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BIOSYNTHESIS OF GOLD NANOPARTICLES, SCOPE AND APPLICATION: A REVIEW

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ABSTRACT

The synthesis of gold nanoparticles has received considerable attention and has been a focus of research due to their high chemical and thermal stability, fascinating optical, electronic properties, and promising applications such as nanoelectronics, biomedicine, sensing, and catalysis. Different physical and chemical methods for gold nanoparticles synthesis are known but these methods are either expensive or are not eco-friendly due to use of hazardous chemicals, stringent protocol used during the process. These drawbacks necessitate the development of nonhazardous and greener methods for gold nanoparticles synthesis. Therefore, there has been tremendous excitement in the study of gold nanoparticles synthesis by using natural biological system. Microorganisms thus play a very important role in the eco-friendly and green synthesis of metal nanoparticles. The inherent, clean, nontoxic and environment friendly ability of eukaryotic and prokaryotic microorganisms, plants system to form the metal nanoparticles is particularly important in the development of nanobiotechnology. This review contains a brief outlook of the biosynthesis of gold nanoparticles using various biological resources, characterization and their potential application in various fields.

INTRODUCTION: The field of nanotechnology is an immensely developing field as a result of its wide-ranging applications in different areas of science and technology. The word, nanoparticle (10^{-9}m) can be defined in nanotechnology as a small object that acts as a whole unit in terms of its transport and properties. The word "nano" is derived from a Greek word meaning dwarf or extremely small [1].

Nanotechnology has a wide variety of applications in various fields like optics, electronics, catalysis, bio-medicine, magnetics, mechanics, energy science, etc. Nanobiotechnology is a multidisciplinary field involving research and development of technology in different fields of science like biotechnology, nanotechnology, physics, chemistry, and material science [1-2]. It deals with bio-fabrication of nano-objects or bi-functional macromolecules usable as tools to construct or manipulate nano-objects. Since, microbial cells offer many advantages like wide physiological diversity, small size, genetic manipulability and controlled culturability, they are thus regarded as ideal producers for the synthesis of diversity of nanostructures, materials and instruments for nanosciences [3].

The methods of biosynthesis can employ either microbial cells or plant extract for production of nanoparticles. Biosynthesis of nanoparticles is an exciting recent area to the large repertoire of various methods of nanoparticles synthesis and now,

nanoparticles have entered a commercial exploration period. Gold nanoparticles (GNPs) are presently under intensive study for applications in optoelectronic devices, ultrasensitive chemical and biological sensors and as catalysts [3]. Nanoparticles are metal particles and exhibit different shapes like spherical, triangular, rod, etc. Research on synthesis of nanoparticles is the current area of interest due to the unique visible properties (chemical, physical, optical, etc.) of nanoparticles compared with the bulk material [4-5].

GNPs are some of the most extensively studied material. These can be easily synthesized, exhibit intense surface plasmon resonance and display high chemical as well as thermal stability [6]. A variety of gold structures including rods, triangles, hexagons, octagons, cubes and nanowires can be synthesized by using different techniques [7-10]. In biomedicine, GNPs are used in several purposes such as leukemia therapy [11], biomolecular immobilization [12] and biosensor design. The use of GNPs as anti-angiogenesis, anti-malaria and anti-arthritic agents is also reported by [13]. Because of the increased demand of gold in many industrial applications, there is a growing need for cost effectiveness as well as to implement green chemistry in the development of new nanoparticles [14].

Advanced synthesis of Metallic Nanoparticles: The nanoparticles can be synthesized using the top-down (physical) approach which deals with methods such as thermal decomposition, diffusion, irradiation, arc discharge, etc., and bottom-up (chemical and biological) approach which involves seeded growth method, polyol synthesis method, electrochemical synthesis, chemical reduction, and biological entities for fabrication of nanoparticles.

In the top-down approach, the bulk materials are gradually broken down to nano-sized materials by machining and etching techniques. In contrast, the atoms or molecules are assembled into molecular structures in the nanometer range in the bottom-up approach, which is commonly applied for chemical and biological synthesis of nanoparticles [14]. Generally, the methods used for nanoparticles synthesis employing chemical routes involves conditions such as high temperature and high pressure and also incorporates the use of strong and weak chemical reducing agents along with protective agents (sodium borohydride, sodium citrate and alcohols). These agents are mostly toxic, flammable and they cannot be easily released in environmental and also show a low production rate [15-16]. Moreover, these are capital intensive and are inefficient in materials and energy use [17-18].

Furthermore, the use of toxic chemicals and organic solvents during nanoparticles synthesis and their occurrence on the surface of nanoparticles limit their applications. Such drawbacks necessitate the development of clean, biocompatible, nonhazardous, and eco-friendly methods for GNPs synthesis. Consequently, biological systems have been focused on and exploited for the synthesis of nanoparticles [19] providing a safer alternative to physical and chemical methods.

