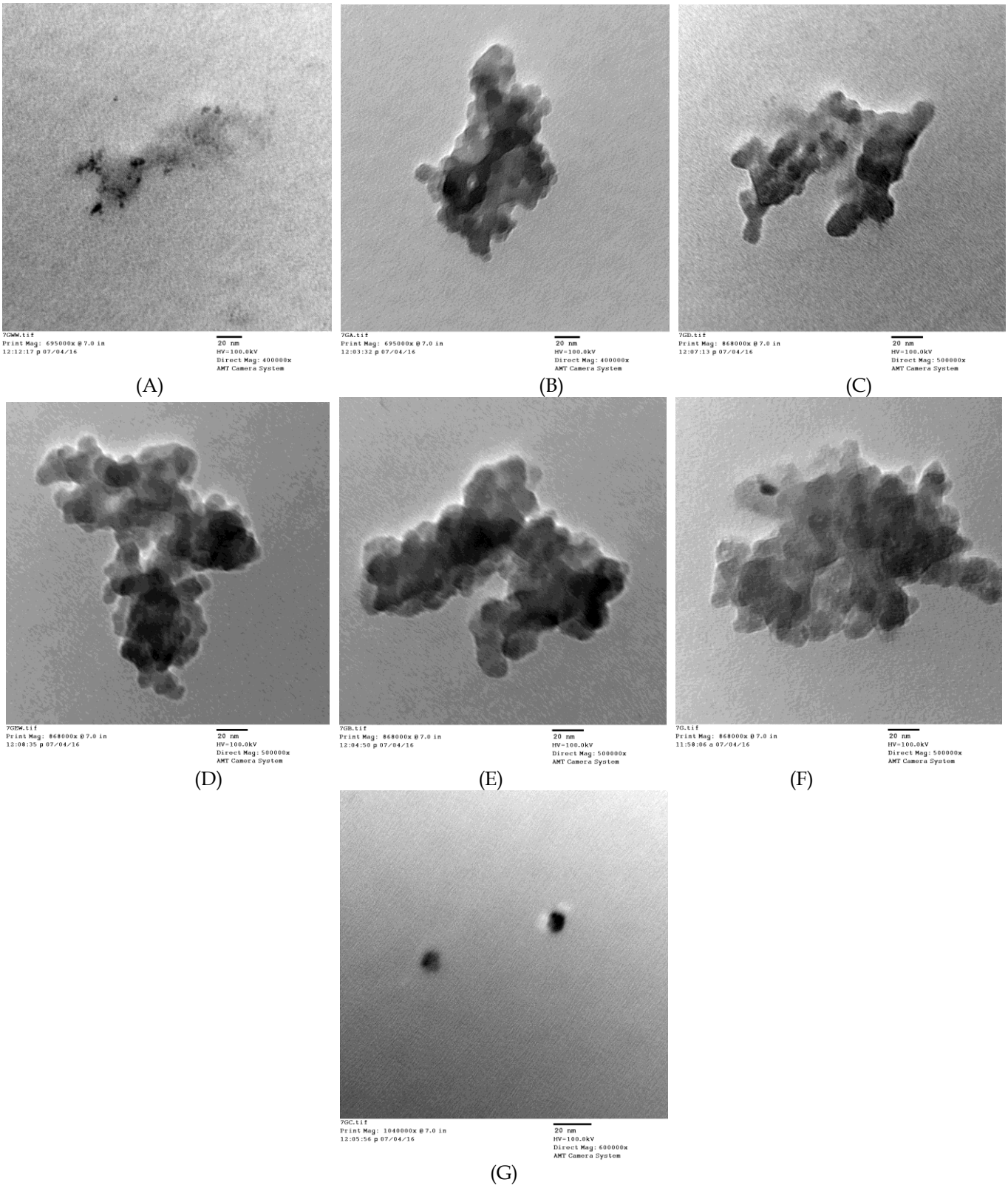


Figure 2 (A) – (G) shows Transmission Electron Microscope images of Gold Bhasma medicine. These figures shows that the material mainly consisted of spherical to dumbbell sized particles with 10–20 nm in diameter, and has a smaller aggregated particle size.

