Study of bio mediated synthesis of metallic and bimetallic nanoparticles and their characterization pharmacological applications

P Lingeswara Reddy[1], M E Rani [2]

Research Scholar [1], Dept. of Chemistry, Rayalaseema University, Kurnool, A.P, India

Professor [2], Dept. of Chemistry, Rayalaseema University, Kurnool, A.P, India.

Abstract - The advances are being finished in the physico-chemical understanding and optoelectronic properties of materials at nano-scale for enhancing the nanomaterial's of impressive functional along with the applications in diverse regions of science and technology in the present nanotechnology era. The physical as well as the chemical methods for formulation metal nanoparticles are usually utilized, but these are high-priced and hazardous for the environment. Biosynthesis of metal nanoparticles is one of the cost-effective, safe, & environmentally sound methodologies. Synthesis of metal nanoparticles [such as gold (Au), silver (Ag), lead (Pb), platinum (Pt), copper (Cu), iron (Fe), cadmium (Cd), & other metal oxides like zinc oxide (ZnO), titanium oxide (TiO), etc.] by several physical as well as chemical approaches & the biological approaches mediated by numerous microorganisms that have been found actively. Additionally, the metallic nano-particle's biological synthesis is one-step, economical, as well as eco-friendly method. In addition to it, the nanoparticles are utilized as the agents of potential pharmaceutical for a variety of diseases like HIV, malaria, hepatitis, cancer, and other diseases. Some other related details about the nano-pharmaceutical products, companies that have been involved in the commercialization & manufacturing method and their clinical trial status have also been discussed. The metal nanoparticles' synthesis, probable compounds, & mechanisms that might be accountable for the diminution process as well as the potential pharmacological applications.

I. INTRODUCTION

The wide field of nano-technology has been sparked immense interest as well as the enthusiasm for its sufficient potential for developing helpful materials & devices along with the functions in diverse science and technology regions. The contemporary plan of nano-technology was introduced principally in 1959 when the enormous physicist and Nobel laureate Richard Feynman, in his creative talk 'There's Plenty of Room at the Bottom' recommended the chance to specifically control the matter at atomic level to attain the materials of novel along with extremely desirable properties. Nano-technology would be dealing with all the materials which will be having at least one dimension in the range of nanometer scale (≤100 nm). It would show a new behaviour and properties that are dissimilar from its bulk counterparts & these properties are size- and shape- dependent as the material approaches dimensions of the nanoscale. The minute size of the nanomaterial would direct to an enlarged surface region to the ratio of volume that would be ensuring an increase in the numerous atoms at the surface in comparison to those in interior. The latest progressions in considering the nanomaterials' [1] properties have enabled examiners in creating the new materials that are displaying the novel behavior for several applications. The nanomaterials could be fabricated utilizing either of 2 methods:

***Top-Down approach*:** It would be utilizing the workshop which is of traditional as well as the methods of micro fabrication for subdividing the bulk precursors into nanoparticles. This is attained generally through employing the techniques of lithographic (for example: electron or ion beam, scanning probe, UV, optical near field), processing the laser-beam, and mechanical techniques (e.g., grinding, polishing & machining).

***Bottom-Up approach*:** It would exploit the chemical properties of atoms as well as molecules that are causing them to self-assemble in a controlled way for providing a few valuable conformations. The approaches of bottom-up would be including the chemical synthesis, deposition of chemical vapor, laser-induced assembly, self-assembly & colloidal aggregation. This method would produce much smaller sized particles and is more cost effective for mass-production of metal nanoparticles.