The biological method for the synthesis of nanoparticles employs use of biological agents like bacteria, fungi, actinomycetes, yeast, algae and plants [20-21] thereby providing a wide range of resources for the synthesis of nanoparticles. The rate of reduction of metal ions using biological agents is found to be much faster and also at ambient temperature and pressure conditions. It is well known that microbes such as bacteria [22], yeast [23], fungi [24] and alga [25-26] are capable of adsorbing and accumulating metals. The biological agents secrete a large amount of enzymes, which are capable of hydrolyzing metals and thus bring about enzymatic reduction of metals ions [27].

In case of fungi, the enzyme nitrate reductase is found to be responsible for the synthesis of nanoparticles [28-29]. The biomass used for the synthesis of nanoparticles is simpler to handle, gets easily disposed of in the environment and also the downstream processing of the biomass is much easier. Synthesis of nanoparticles can be carried out at ambient temperature and pressure conditions that require lesser amounts of chemical [17]. The synthesizing process is less labor-intensive, low-cost technique, nontoxic and is more of a greener approach.

Thus, considering the above points the biological method employed for the synthesis of nanoparticles proves to be superior compared with the physical and chemical methods of synthesis due to its environment friendly approach and also as a low cost technique [30].

Therefore, based on their enormous biotechnological applications, microorganisms such as bacteria, fungi, and yeast are regarded as possible eco-friendly "nano-factories" for nanoparticles synthesis.

Mechanism of Biosynthesis of Nanoparticles: Biosynthesis is the phenomena which takes place by means of biological processes or enzymatic reactions. These eco-friendly processes are referred as green and clean technology, and can be used for better synthesis of metal nanoparticles from microbial cells [31]. Microorganisms can survive and grow in high concentration of metal ion due to their ability to fight against stress [32]. The exact mechanism for the synthesis of nanoparticles using biological agents has not been devised yet as different biological agents react differently with metal ions and also there are different biomolecules responsible for the synthesis of nanoparticles. In addition, the mechanism for intra- and extracellular synthesis of nanoparticles is different in various biological agents [30].

According to Beveridge (1997), the mechanisms which are considered for the biosynthesis of nanoparticles includes efflux systems, alteration of solubility and toxicity via reduction or oxidation, bioabsorption, bioaccumulation, extracellular complexation or precipitation of metals, and lack of specific metal transport systems [33]. The cell wall of the microorganisms also plays a major role in the intracellular synthesis of nanoparticles. The cell wall being negatively charged interacts electrostatically with the positively charged metal ions. The enzymes present within the cell wall bioreduce the metal ions to nanoparticles, and finally the smaller sized nanoparticles get diffused of through the cell wall [34].

Mukherjee *et al*., (2001) reported stepwise mechanism for intracellular synthesis of nanoparticles using *Verticillium* species. The mechanism of synthesis of nanoparticles was divided into trapping, bioreduction and synthesis. Similar mechanism was also found in fungus for the synthesis of nanoparticles. Moreover, in the case of bacteria *Lactobacillus* sp, Nair and Pradeep (2002) observed that during the initial step of synthesis of nanoparticles, nucleation of clusters of metal ions takes place, and hence there is an electrostatic interaction between the bacterial cell and metal clusters which leads to the formation of nanoclusters [35]. Lastly, the smaller sized nanoclusters get diffused through the bacterial cell wall. In actinomycetes also, the reduction of metal ions occur on the surface of mycelia along with cytoplasmic membrane leading to the formation of nanoparticles [36-37].

The mechanism of extracellular synthesis of nanoparticles using microbes is basically found to be nitrate reductase-mediated synthesis. The enzyme nitrate reductase secreted by the fungi helps in the bioreduction of metal ions and synthesis of nanoparticles. A number of researchers supported nitrate reductase for extracellular synthesis of nanoparticles [17, 28-29, 38-40]. A similar mechanism was also reported in the case of extracellular synthesis of GNPs using *Rhodopseudomonas capsulata* [39].

The bacterium *R. capsulata* is known to secrete cofactor NADH and NADH-dependent enzymes. The bioreduction of gold ions was found to be initiated by the electron transfer from the NADH by NADH-dependent reductase as electron carrier. Next, the gold ions (Au^{3+}) obtain electrons and are reduced to elemental gold (Au^0) and hence result in the formation of GNPs. Nangia *et al*., (2009) proposed the synthesis of GNPs by bacterium *Stenotrophomonas maltophilia* and suggested that the biosynthesis of GNPs and their stabilization via charge capping in *S. maltophilia* involved NADPH-dependent reductase enzyme which converts Au^{3+} to Au^0 through electron shuttle enzymatic metal reduction process as shown in **Fig. 1** [40].