Investigations well confirm the presence of gold particles with nanometric size between 10 and 20 nm.

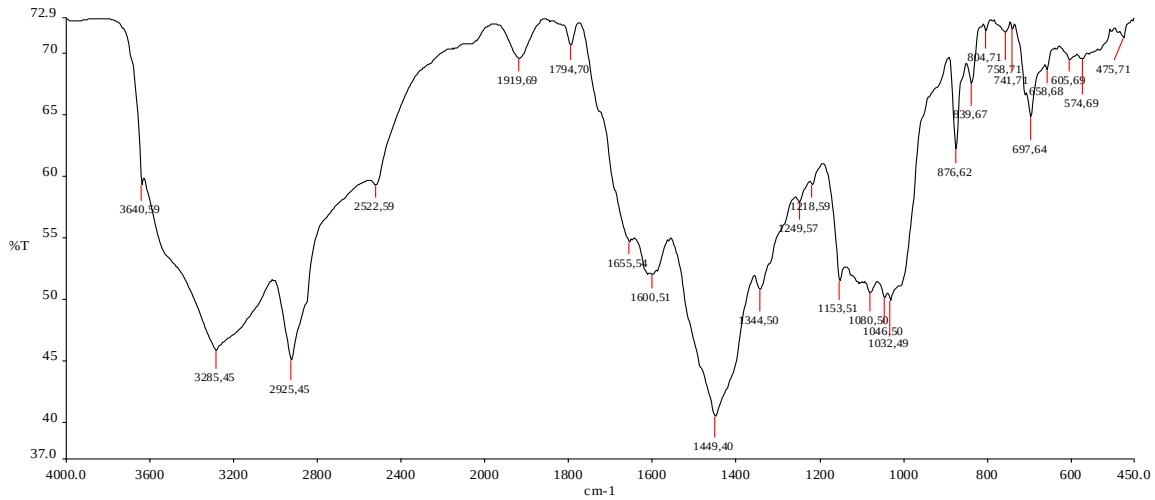


Figure 3. FTIR Spectra of Gold Bhasma medicine

Interpretation of FTIR Spectra of Gold Bhasma medicine can be done as follows:

S.N.	Spectral Region Wave number cm^{-1}	Bond causing absorption	Pattern and Intensity of Band
1	3640.59	Alcohols - Secondary CH–OH	Broad and Moderate Intensity
2	3285.45	Alcohols - Secondary CH–OH	Broad and Strong Intensity
3	2925.45	–	Broad and Strong Intensity
4	2522.59	–	Broad and Moderate Intensity
5	1919.69	–	Broad and Low Intensity
6	1794.70	–	Broad and Low Intensity
7	1655.54	–	Broad and Moderate Intensity
8	1600.51	–	Broad and Moderate Intensity
9	1449.40	–	Broad and Strong Intensity
10	1344.50	–	Broad and Moderate Intensity
11	1249.57	–	Broad and Moderate Intensity
12	1218.59	–	Broad and Moderate Intensity
13	1153.51	–	Broad and Moderate Intensity
14	1080.50	–	Broad and Moderate Intensity
15	1046.50	–	Broad and Moderate Intensity
16	1032.49	–	Broad and Moderate Intensity
17	876.62	Alkane - Ethyl, n - propyl, tertiary butyl	Sharp and Low Intensity
18	839.67	Alkane - n - propyl	Sharp and Low Intensity
19	804.71	–	Sharp and Low Intensity
20	758.71	–	Sharp and Low Intensity
21	741.71	Aromatic –Vicinal trisustituted Benzene 	Sharp and Low Intensity
22	697.64	Aromatic – Meta disustituted Benzene  Vicinal trisustituted Benzene 	Sharp and Low Intensity
23	658.68	–	Sharp and Low Intensity
24	605.69	–	Sharp and Low Intensity
25	574.69	–	Sharp and Low Intensity
26	475.71	Aromatic – Monosustituted Benzene  , Ortho disustituted Benzene  , Meta disustituted Benzene 	Sharp and Low Intensity