Metal Nanoparticles (NPs)

Metal NPs have attracted considerable attention because of their unique and fascinating optical, electronic, chemical, and magnetic properties that are strikingly different from those of the individual atoms as well as their bulk counterparts. Of these, Au, Ag and Cu NPs show very intense colour which is attributed to collective oscillation of the free conduction electrons with respect to fixed ionic cores in resonance with interacting electromagnetic field. This phenomenon is commonly known as a localized surface plasmon resonance (LSPR) mode and is illustrated in **Figure 1.1**. The LSPR frequency of metal NPs depends on the size, shape, composition of the metal NP, its surface charge, surface-adsorbed species, interparticle interactions and the refractive index of the surrounding medium (Kreibig and Vollmer, 1995; Kelly et al., 2003). For copper, silver and gold, the absorption band lies in the visible region of the electromagnetic spectrum [2]. The LSPR is responsible for generating enhanced electric fields on NP surface that gives rise to extraordinarily large enhancements of the Raman scattering spectra of adsorbed or adjacent molecules, an effect known as surface-enhanced Raman scattering (SERS). Recently, SERS has become an attractive bioanalytical method for sensing and diagnostics owing to its extremely high sensitivity to single molecule detection (Nie and Emory, 1997). The optical properties of metal NPs can be easily controlled and tailored for successful use in various areas such as photonics, electronics, biological microscopy, medicine, catalysis, sensors and optoelectronics.

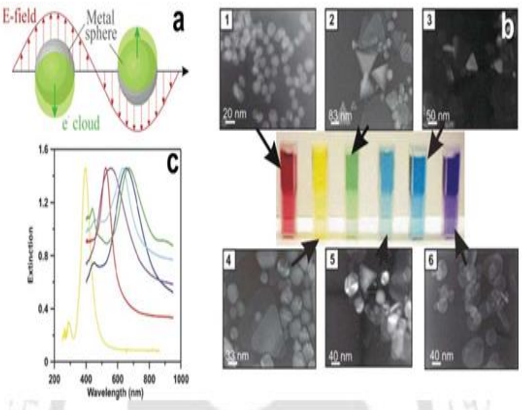

Figure 1.1. (a) Schematic of plasmon oscillation for a sphere, showing the displacement of the conduction electron charge cloud relative to the nuclei. Reprinted with permission from (Kelly et al., 2003). Copyright (2003) American Chemical Society. **(b, c)** Tunable Ag and Au NP solutions. **(b)** Corresponding transmission electron micrographs. *1* The red solution consists of homogeneous Au nanospheres (13- nm diameter). *2* The green solution consists of Ag NPs (nanospheres, trigonal prisms, and polygon platelets). *3* The dark blue solution consists of Ag NPs (trigonal prisms with rounded tips and polygon platelets). *4* The yellow solution consists of inhomogeneous Ag NPs (nanospheres, trigonal prisms, and polygon platelets). *5* The light blue solution consists of Ag NPs (trigonal prisms and polygon platelets). *6* The purple solution is made up of inhomogeneous oblong Ag NPs **(c)** UV-Vis extinction spectra of the corresponding solutions (*color of line* corresponds to solution color) (Courtesy: Haes and Duyne, 2004).

Nanoparticle has multifunctional properties and very interesting applications in various fields such as medicine, nutrition and energy (Chandran et al., 2006). The biogenic syntheses of monodispersed nanoparticles with specific sizes and shapes have been a challenge in biomaterial science. Also, it has created remarkable advantages in the pharmacological industry to cure various bacterial and viral diseases (Song et al., 2008). Biosynthesis methods have more compensation over other classical synthesis procedures due to the availability of more biological entities and eco-friendly procedures. The rich biodiversity and easy availability of plant entities have been highly explored for the nonmaterials synthesis (Monda et al., 2011). Recently, the biosynthesis of man-sized particles, wires, flowers, tubes were reported successfully. These biological synthesized nanomaterials have potential applications in different areas such as treatment, diagnosis, development surgical nano devices and commercial product manufacturing (Bar et al., 2009). Nanomedicine makes a huge impact in healthcare sector in treating various chronic diseases. Hence, ecofriendly synthesis of nanoparticles is considered as building blocks of the forthcoming generations to control various diseases (Cruz et al., 2010).

1.1 Classical approaches of metals

Anciently, the gold metal is known as a symbol of power and wealth. The gold metal is used in different forms to improve the human health ever since. Even today, the biological aspects of metallic gold nanoparticles (GNPs) are very useful to human health and cosmetics applications (Alanazi et al., 2010). In the 18th century, Egyptians used gold metal solubilized water for mental and spiritual purification. The restorative property of gold is still honoured in rural villages, where peasants cook their rice with a gold pellet to replace the minerals in the body via food intake. Traditionally, silver metal is used to control bodily infection and prevent food spoilage. Silver is used as a wound healer agents and ulcer treatment (Singh et al., 2013). In fact, nowadays the colloidal silver nanoparticles have using as antimicrobial agent, wound dressing material, bone and tooth cement and water purifier as well (Narayanan et al., 2011).