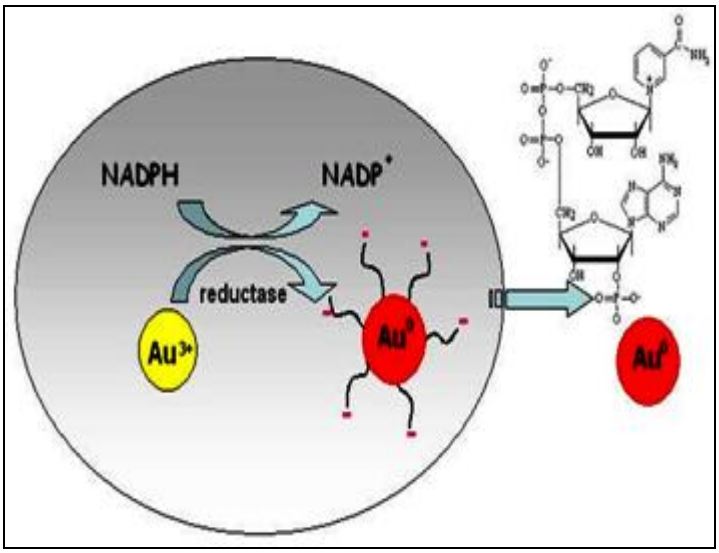

FIG. 1: PROPOSED MECHANISM OF GOLD IONS BIOREDUCTION VIA NADPH-DEPENDANT REDUCTASES

General Chemistry of Gold: Gold can occur in one of the six oxidation states, from -1 to +5, which can be related to its relatively high electronegativity. The most common form of gold complexes is in aurous [Au (I)] and auric [Au (III)] oxidation states [41]. The dissolution of gold in aqueous solution is a combination process of oxidation and complexation. Au (I) and Au (III) can form stable complexes in the presence of a complexing ligand, otherwise they can be reduced in solution to metallic gold [42]. The stability of gold complexes is related not only to the properties of the complexing ligand, but also more specifically to the donor atom of the ligand that is bonded directly to the gold atom.

According to Nicol *et al*., (1987), the first rule is that the stability of gold complexes tends to decrease when the electronegativity of the donor atom increases. For example, the stability of gold halide complexes in solution follows the order I^-> Br^-> Cl^-> F^-. The second rule is that Au (III) is generally favored over Au (I) with hard ligands and Au (I) over Au (III) with soft ligands. The preferred co-ordination number of Au (I) is 2, tending to form linear complexes, and that of Au (III) is 4, tending to form square planar complexes. The two precursors which are used for the synthesis of GNPs are gold (III)–chloride complex and gold (I) thiosulfate, in that also, gold (III)–chloride complex is widely used as a precursor in most of the GNPs biosynthesis process.

Biosynthesis of Gold Nanoparticles: The use of microbial cells is now emerging as a novel and green approach for the synthesis of metal nanoparticles. Basic steps for metal nanoparticles biosynthesis includes growth of microorganism in culture media, harvesting biomass from medium and finally incubation of biomass with sub-inhibitory concentration of target metal salts. During the different phases of microbial growth, the metal reduction process may take place by intercellular or extracellular bioreductant ingredients [38]. The reaction condition can be optimized by changing experimental factors such as pH, incubation time, presence of light source, temperature, the composition of the culture medium, etc. This optimization will improve the chemical composition, shape and size of the particles synthesized [43].

In general, GNPs precipitate intracellularly and/or extracellularly depending on the species as in **Fig. 2** and reaction condition. The shape of GNPs precipitated by bacteria, cyanobacteria, algae, fungi, plants includes spherical, oval, irregular, triangular, tetragonal, hexagonal, octahedral, rod, cubicl, icosahedral, coil or wire, plate, and thin foil, with size ranging from 1 nm to several mm as discussed in **Fig. 3**.

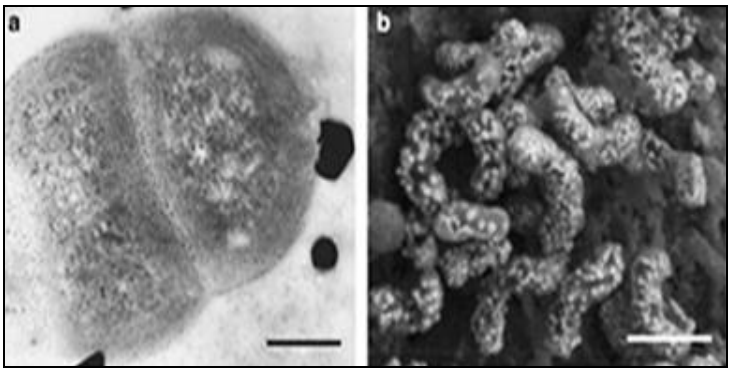

FIG. 2(a): A TEM MICROGRAPH OF A THIN SECTION OF CYANOBACTERIA CELL WITH THE GOLD NANOPARTICLES INSIDE THE CELL, 2(b): A SEM MICROGRAPH OF GOLD NANOPARTICLES ON THE SURFACE OF SULFATE-REDUCING BACTERIA (*DESULFOVIBRIO SP*). SCALE BARS IN (a) AND (b) ARE 0.5 AND 1.5 mm, RESPECTIVELY [14]