Interpretation of FTIR Spectra of Gold Bhasma medicine shows presence of various functional groups such as Alkane - Ethyl, n - propyl, tertiary butyl; Alcohols - Secondary CH–OH; Aromatic – Monosustituted Benzene  , Ortho disustituted Benzene  , Meta disustituted Benzene  Vicinal trisustituted Benzene  .

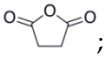
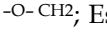
CONCLUSION

Scanning Electron Microscope images of Diamond Cellular Anti-Ageing Cream shows that the material mainly consisted of spherical particles with 5–10 µm in diameter, and has a smaller aggregated particle size. Although the majority of material consists of micrometer or grains, smaller particles with nanoscale (10–20 nm) are also present in the TEM images.

Transmission Electron Microscope images of Diamond Cellular Anti-Ageing Cream shows that the material mainly consisted of spherical particles with 10–20 nm in diameter, and has a smaller aggregated particle size.

Investigations well confirm the presence of diamond crystals with nanometric size between 10 and 20 nm.

FTIR can be routinely used to identify the functional groups and identification/quality control of raw material/finished products.

Interpretation of FTIR Spectra of Diamond Cellular Anti-Ageing Cream shows presence of various functional groups such as Alkane - Ethyl, n - propyl, Iso propyl, tertiary butyl; Alkene - Vinyl –CH=CH_2, –CH–CH– (Trans), –CH–CH– (Cis), >CH=CH2, >CH=CH–; Acids – Carboxylic acids COOH; Alcohols - Primary alcohols CH_2–OH, Secondary CH–OH, Aromatic  ; Aldehydes - Aliphatic Aldehydes –CH_2CHO, Aromatic Aldehydes  ; Anhydrides – Normal anhydrides C–CO–O–CO–C, Cyclic anhydrides  ; Aromatic – Meta disustituted Benzene  , Vicinal trisustituted Benzene  , Monosustituted Benzene  ; Amides – Amide –CO–NH_2; Amines –  , Primary amines CH_2–NH_2; Amines (Cont) – Hydrochloride C–$NH_3^+Cl^-$; Imines – Substituted Imines >C=N–C; Ethers - Aliphatic ethers CH_2–O–CH_2, Aromatic Ethers -  ; Esters – Acetates –CH_2–CO–O–R, Acrylates =CH–CO–O–R, Fumarates =CH–CO–O–R, Maleates =CH–CO–O–R, Benzoates, phthalates .