1.2 Different methods for metallic nanoparticles synthesis

Several methods are used for synthesis of nanoparticles (NPs) such as physical, chemical, enzymatic and biological [3]. Physical methods are including plasma arcing, ball milling, thermal evaporate, spray pyrolysis, ultra thin films, pulsed laser desorption, lithographic techniques, sputter deposition, layer by layer growth, molecular beam epistaxis and diffusion flame synthesis of nanoparticles (Joerger et al., 2000). Similarly, the chemical methods are used to synthesised NPs by electro deposition, sol-gel process, chemical solution deposition, chemical vapour deposition (Panigrahi et al., 2004; Oliveira et al., 2005), soft chemical method, Langmuir Boldgett method, catalytic route, hydrolysis (Pileni, 1997), co-precipitation method and wet chemical method (Gan et al., 2012). Physical and chemical methods have been using high radiation and highly concentrated reductants and stabilizing agents that are harmful to environmental and to human health. Hence, biological synthesis of nanoparticles is a single step bioreduction method and less energy is used to synthesize ecofriendly NPs (Sathishkumar et al., 2009). Apart from that, the biological methods are using eco-friendly resources such as plant extracts, bacteria, fungi, micro algae such as cyanobacteria, diatom, seaweed (macroalgae) and enzymes (Iravani et al., 2011). Fig. 1 shows different types of metallic nanoparticles synthesized from plant resources.

1.3 Bio-reduction mechanism

Silver: The biochemical reaction of AgNO3 reacts with plant broth leads to the formation of AgNPs by following reaction (Tripathy et al., 2010). Fig. 2 explains the proposed mechanism of biological synthesis of nanoparticles.

HAu+Cl4. 4H20+ plant extracts -------→ Au0NPs + byproducts

Platinum: Platinum is involved in the following reduction process such as

H2Pt+Cl2. 6H20+ Plant extracts ---------→ Pt0NPs + byproducts

Copper: The copper nanoparticles is synthesised from plant extracts and the reduction mechanism was proposed by Ramanathan et al., (2013)

CuSO4. 5H2O + Plant metabolites -------→ Cu0NPs + byproducts

Zinc oxide: A typical procedure was employed in ZnO nanoparticles production, the zinc nitrate was dissolved in the aloe plant extract to produce the nanosized particles. The method followed by (Sangeetha et al., 2011).

Zinc nitrate + Plant extract --------→ ZnO + byproducts

Bimetallic Nanoparticles

Bimetallic NPs are a novel class of nanomaterials that would be containing 2 types of metals in a solitary NP. The bimetallic NPs have unique electronic, chemical, optical, catalytic as well as biological properties which are different & superior to the constituent monometallic counterparts because of the latest synergistic & bi-functional effects. These properties would rely on composition, size as well as arrangement of 2 factors in NP [4]. NPs of bimetallic are arranged from respective metal salts by either co-reduction or successive reduction of 2 metal salts. The co-reduction of 2 ions of metal would often lead to the alloys' formation & successive lessening of one metal ion after another would be usually leading to core shell NP. The NPs of bimetallic will be having an exploration for a broad application choice in the SERS, optoelectronics, catalysis and sensors. There is vast scientific data accessible on the characterization & preparation of bimetallic NPs utilizing several metal arrangements including Au-Pd, Au-Pt, Ag-Pt, Ag-Au & Ag-Pd. A 3 layer (Pd@Au@Pd) in this situation, 4-layer (Ag@Au@Ag@Ag) structures of the core-shell for gold-palladium & gold-silver systems respectively as well as Ag-Au core shell NPs along with hollow cores and alloyed shells have also been reported (Ferrer et al., 2007; Rodríguez-González et al., 2005; Ferrer et al., 2009).