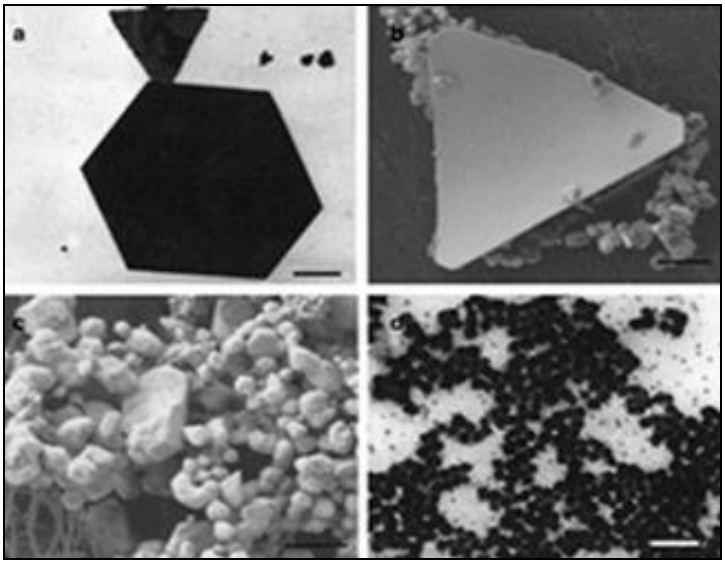

FIG. 3: TEM AND SEM MICROGRAPHS OF SELECTED GOLD NANOPARTICLES FORMED BY CYANOBACTERIAL INTERACTIONS WITH GOLD (III) CHLORIDE AND GOLD (I) THIOSULFATE COMPLEXES. SCALE BARS IN (a), (b), (c), and (d) are 0.5, 2, 1, AND 0.1 mm, RESPECTIVELY [14]

Synthesis of Gold Nanoparticles by Bacterial System: Ahmad *et al*., (2003a) demonstrated bacterial synthesis of monodispersed GNPs with extremophilic *Thermomonospora* sp. biomass via reduction of auric chloride ions ($AuCl_4^-$) through enzymatic processes [36].

Konishi *et al*., (2004) reported GNPs synthesis using the mesophilic bacterium *Shewanella*, where H_2 is acting as an electron donor [44]. Shiying *et al*., (2007) showed that the bacterium *Rhodopseudomonas capsulata* produced spherical GNPs in the range of 10-20 nm, upon incubation of bacterial biomass with aqueous chlorauric acid ($HAuCl_4$) solution at a pH range of 4.0-7.0 upon 48 h of incubation [45]. Further, also discussed that solution pH is an important factor in controlling the morphology of biogenic GNPs and location of gold deposition in cells [39]. Alkalotolerant *Rhodococcus* sp. produced more intracellular monodispersed GNPs on the cytoplasmic membrane than on the cell wall due to reduction of the metal ions by enzymes present in the cell wall and on the cytoplasmic membrane, but not in the cytosol [37].

Bacterial cell supernatants of *Pseudomonas aeruginosa* have been used for reduction of gold ions and for extracellular biosynthesis of GNPs [46]. *Bacillus subtilis* 168 has been reported to reduce water-soluble Au^{3+} ions to Au^0 and produce nanoparticles of octahedral morphology and dimensions of 5-25 nm inside cell walls [22].

Heterotrophic sulfate-reducing bacterial enrichment from a gold mine has been exploited to reduce gold (I)-thiosulfate complex $Au(S_2O_3)^2$ to elemental gold of 10 nm size in the bacterial cell envelope, releasing H_2S as an end product of metabolism [36, 47]. *E. coli* DH5α-mediated bioreduction of chloroauric acid to Au^0 resulted in accumulation of nanoparticles, mostly spherical and some triangles and quasi-hexagons, on the cell surface. These cell-bound nanoparticles offer promising applications in electrochemistry of hemoglobin and other proteins [48].

Bioreduction of trivalent aurum has also been reported in the photosynthetic bacterium *Rhodobacter capsulatus*, which has a higher biosorption capacity for $HAuCl_4$ per gram dry weight in the logarithmic phase of growth. The carotenoids and NADPH-dependent enzymes embedded in the plasma membrane and/or secreted extracellularly have been found to be involved in the biosorption and bioreduction of Au^{3+} to Au^0 on the plasma membrane and also outside the cell [49]. Konishi *et al*., 2004 found intracellular synthesis of gold by microbial reduction of $AuCl_4^-$ ions using the anaerobic bacterium *Shewanella* [44].

The synthesis of stable gold nanocubes by the reduction of aqueous $AuCl_4^-$ by *Bacillus licheniformis* has been described by Kalishwaralal (2009) [50]. The size of gold nanocubes (10–100 nm) in aqueous solution has been calculated using UV–Vis spectroscopy, X-ray diffraction (XRD) and scanning electron microscope (SEM) measurements.

Synthesis of Gold Nanoparticles by Fungal System: The fungi are one of the good biological agents in the synthesis of metal nanoparticles. Biosynthesis of metal nanoparticles using fungi such as *F. oxysporum* [51-53], *Colletotrichum* sp. [54], *Trichothecium* sp., *Trichoderma asperellum*, *T. viride*, [55-57], *Phaenerochaete chryso sporium* [58], *Fusarium semitectum* [59], *Aspergillus fumigates* [60], *Coriolus versicolor* [61], *Phoma glomerata* [62], *Penicillium brevicompactum* [63], *Cladosporium cladosporioides* [64], *Penicillium fellutanum* [65] and *Volvariella volvacea* [66] has been extensively studied. Indeed, fungi are regarded as more advantageous for GNPs biosynthesis as compared to other microorganisms because;

(1) fungal mycelial mesh can withstand flow pressure, agitation, and other conditions in bioreactors compared to bacteria,

(2) they are fastidious to grow and easy to handle, and;

(3) they produce more extracellular secretions of reductive proteins and can easily undergo downstream processing [19].