REFERENCES

1. Bernhard Wessling, Conductive Polymer / Solvent Systems: Solutions or Dispersions?, 1996
2. University of Wisconsin–Madison: Making and conjugating colloidal metals.
3. Paul Mulvaney, University of Melbourne, The beauty and elegance of Nanocrystals, Use since Roman times
4. C. N. Ramachandra Rao, Giridhar U. Kulkarni, P. John Thomasa, Peter P. Edwards, Metal nanoparticles and their assemblies, Chem. Soc. Rev., 2000, 29, 27–35. (on-line here; mentions Cassius and Kunchel)
5. S.Zeng; Yong, Ken-Tye; Roy, Indrajit; Dinh, Xuan-Quyen; Yu, Xia; Luan, Feng; et al. (2011). "A review on functionalized gold nanoparticles for biosensing applications" (PDF). Plasmonics. 6 (3): 491–506. doi:10.1007/s11468-011-9228-1.
6. Sharma, Vivek; Park, Kyoungweon; Srinivasarao, Mohan (2009). "Colloidal dispersion of gold nanorods: Historical background, optical properties, seed-mediated synthesis, shape separation and self-assembly". Material Science and Engineering Reports. 65 (1–3): 1–38. doi:10.1016/j.mser.2009.02.002.
7. The Lycurgus Cup". British Museum. Retrieved 2015-12-04.
8. Antonii, Francisci (1618). Panacea aurea sive Tractatus duo de ipsius auro potabili. Ex Bibliopolio Frobeniano.
9. Culpeper, Nicholas (1657). Mr. Culpepper's Treatise of aurum potabile Being a description of the three-fold world, viz. elementary celestial intellectual containing the knowledge necessary to the study of hermetick philosophy. Faithfully written by him in his life-time, and since his death, published by his wife. London.
10. Kunckel von Löwenstern, Johann (1678). Utiles observationes sive animadversiones de salibus fixis et volatilibus, auro et argento potabili (etc.). Austria: Wilson.
11. V. R. Reddy, "Gold Nanoparticles: Synthesis and Applications" 2006, 1791, and references therein
12. Michael Faraday, Philosophical Transactions of the Royal Society, London, 1857
13. Michael Faraday's gold colloids | The Royal Institution: Science Lives Here".www.rigb.org. Retrieved 2015-12-04.
14. Gay-Lussac (1832). "Ueber den Cassius'schen Goldpurpur". Annalen der Physik. 101 (8): 629–630. Bibcode:1832AnP...101..629G.doi:10.1002/andp.18321010809.
15. Berzelius, J. J. (1831). "Ueber den Cassius' schen Goldpurpur". Annalen der Physik. 98 (6): 306–308. Bibcode:1831AnP....98..306B.doi:10.1002/andp.18310980613.