bimetallic nanoparticles (NPs), containing two kinds of metals in a single NP have attracted attention as a novel class of nanomaterials owing to their unique electronic, optical, chemical and catalytic properties which are distinct and superior to their constituent monometallic counterparts due to new synergistic and bifunctional effects (Toshima and Yonezawa, 1998). The bimetallic NPs, in the form of alloys or core-shell structures, have potential applications in sensors, optoelectronics and catalysis. Bimetallic core-shell NPs are nanostructures, where one metal element forms an inner core and is surrounded by concentric shell of another metal. Of these, noble core-shell NPs containing gold and silver have received immense interest. Au colloids have advantages of easy preparation, homogeneity and biocompatibility with biomolecules like antigen, antibody, DNA, etc in contrast to Ag NPs which are not biocompatible and less stable under biological conditions (Chandran et al., 2007). But the extinction coefficient of the surface plasmon band of Ag NP is approximately four times as large as that for an Au NP [5] of same size (Cao et al., 2001). Several groups have made efforts to deposit silver on gold to obtain Au@Ag core-shell NPs that have homogeneity and stability of gold and optical properties of silver (Freeman et al., 1996; Rivas et al., 2000; Hodak et al., 2000; Mallik et al., 2001; Lu et al., 2002; Selvakannan et al., 2004; Mandal et al., 2004; Chandran et al., 2007; Pande et al., 2007; Yang et al., 2008). Importantly, they serve as useful surface-enhanced Raman spectroscopy (SERS) active substrates, which display SERS activity greater than individual AgNPs and AuNPs. In addition, studies have also been done on the synthesis of inverted Ag@Au core-shell NPs (Mulvaney et al., 1993; Srnová-Šloufová et al., 2000; Cao et al., 2001; Cui et al., 2006), which have been explored for biological applications, such as, oligonucleotide conjugation and SERS based immunoassay.

In addition, core-shell nanostructures showing antibacterial properties have also been investigated (Rana et al., 2005; Rosemary et al., 2006; Kim et al., 2007b; Jang and Kim, 2008). Ag NPs have strong bactericidal properties [6] and substantial research has been done to use them either alone or in composite with polymer (Morones et al., 2005; Gogoi et al., 2006; Sanpui et al., 2008; Banerjee et al., 2010; Banerjee et al., 2011). Though the antibacterial core-shell NPs comprising of silver shell supported on organic and inorganic cores have been studied, the antibacterial efficacy of bimetallic core-shell NPs containing silver remains largely an unexplored area.

II. LITERATURE REVIEW

Liu et al. [7] has been synthesized gold nanoparticles utilizing *Chrysanthemum* extracts as well as beverages of tea. Apart from these, nanoparticles of gold were also been synthesized utilizing *Syzygiumaromtaicum* buds. The synthesized gold nanoparticles were crystalline in nature and were 5–100 nm in size. The researchers later found that flavonoids available in buds are responsible for the gold nanoparticles synthesis. A huge number of plants have been reported for metal nanoparticles biosynthesis, which are stated and are briefly discussed in this review document.

Synthesis of gold as well as the nanoparticles of silver has been attained successfully utilizing *Aloe vera* leaf extract [32] & *Camellia sinensis* [33]. The attained outcomes have recommended that the nanoparticles optical properties primarily rely on the preliminary attentiveness of the metal salts & the extract *of C. sinensis* [8]. It consists of caffeine and theophylline which might have contributed to the metal ions diminution and nanoparticles formation. The spherical production and triangular-shaped silver and gold nanoparticles utilizing the fruit extract of *Tanacetum vulgare* has been obtained by Dubey et al. [34]. FTIR analysis of this has been revealed that the carbonyl groups were engaged in the metal ions reduction. It has also been reported that the zeta potential of the silver nanoparticles has revealed to dissimilarity when pH is unstable, and a low zeta potential has been recorded at strongly acidic pH [34]. The greater size of nanoparticles could be attained through lessening the pH of the reaction.