Absar and coworkers (2005) reported extra- and intracellular biosynthesis of GNPs by fungus *Trichothecium* sp [67]. It was observed that when the gold ions reacted with the *Trichothecium* sp. fungal biomass under stationary condition, it resulted in the rapid extracellular formation of GNPs of spherical rod-like and triangular morphology whereas reaction of the biomass under shaking conditions resulted in intracellular growth of the GNPs. The synthesis of GNPs by the reduction of gold ions using Chinese herbal extract *Barbated Skullcup* has also been reported [68]. It has been observed that the extremophilic actinomycete, *Thermomonospora* sp. when exposed to gold ions reduced the metal ions extracellularly, yielding GNPs with a much improved polydispersity [69].

Ahmad *et al*., (2003a) carried out the reduction of $AuCl_4^-$ ions by using an extremophilic *Thermomonospora* sp. biomass that has resulted in efficient synthesis of monodisperse GNPs [36]. The reduction of metal ions and stabilization of the GNPs were believed to occur by an enzymatic process [37-38].

Synthesis of Gold Nanoparticles by Cyanobacteria: In the cyanobacterial system, the mechanisms of gold reduction by *Plectonema boryanum* UTEX 485 from gold(III)–chloride solutions have been studied at several gold concentrations (0.8-7.6 mmol/L) and at 25-80^{o}C, using both fixed time laboratory and real-time synchrotron radiation XAS experiments [70-71]. The X-ray absorption spectroscopy (XAS) results showed that Au (III) was reduced to Au (I) in a very fast reaction (within minutes), and Au (I) was immediately coordinated with sulfur atoms from cyanobacteria forming gold (I)–sulfide for all gold concentrations and temperatures. The reduction of gold (I)–sulfide to elemental gold was found to be slower at 25^{o}C than at 60 ^{o}C and 80^{o}C. The steps of mechanism of gold reduction and precipitation by cyanobacteria are deduced:

Gold (III) – Chloride ($AuCl_4^-$) ⟶ Gold (I) – Sulfide (Au_2S) ⟶ Gold (Au)

Synthesis of Gold Nanoparticles By Algae: In the algae system, the mechanisms of gold reduction by *Chlorella vulgaris* biomass from gold (III) chloride solutions have been studied using XAS [72]. The XAS results showed that Au (III) was partly reduced to Au (I) and Au (I) was coordinated with sulfur atoms from free sulfhydryl residues and also to a light-atom element, probably nitrogen. Kuyucak and Volesky (1989b) showed that elemental gold was mostly precipitated on the cell wall of *Sargassum natans* biomass and suggested that the carbonyl (C≡O) groups of the cellulosic materials were the main functional group in the gold binding with N-containing groups involved in a lesser degree [73].

Lin *et al*., (2005) suggested that the hydroxyl group of saccharides, the carboxylate anion of amino-acid residues, from the peptidoglycan layer on the cell wall appeared to be the sites for gold binding [74]. However, in case of algal biomass, gold uptake was increased after esterification, suggesting that carboxyl groups played a minor role in gold binding [75].

Romero-Gonza˜lez et al. (2003) studied the mechanisms of gold biosorption by dealginated seaweed biomass using fourier transform infrared spectroscopy (FT-IR) and XAS [76]. FT-IR showed the presence of carboxylate groups on the surface of the biomass and XAS showed that the reduction of gold species occurred on the biomass surfaces to form GNPs and was followed by retention of Au (I) at the sulfur containing sites. Therefore, it was found that the steps of mechanism of gold reduction and precipitation by algae are similar to cyanobacteria (as per above reaction) [14] .

The biosynthesis of GNPs using marine alga *Sargassum wightii* has also been investigated [77]. The stable GNPs in size range of 8 nm to 12 nm were obtained by reduction of aqueous $AuCl_4^-$ ions by extract of marine algae and 95 % of the gold recovery occurred after 12 h of reaction.

Synthesis of Gold Nanoparticles by Plant System: One of the important approaches for biosynthesis of nanoparticles is employing the use of plant extract for biosynthesis reaction. In the case of *Azadirachta indica* leaf extract a competition bioreduction of Au^{3+} and Ag^+ ions presented simultaneously in solution was observed. A bimetallic Au core-Ag shell nanoparticles synthesis occurred in solution [78]. *Aloe vera* leaf extract has been used for gold nanotriangle and spherical silver nanoparticles synthesis [79]. The kinetics of GNPs formation was monitored by UV-vis absorption spectroscopy and transmission electron microscopy (TEM).

It was found that after about 5 h of addition of *Aloe vera* extract to 10^{-3} M aqueous solution of $HAuCl_4$ led to the appearance of a red color in solution. An analysis of the percentage of triangles formed in the reaction medium as a function of varying amounts of the *Aloe vera* extract showed that more spherical particles were formed with increasing in amount of *Aloe vera* leaf extract. Leaf extracts of two plants *Magnolia kobus* and *Diopyros kaki* were investigated for extracellular synthesis of GNPs [80]. The GNPs were formed by treating an aqueous $HAuCl_4$ solution by the plant extract. More than 90% recovery of GNPs was observed in a few minute of reaction at a reaction temperature of 90^{o}C.