16. Faraday, M. (1857). "Experimental Relations of Gold (and Other Metals) to Light,". Philosophical Transactions of the Royal Society. 147: 145.doi:10.1098/rstl.1857.0011.
17. Zsigmondy, Richard (December 11, 1926). "Properties of colloids" (PDF). Nobel Foundation. Retrieved 2009-01-23.
18. Zeng, Shuwen; Yu, Xia; Law, Wing-Cheung; Zhang, Yating; Hu, Rui; Dinh, Xuan-Quyen; Ho, Ho-Pui; Yong, Ken-Tye (2013). "Size dependence of Au NP-enhanced surface plasmon resonance based on differential phase measurement". Sensors and Actuators B: Chemical. 176: 1128.doi:10.1016/j.snb.2012.09.073.
19. Hurst, Sarah J., ed. (2011-01-01). Nanoparticle Therapeutics: FDA Approval, Clinical Trials, Regulatory Pathways, and Case Study - Springer. Methods in Molecular Biology. Humana Press. doi:10.1007/978-1-61779-052-2_21.ISBN 978-1-61779-051-5.
20. Hirsch LR, Jackson JB, Lee A, et al. A whole blood immunoassay using gold nanoshells. Anal Chem.2003a;75:2377–2381.
21. Hirsch LR, Halas NJ, West JL. Whole-blood immunoassay facilitated by gold nanoshell-conjugate antibodies. Methods Mol Biol. 2005;303:101–111.
22. Liu X, Dai Q, Austin L, et al. A one-step homogeneous immunoassay for cancer biomarker detection using gold nanoparticle probes coupled with dynamic light scattering. J Am Chem Soc. 2008;130:2780–2782.
23. Tang D, Yuan R, Chai Y. Biochemical and immunochemical characterization of the antigen-antibody reaction on a non-toxic biomimetic interface immobilized red blood cells of crucian carp and gold nanoparticles. Biosens Bioelectron. 2007;22:1116–1120.
24. Kim YP, Oh E, Hong MY, et al. Gold nanoparticle-enhanced secondary ion mass spectrometry imaging of peptides on self-assembled monolayers. Anal Chem. 2006;78:1913–1920.
25. Tseng WL, Huang MF, Huang YF, et al. Nanoparticle-filled capillary electrophoresis for the separation of long DNA molecules in the presence of hydrodynamic and electrokinetic forces. Electrophoresis.2005;26:3069–3075.
26. Kah JC, Kho KW, Lee CG, et al. Early diagnosis of oral cancer based on the surface plasmon resonance of gold nanoparticles. Int J Nanomedicine. 2007;2:785–798.
27. Medley CD, Smith JE, Tang Z, et al. Gold nanoparticle-based colorimetric assay for the direct detection of cancerous cells. Anal Chem. 2008;80:1067–1072.
28. Xie H, Gill-Sharp KL, O'Neal DP. Quantitative estimation of gold nanoshell concentrations in whole blood using dynamic light scattering. Nanomedicine. 2007;3:89–94.
29. Jensen RA, Sherin J, Emory SR. Single nanoparticle based optical pH probe. Appl Spectrosc.2007;61:832–838.
30. Wang Y, Qian W, Tan Y, et al. A label-free biosensor based on gold nanoshell monolayers for monitoring biomolecular interactions in diluted whole blood. Biosens Bioelectron. 2008b;23:1166–1170.
31. Zharov VP, Mercer KE, Galitovskaya EN, et al. Photothermal nanotherapeutics and nanodiagnostics for selective killing of bacteria targeted with gold nanoparticles. Biophys J. 2006b;90:619–627.
32. Loo C, Lowery A, Halas N, et al. Immunotargeted nanoshells for integrated cancer imaging and therapy.Nano Lett. 2005b;5:709–711.
33. Huang X, El-Sayed IH, Qian W, et al. Cancer cell imaging and photothermal therapy in the near-infrared region by using gold nanorods. J Am Chem Soc. 2006a;128:2115–2120.
34. Huang X, Jain PK, El-Sayed IH, et al. Determination of the minimum temperature required for selective photothermal destruction of cancer cells with the use of immunotargeted gold nanoparticles. Photochem Photobiol. 2006b;82:412–417.
35. Tong L, Zhao Y, Huff TB, et al. Gold nanorods mediate tumor cell death by compromising membrane integrity. Adv Mater. 2007;19:3136–3141.
36. Chen J, Wang D, Xi J, et al. Immuno gold nanocages with tailored optical properties for targeted photothermal destruction of cancer cells. Nano Lett. 2007a;7:1318–1322.
37. Huang X, Qian W, El-Sayed IH, et al. The potential use of the enhanced nonlinear properties of gold nanospheres in photothermal cancer therapy. Lasers Surg Med. 2007c;39:747–753.
38. Lowery AR, Gobin AM, Day ES, et al. Immunonanoshells for targeted photothermal ablation of tumor cells. Int J Nanomedicine. 2006;1:149–154.
39. van Horssen R, Ten Hagen TL, Eggermont AM. TNF-alpha in cancer treatment: molecular insights, antitumor effects, and clinical utility. Oncologist. 2006;11:397–408.
40. Mocellin S, Nitti D. TNF and cancer: the two sides of the coin. Front Biosci. 2008;13:2774–2783.
41. Visaria RK, Griffin RJ, Williams BW, et al. Enhancement of tumor thermal therapy using gold nanoparticle-assisted tumor necrosis factor-alpha delivery. Mol Cancer Ther. 2006;5:1014–1020.
42. Paciotti GF, Myer L, Weinreich D, et al. Colloidal gold: a novel nanoparticle vector for tumor directed drug delivery. Drug Deliv. 2004;11:169–183.
43. Goel R, Swanlund D, Coad J, et al. TNF-alpha-based accentuation in cryoinjury – dose, delivery, and response. Mol Cancer Ther. 2007;6:2039–2047.
44. Visaria R, Bischof JC, Loren M, et al. Nanotherapeutics for enhancing thermal therapy of cancer. Int J Hyperthermia. 2007;23:501–511.
45. Han G, Ghosh P, Rotello VM. Functionalized gold nanoparticles for drug delivery. Nanomedicine (Lond) 2007;2:113–123.
46. Han G, Ghosh P, Rotello VM. Multi-functional gold nanoparticles for drug delivery. Adv Exp Med Biol 2007;620:48–56.
47. Langer R. Biomaterials in drug delivery and tissue engineering: one laboratory's experience. Acc Chem Res 2000;33:94–101.
48. Paclitaxel-Functionalized Gold Nanoparticles Jacob D. Gibson, Bishnu P. Khanal, and Eugene R. Zubarev J. Am. Chem. Soc. 2007, 129, 11653–11661doi:10.1021/ja075181k
49. Conde, J.; de la Fuente, JM; Baptista, PV. "Nanomaterials for reversion of multidrug resistance in cancer: a new hope for an old idea?." Front. Pharmacol.2013. Vol 4 No 134.