In another study, Banerjee and Narendhirakannan [9] synthesize silver nanoparticles using *Syzygium cumini* seed extract as a reducing agent. They also studied their antioxidant activities. The synthesized nanoparticles have average size ranges of 93 nm. They also concluded that the greensynthesized nanoparticles have greater antioxidant activity as compared to seed extract of *S. cumini.* Similar work was carried out by Velusamy et al. and they reported silver nanoparticle biosynthesis using leaf extract of *Azadiracta indica* and studied their antimicrobial activities. The synthesized nanoparticles have size ranges of < 30 nm and they were monodispersed and spherical in shapes. They also demonstrated that the synthesized nanoparticles have great antibacterial activity, which is confirmed by the degradation of test bacterial DNA. Results also suggested that the gum-mediated synthesized nanoparticles could be used as an antibacterial agent against a diverse range of clinical pathogens. It has been found that carbonyl compound of the plant extract plays a key role in the formation of gold nanotriangles by the slow reduction of gold ions (HAuCl4) with the shape-controlling effect of.

Similarly, when aqueous solution of silver ions [10] was incubated with *A. vera* extract, it produces only spherical silver nanoparticles. The colour change of brownish red colour and faint yellow colour in the reaction mixture indicates the formation of gold and silver nanoparticles, respectively. The leaf extract of *Cinnamomum camphora* has been recently known for the production of gold and silver nanoparticles. Water-soluble heterocyclic compounds and polyol compounds are mainly found to be responsible for the reduction of silver ions or chloroaurate ions and the stability of nanoparticles, respectively.

Rhizome extract of *Discorea batatas* was also used for synthesis of silver nanoparticles [11]. These nanoparticles have antimicrobial properties against yeast *C. albicans* and *S. cerevisiae*. Silver nanoparticles of 10–20 nm were fabricated using the latex of *Jatropha curcus* which act as a reducing and capping agent [39]. Ankamar et al. used fruit extract of *Emblica officinalis* for the synthesis of highly stable silver and gold nanoparticles Parida et al. reported the synthesis of gold nanoparticles using the extracts of *Allium cepa*. They have an average size of 100 nm and have significant toxicity against several cancerous cell lines, specifically MCF7 breast cancer cell line. Further study revealed that they can be internalized by MCF7 breast cancer cells via endocytosis process. Ravindra et al. carried out a study to synthesize silver nanoparticles within cotton fibres loaded with silver ions. The leaf extract of *Eucalyptus citriodora* and *Ficus bengalensis* plants was used for the synthesis of the same. The synthesized nanoparticles have size ranges of 20 nm. They also show antibacterial activity against *E. coli*. Prasad and Elumalai reported the silver nanoparticle synthesis through leaf extract of *Polyalthia longifolia*. Nanoparticles synthesize, where size ranges of 58 nm. Njagi et al. used aqueous extract of Sorghum bran to produce Fe (iron) and silver nanoparticles at room temperature.

Valodkar et al. [12] synthesized nanoparticles of 5–10 nm of silver and copper using latex of Euphorbiaceae. These nanoparticles have excellent antibacterial activity towards Gram +ve and Gram −ve bacteria. Similarly, Velayutham et al. used leaf extract of *Catharanthus roseus* to synthesize titanium dioxide nanoparticles. They have size ranges of 25–110 nm with irregular shape. Aqueous extract of these nanoparticles has been tested for larvicidal and adulticidal activities against the hematopathogens fly *Hippobosca maculate* and Sheep louse *Basicola ovis*. Obtained results confirm its significant larvicidal and adulticidal activities against test pathogens.

Huang et al. also reported a one-step synthesis processof gold–palladium core shell nanoparticles using aqueous solution of Bayberry tannin at room temperature. The tannin preferentially reduced the Au3+- to-gold nanoparticles when a mixture of Au 3+ and Pd 2+ was bringing into contact with the tannin.

Peel extract of *Punica granatum* was used for the synthesis of zinc oxide nanoparticles. Its antimicrobial activity was tested against *Aspergillus niger* and *Proteus vulgaris*. Results showed the highest antifungal activity against these two fungal strains. Synthesized nanoparticles were monodispersed and crystalline in nature with the size range of 25–30 nm.