With the use of *Emblica Officinalis* fruit extract as reducing agent, the extracellular synthesis of highly stable Ag and Au nanoparticles has also been achieved [81]. Adding to the list of plants which are showing potential for nanoparticles production for example *Cinnamomum camphora* leaf extract has been identified very recently for the production of gold as well silver nanoparticles [2]. There was a marked difference of shape control between gold and silver nanoparticles which was attributed to the comparative advantage of protective biomolecules and reductive biomolecules. In this case, the polyol components and the water soluble heterocyclic components were mainly found to be responsible for the reduction of silver ions or chloroaurate ions and the stabilization of the nanoparticles, respectively. An overview of some of the reported biological agent synthesizing gold nanoparticles is focused in **Table 1**.

TABLE 1: BIOLOGICAL AGENTS USED FOR GOLD NANOPARTICLES BIOSYNTHESIS

Biological entity	Extracellular/Intracellular	Size	Reference
Bacteria			
Pyrobaculum Islandicum (DSM 4184)	Extracellular	few nm	82
Lactobacillus sp.	Extracellular and intracellular	20–50 nm and >100 nm	35
Shewanella algae ATCC 51181	Intracellular	10–20 nm	44
Escherichia coli	Extracellular and intracellular	<10 nm(intracellular), 20–50 nm(extracellular)	83
Rhodopseudomonas capsulata	Extracellular	10–50 nm	39
Pseudomonas aeruginosa	Extracellular	15 - 5 nm	46
Stenotrophomonas maltophilia	Intracellular	40 nm	40
Fungus			
Colletotrichum sp.	Extracellular	20–40 nm	54
Verticillium	Intracellular	20 nm	34
V. luteoalbum	Intracellular	Few to 100 nm	84
Thermomonospora sp. (Actinomycetes)	Extracellular	8 nm	37
Rhodococcus sp.(Actinomycete)	Intracellular	5–15 nm	36
Cyanobcteria			
*Plectonema boryanum*UTEX 485	At the cell wall	6 μm to 10 nm	47, 85
Plectonema terebrans	Extracellular and intracellular	-	86
Algae			
Dealginated seaweed waste	Extracellular	20 nm to 5 mm	79
Saccharomyces cerevisiae	Extracellular	---	74
Sargassum wightii	Extracellular	8–12 nm	77
Fucus vesiculosus	Extracellular		87
Plant			
Avena sativa	Intracellular	5–20 nm	88
Azadirachta indica	Extracellular	50–100 nm	78
Emblica Officinalis	Extracellular	15–25 nm	81
Cinnamomum camphora	Extracellular	55–80 nm	2
Tamarind Leaf Extract	Extracellular	20–40 nm	89

Scope and application of Gold Nanoparticles: Production of inorganic and metal-based nanomaterials has stimulated the development of a new field that links many disciplines of sciences for the quest for different types of nanoparticles with unique properties. Designing and development of novel and affordable techniques for scale-up production of nanomaterials have not only provided an interesting area of study but in future will also address the expanding human requirements including health safety and environmental issues etc.

In industry, the application of nanomaterials is increasing day by day, and they will soon replace the harmful or toxic chemicals conventionally used as antimicrobial agents [90]. Application of nanoparticles and their nanocomposites also offers a sound and relatively safer alternative [91-92] and, therefore, open up new opportunities for development of antimicrobials. Gold is a nobel metal and has been used by many ancient cultures (Egypt, India, and China) to treat diseases such as smallpox, skin ulcers, syphilis, and measles [93-96].

Gold is currently used for medical devices like pacemaker and gold plated stents [97-98] are used for the management of heart disease, middle ear gold implants, and gold alloys areused in dental restoration [98]. Organogold compounds are widely used for the treatment of rheumatoid arthritis but side effects such as proteinuria and skin reactions has been observed at high doses [91, 99].

The properties of GNPs remarkably differ from the bulk gold because of quantum size confinement imposed by nano-size regimen. The electronic, magnetic, and catalytic properties of GNPs depend mainly on their size and shape [100]. For example, spherical GNPs show a strong absorption band in the visible region of electromagnetic field (~520 nm) but is absent for very small particles (≤ 2 nm) as well as in the bulk gold. With a variety of unique properties, when GNPs are manipulated effectively, it can be applied to many different applications across the field of biology and medicine, environment, and technology [101].

Medical Application: GNPs are excellent labels and have been primarily used for labeling and bioimaging applications for biosensors because they can be detected by numerous techniques, such as optic absorption fluorescence and electric conductivity. GNPs are a very attractive contrast agent [96, 102].The GNPs are directed and enriched at the region of interest, where it provides contrast for observation and visualization. With the characteristic of strongly absorption and scattering visible light, the light energy excites the free electrons in the GNPs to a collective oscillation, known as surface plasmon.