50. Partha Ghosh, Gang Han, Mrinmoy De, Chae Kyu Kim, Vincent M. Rotello, Gold nanoparticles in delivery applications, Advanced Drug Delivery Reviews, Volume 60, Issue 11, 17 August 2008, Pages 1307–1315
51. Dakrong Pissuwan[a], Takuro Niidome[a, b, ,], Michael B. Cortie, The forthcoming applications of gold nanoparticles in drug and gene delivery systems, Journal of Controlled Release, Volume 149, Issue 1, 5 January 2011, Pages 65–71
52. Weibo Cai,[1,2] Ting Gao,[3] Hao Hong,[1] and Jiangtao Sun, Applications of gold nanoparticles in cancer nanotechnology, Nanotechnol Sci Appl. 2008 Sep; 2008(1): 10.2147/NSA.S3788.
53. Qian, Ximei. "In vivo tumor targeting and spectroscopic detection with surface-enhanced Raman nanoparticle tags." Nature Biotechnology. 2008. Vol 26 No 1.
54. Sajjadi AY, Suratkar AA, Mitra KK, Grace MS. Short-Pulse Laser-Based System for Detection of Tumors: Administration of Gold Nanoparticles Enhances Contrast. J. Nanotechnol. Eng. Med.. 2012;3(2):021002-021002-6. doi:10.1115/1.4007245.
55. Conde J, Tian F, Hernández Y, Bao C, Cui D, Janssen KP, Ibarra MR, Baptista PV, Stoeger T, de la Fuente JM. In vivo tumor targeting via nanoparticle-mediated therapeutic siRNA coupled to inflammatory response in lung cancer mouse models. Biomaterials. 2013;34(31):7744–53. doi: 10.1016/j.biomaterials.2013.06.041.
56. Conde J, Ambrosone A, Sanz V, Hernandez Y, Marchesano V, Tian F, Child H, Berry CC, Ibarra MR, Baptista PV, Tortiglione C, de la Fuente JM. Design of multifunctional gold nanoparticles for in vitro and in vivo gene silencing. ACS Nano. 2012;6(9):8316–24. doi: 10.1021/nn3030223.
57. Conde J, de la Fuente JM, Baptista PV. In vitro transcription and translation inhibition via DNA functionalized gold nanoparticles. Nanotechnology. 2010;21(50):505101. doi: 10.1088/0957-4484/21/50/505101.
58. Giljohann DA, Seferos DS, Prigodich AE, Patel PC, Mirkin CA. Gene regulation with polyvalent siRNA-nanoparticle conjugates. J Am Chem Soc 2009;131:2072–2073.
59. Conde J, Rosa J, de la Fuente JM, Baptista PV. Gold-nanobeacons for simultaneous gene specific silencing and intracellular tracking of the silencing events. Biomaterials. 2013;34(10):2516–23. doi: 10.1016/j.biomaterials.2012.12.015.
60. Rosa J, Conde J, de la Fuente J M, Lima J C, Baptista P V. Gold-nanobeacons for real-time monitoring of RNA synthesis. Biosens Bioelectron. 2012; 36 (1) : 161-7. doi: 10.1016/j.bios. 2012.04.006.
61. Conde J, Rosa J, Baptista P. Gold-Nanobeacons as a theranostic system for the detection and inhibition of specific genes. Community Contributed Protocol Exchange. 27 November 2013. doi:10.1038/protex.2013.088.
62. Kennedy L.C., Bickford L.R., Lewinski N.A., Coughlin A.J., Hu Y., Day E.S., West J.L., Drezek R.A..Small. 2011;7:169–183.