The excited electron gas relaxes thermally by transferring the energy to the gold lattice, and finally the light absorption leads to heating of the GNPs. The interaction of GNPs with light can be used for the visualization of particles using optical microscopy, fluorescence microscopy, photothermal, and photoacoustic imaging. In addition, the interaction of GNPs with both electron waves and X-rays can also be used for visualization using transmission electron microscopy [14]. Gold nanoparticles have been used for a long time for delivery of drug molecules into cells [96, 102]. The molecules are adsorbed on the surface of GNPs and then are introduced into the cells using gene guns or particle ingestion.

Inside the cells, these molecules will eventually detach themselves from the GNPs [14]. It gives non-toxic routes to drug and gene delivery application. GNPs are capable of delivering large biomolecules (peptides, proteins, or nucleic acids like DNA or RNA) [103].

GNPs due to its biocompatibility and strong interaction with soft bases like thiols play a major role in the treatment of cancer [104]. Epithelial ovarian cancer a common malignancy of female genital tract could be cured with the use of GNPs. Vascular endothelial growth factor (VEGF) performs a vital role in the progression of ovarian cancer and also tumor growth and GNPs possess the capability to inhibit the progression of ovarian growth and metastasis [96-97]. Also, in case of multiple myeloma (MM), a cancer of plasma cells, GNPs are observed to inhibit the function of VEGF which induces cell proliferation. This inhibition of VEGF further leads to upregulation of cell cycle inhibitor proteins like p21 and p27 which inhibit proliferation [104, 106].

Chronic lymphocytic leukemia (CLL), a cancer caused due to the overproduction of lymphocytes, starts in the bone marrow but could spread to other organs also. It was reported that as GNPs possess the ability to inhibit the function of heparin-based growth factor, GNPs alone can inhibit the function of factors secreted by CLL cells and induce apoptosis [104, 106-107].

Rheumatoid arthritis which is considered as an incurable disease, bare GNPs are found to serve as a possible cure. Newly functionalized GNPs (dendrimers) have been designed for not only targeting and killing tumors but also to fight cancer [108-109]. GNPs is engineered not only to identify, target, and kill tumors but also to carry the additional drug to slow down the growth of cancer cells or kill the cancer cells. Dendrimers acts as an arm to the GNPs so that different molecules are attached to the arms.

Once the cancer cells are surrounded by GNPs, lasers or infrared light heats the gold particles and the dendrimers release the various molecules to kill the tumors [14]. GNPs surface plasmon resonance scattering is predicted in the Mie equations and is found to increase as the size of the nanoparticles increases. By conjugating GNPs to anti-EGFR antibody, it gave the ability to distinguish between cancer and non-cancer

cells from the strong scattering images of the GNPs conjugated to antibodies that binds only to the cancer, but not to the non-cancer cells [110]. This scattering is observed from a simple optical microscope. They obtain a 600% greater binding ratio to the cancerous cells than to non-cancerous cells, enabling detection of cancerous cells by observing the scattered light on a dark field microscope.

Fig. 4 shows the scattering obtained with GNPs nonspecifically adsorbed on the surface (a–c) and GNPs with anti-EGFR (d–f) antibodies specifically bound to the cancerous cells but not to the non-cancerous cells. Because of this difference, the band shape and the surface plasmon absorption maximum are found to be different and therefore it can be used in medical field to differentiate cancerous cells. These results show that GNPs have enormous power as a diagnostic tool.

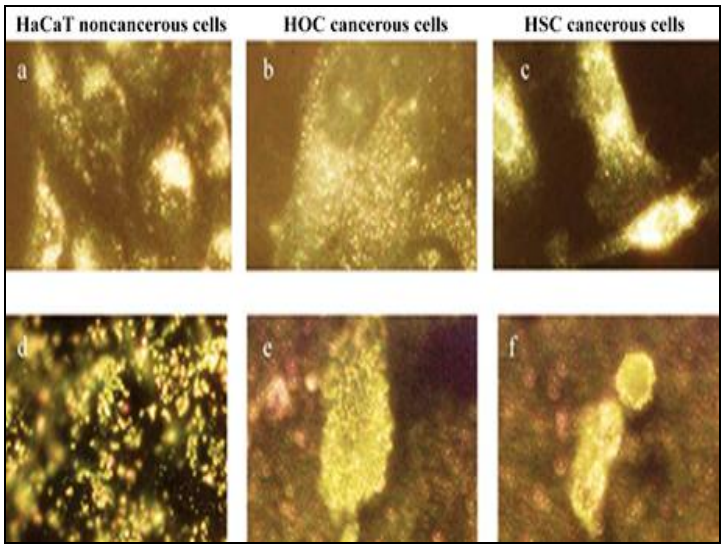

FIG. 4: LIGHT SCATTERING OF CELL LABELED WITH (a–c) GOLD NANOPARTICLES AND (d–f) anti-EGFR COATED GOLD NANOPARTICLES. THE anti-EGFR COATED GOLD NANOPARTICLES BIND SPECIFICALLY TO THE CANCEROUS CELLS, WHILE ALL OTHER GOLD NANOPARTICLES ARE NON-SPECIFICALLY BOUND. (a & d) NONMALIGNANT EPITHELIAL CELL LINE HaCaT (HUMAN KERATINOCYTES), (b & e) MALIGNANT EPITHELIAL CELL LINES HOC 313 CLONE 8 (HUMAN ORAL SQUAMOUS CELL CARCINOMA) (c & f) MALIGNANT EPITHELIAL CELL LINES HSC 3 (HUMAN ORAL SQUAMOUS CELL CARCINOMA)

GNPs can also be used for active sensor applications to determine the presence of analyte and to provide its concentration [102]. The plasmon resonance frequency is a reliable feature of GNPs that can be used for sensing. The binding of molecules to the particle surface can change the plasmon frequency directly.

On the other hand, the plasmon resonance frequency is changed when the average distance among GNPs is reduced by forming small aggregates. The effect of plasmon coupling can be used for colorimetric detection of the analyte, known as a gold-based sensor. Raman scattering is enhanced if the analyte is close to a gold surface, called as surface-enhanced Raman scattering.

GNPs modified with Raman-active reporter molecules have been used for the detection of DNA [111], protein [112], and two-photon excitation [113]. GNPs can also be used for the transfer of electrons in redox reactions [114]. The enzyme is conjugated to the surface of the gold particles and is immobilized on the surface of an electrode [115]. An electrode covered with a layer of GNPs has a much higher surface roughness and larger surface area which lead to higher currents. Another application of gold compounds is as an anti-inflammatory agent due to their ability to inhibit expression of NF-kappa B and subsequent inflammatory reactions [116-118].

One of the major drawbacks of ionic gold is that they easily get inactivated by complexation and precipitation that limits their desired functions in human system. Here zerovalent GNPs can be a valuable alternative replacing the potential of metallic gold [50]. GNPs, an emerging nanomedicine is renowned for its promising therapeutic possibilities, due to its significant properties such as biocompatibility, high surface reactivity, resistance to oxidation and Plasmon resonance [119]. The inhibitory activity of GNPs against VPF/VEGF165 induced proliferation of endothelial cells provides clear evidence over their therapeutic potential in the treatment of diseases like chronic infiammation, pathological neo-vascularization, rheumatoid arthritis, and neoplastic disorders [120].

Thus, gold nanoparticles have so many advantages in meadiacal field as they are in nanometer-size systems that can get easily into the bloodstream and around cells. Also, the multi-functional gold nanoparticles have been demonstrated to be highly stable and versatile scaffolds for drug delivery due to their properties like unique size, along with their chemical and physical properties. Their ability to tune the surface of the particle provides access to cell-specific targeting and thus controlled drug release [121].

Technological application: GNPs have been designed to improve computer memory [11]. A three-dimensional computer memory device composed of layers of GNPs has been developed to increase the memory capacity of a single chip. Another development of computer memory using GNPs is an organic nonvolatile bistable memory, which is a mixture of plastic and gold [49].

Environmental application: Technologies based on GNPs are currently being developed for the environmental applications for pollution control and water purification [115]. It has been investigated that bimetallic gold–palladium nanoparticles provides an active catalyst which can be used to degrade trichloroethene (TCE), which is one of the major pollutants in groundwater, into a non-toxic form [116]. GNPs incorporated in a water purification device can effectively capture and remove halocarbon-based pesticides from drinking water [115] and can also enhance the oxidation of mercury generated from coal power plants [122].

The use of GNPs as a catalyst has a major role to play in green chemistry [123-124]. Most industrial oxidation processes tend to use chlorine or organic peroxides which generates large amounts of chloride salts and chlorinated organic byproducts. GNPs supported on carbon active molecular oxygen are found to be able convert alkenes to partial oxidation products such as epoxides at atmospheric pressure and at 60^{o}C-80^{o}C [125].

GNPs have been developed for selective oxidation of the biomass-derived chemicals, furfural and hydroxymethyl furfural, to form methyl esters as well as for oxidation of carbon monoxide (CO) and trimethylamine. These chemicals are used for flavor and fragrance applications, in plastics and industrial solvents [126]. Gas sensors based on Au nanoparticles have been developed for detecting a number of gases, including CO and nitrogen oxides (NOx) [127].

CONCLUSION: Nanoparticles synthesis from biological route serves as an important alternative in the development of clean, nontoxic, economical and environmentally friendly procedures for the synthesis and assembly of GNPs and has tremendous advantages in comparison to conventional methods for nanoparticles synthesis.

In general, many biological agents have the ability to produce GNPs intracellular as well as extracellular environment. The work on the biosynthesis of GNPs is still largely in the discovery phase. Given the anticipated wide application of GNPs for commercial applications, continuing work is recommended to focus on the mechanisms of the biosynthesis of GNPs and the development of GNPs of well-defined size and shape. Changing properties simply by changing the size or shape of the GNPs is attractive and will continue to be employed in new applications in the future.

GNPs have a number of applications from electronics and catalysis to biology, pharmaceutical and medical diagnosis and therapy. However more research needs to be focused on the mechanistics and kinetics of GNPs formation which may lead to fine tuning of the process ultimately leading to the synthesis of GNPs with a strict control over the size, shape and large scale production of GNPs.

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