63. Huang X., El-Sayed I.H., Qian W., El-Sayed M.A.. J. Am. Chem. Soc. 2006;128:2115–2120.
64. Huff T.B., Tong L., Zhao Y., Hansen M.N., Cheng J.X., Wei A.. Nanomedicine. 2007;2:125–132.
65. Hirsch L.R., Stafford R.J., Bankson J.A., Sershen S.R., Price R.E., Hazle J.D., Halas N.J., West J.L.. Proc. Natl. Acad. Sci. USA. 2003;100:13549–13554.
66. Loo C., Lowery A., Halas N.J., West J.L., Drezek R.. Nano Lett. 2005;5:709–711.
67. Hu M., Petrova H., Chen J., McLellan J.M., Siekkinen A.R., Marquez M., Li X., Xia Y., Hartland G.V.. J. Phys. Chem. B. 2006;110:1520–1524.
68. Chen J., Wang D., Xi J., Au L., Siekkinen A., Warsen A., Li Z.-Y., Zhang H., Xia Y., Li X.. Nano Lett.2007;7:1318–1322.
69. Terentyuk G.S., Maslyakova G.N., Suleymanova L.V., Khlebtsov N.G., Khlebtsov B.N., Akchurin G.G., Maksimova I.L., Tuchin V.V.. J. Biomed. Opt. 2009;14
70. Khlebtsov B.N., Khanadeev V.A., Maksimova I.L., Terentyuk G.S., Khlebtsov N.G.. Nanotechnologies in Russia. 2010;5:454–468.
71. Hainfeld, James et al. "The use of gold nanoparticles to enhance radiotherapy in mice." Phys. Med. Biol. 2004. Vol 49, N309–315
72. McMahon, Stephen et al. "Biological consequences of nanoscale energy deposition near irradiated heavy atom nanoparticles." Nature Scientific Reportshttp://www.nature.com/srep/2011/110620/srep00018/full/srep00018.html
73. Zhang, Zhiyang; Zhaopeng Chen; Shasha Wang; Chengli Qu; Lingxin Chen (2014). "On-site Visual Detection of Hydrogen Sulfide in Air Based on Enhancing the Stability of Gold NanoParticles". ACS Applied Materials & Interfaces. 6 (9): 6300–6307. doi:10.1021/am500564w.
74. ^ Jump up to:[a b c d e] Xu, S. et. al. Gold nanoparticle-based biosensors. Gold Bulletin. 2010, 43, p 29–41.
75. J. Wang, R. Polsky and D. Xu, Langmuir, 2001, 17, 5739.
76. J. Wang, D. Xu and R. Polsky, J Am Chem Soc, 2002, 124, 4028.
77. Meihua Lin, Hao Pei, Fan Yang, Chunhai Fan, Xiaolei Zuo, Applications of Gold Nanoparticles in the Detection and Identification of Infectious Diseases and Biothreats; Advanced Materials, Volume 25, Issue 25, July 5, 2013, Pages 3490–3496.
78. M. C. Daniel and D. Astruc, Chem Rev, 2004, 104, 293.
79. M. Hu, J. Chen, Z.Y. Li, L. Au, G.V. Hartland, X. Li, M. Marquez and Y. Xia, Chem Soc Rev, 2006, 35, 1084.
80. S. Link and M.A. El-Sayed, J. Phys. Chem. B, 1996, 103, 8410.
81. P. Mulvaney, Langmuir, 1996, 12, 788.
82. H. Y. Lin, C. T. chen and Y. C. Chen, Anal Chem, 200, 78, 6873
83. L. He, M.D. Musick, S. R. Nicewarner, F.G. Salinas, Journal of the American Chemical Society, 2000, 122, 9071
84. A.M. Qi, I. Honma and H. Zhou, Opt Lett, 2000, 25, 372
85. K.R. Brown, a.P Fox and M.J. Natan, Journal of the American Chemical society, 1996, 118, 1154.
86. Y. Xiao, et. al. Science, 2003,299, 1877.

87. A. Gole, et. al. Langmuir, 2001, 17, 1674
88. A. Gole, et. al. Colloids and Surfaces B: Biointerfaces, 2002, 25, 129
89. M. Valden, X. Lai and D.W. Goodman, Science, 1998, 281, 1647
90. Y. Lou, M.M. Maye, L. Han, J.Luo and C. –J. Zhong, Chemical Communications, 2001, 473
91. M. Turner, V.B. Golovko, O.P Vaughan, P. Abdulkin, A. Berenguer-Murcia, M.S. Tikhov, B.F. Johnson and R.M Lambert, Narture, 2008, 454, 981
92. York J., Spetzler D., Hornung T., Ishmukhametov R., Martin J., Frasch W.D.. J. Bioenerg. Biomembr.2007;39:435–439.
93. Hu R., Yong K.T., Roy I., Ding H., He S., Prasad P.N.. J. Phys. Chem. C. 2009;113:2676–2684.
94. Bickford L., Chang J., Fu K., Sun J., Hu Y., Gobin A., Yu T.K., Drezek R.. Nanobiotechnology. 2008;4:1–8.
95. Wang S.-H., Lee C.-W., Chiou A., Wei P.-K.. J. Nanobiotechnology. 2010;8
96. Abraham G.E., Himmel P.B.. J. Nutr. Med. 1997;7:295–305.
97. Gu H., Ho P.L., Tong E., Wang L., Xu B.. Nano Lett. 2003;3:1261–1263.
98. Rosemary M.J., MacLaren I., Pradeep T.. Langmuir. 2006;22:10125–10129.
99. Selvaraj V., Alagar M.. Int. J. Pharm. 2007;337:275–281.
100. L.A. Dykman and N.G. Khlebtsov, Gold Nanoparticles in Biology and Medicine: Recent Advances and Prospects, Acta Naturae. 2011 Apr-Jun; 3(2): 34–55.
101. Burangulov, Nail, Alexander Moravsky, Yuiya Kulikova, George Dyachuk, and Raouf Loutfy. "Cosmetic compositions containing fullerene clusters." U.S. Patent Application 10/858,361, filed June 1, 2004.
102. Sharma, Bhumika, and Arvind Sharma. "Future prospect of nanotechnology in development of anti-ageing formulations." Int J Pharm Pharm Sci 4, no. 3 (2012): 57-66.
103. Pageon, H. "Reaction of glycation and human skin: The effects on the skin and its components, reconstructed skin as a model." Pathologie Biologie 58, no. 3 (2010): 226-231.
104. Kim, Ji-hoon, Chung-Oui Hong, Yun-chang Koo, Hee-Don Choi, and Kwang-Won Lee. "Anti-glycation effect of gold nanoparticles on collagen." Biological and Pharmaceutical Bulletin 35, no. 2 (2012): 260-264.
105. Katie Anderson, Assessing Use of Gold Nanoparticles; Cosmetics & Toiletries, May 30, 2013
106. https://www.orogoldcosmetics.com/24k-nano-day-reovery.html
107. https://www.orogoldcosmetics.com/24k-nano-night-recovery.html
108. https://www.orogoldcosmetics.com/24k-nano-hydra-silk-mask.html
109. https://www.orogoldcosmetics.com/24k-nano-ultra-silk-serum.html