The Biosynthesis of cadmium oxide nanoparticles has been obtained by utilizing the flower extract of *Achillea wilhelmsii* which would be acting as a reducing agent. The aqueous solution of cadmiumions when gets exposed to the extract of flower has been condensed and resulted in the cadmium oxide nanoparticles formation.

Li et al. [13] has been synthesized Cu nanoparticles 40–100 nm utilizing leaf extract of *Magnolia*. These Cu nanoparticles also had the activity of antimicrobial against *E. coli* & these are even toxic-to-human adeno carcinomic alveolar basal

epithelial cells (A549 cells). The same kind of work was executed by Naiket al., and they also synthesize copper oxide nanoparticles utilizing leaf extract of *Gloriosa superba*. SEM images would indicate that they have particle size in the range of 5–10 nm. They also include significant antibacterial activity against some Gram −ve bacterial species like *Klebsiella aerogenosa*,
Pseudomonas desmolyticum, as well as *E. coli*.

III. PROPOSED METHOD

Metallic Nanoparticles

Gold (Au) nanoparticles have foremost interest because of its shape, size, as well as the properties of surface. Gold nanoparticles have applications in areas of biosensors, therapy of cancer, drugs & delivery of gene, & as drugs of antibacterial. Along with green chemistry based methods, plants are utilized for synthesizing the nanoparticles of gold. For instance, kar et al (2016) has been reported green synthesis of gold nanoparticles [average size of 32.96 ± 5.25 nm] utilizing *Garcinia mangostana* aqueous extract fruit peels.

Silver (Ag) is usually identified for its activity of antimicrobial and as an outcome, it is utilized commonly in numerous medical preparations against pathogens.[14] The exact mechanism which silver nanoparticles is not known clearly, other than there are a variety of theories on the silver nanoparticles action on microbes to source the antimicrobial effect.

Copper (Cu) and copper oxide (CuO) nanoparticles have been synthesized utilizing a several variety of plant extracts. Cu nanoparticles have been synthesized biologically utilizing *Azadirachta indica* leaves extract for producing cubical shape of stable nanoparticles along with the average size of 48 nm. The antimicrobial researches have revealed that the Cu nanoparticles have potential antibacterial activity against *Staphylococcus*, *Pseudomonas*, *Escherichia coli* etc cells, an ordinary pathogen. Papaya extract could produce Cu nanoparticles along with an average particle size of 20 nm.

In 2014, Palladium nanoparticles were synthesized by Nasrollahzadeh et al. utilizing *Hippophae rhamnoides Linn* leaf extract. Also, in 2017 Majumdar et al. synthesized palladium nanoparticles along with leaf extract of *Chrysophyllum cainito*. Palladium nanoparticles have prepared for the catalytic activity application for instance Mohammed et al. (2017) has been synthesized & characterization of palladium nanoparticles from *Origanum vulgare L.* extract and researched its catalytic activity for selective oxidation of alcohols, [143] whilst the soybean leaf extract (*Glycine max*) has the ability for synthesizing nanoparticles along with a mean size of 15 nm.

Prabhu et al. has reported Platinum nanoparticles synthesis in 2017[15]. This extract is taken from *Fumariae herba* that has also been utilized to synthesize platinum nanoparticles along with a mean particle size of 30 nm from aqueous chloroplatinic acid at a reaction temperature of 90°C. The platinum nanoparticles biological synthesis along with particle size of 32 nm has also been reported by utilizing the Weed Lantana [*Lantana Camara*]. Also Alagu et al (2016) reported synthesis of platinum nanoparticles by utilizing *Azadirachta indica* with particle size in the range of 5-50 nm. Karthik et al (2016) researched the synthesis of platinum nanoparticles of size range 5-15 nm utilizing *Quercus Glauca* extract and characterized along with spectroscopic as well as analytical approaches.

Synthesis of metal oxide nanoparticles such as titanium dioxide (TiO2) and zinc oxide (ZnO) with number of plant extracts has been reported. For example, Santhoshkumar et al. (2017) have found that *Passiflora caerulea* leaf could be used to effectively synthesize zinc oxide nanoparticles, while *Calotropis gigantea* leaf extracts have been found to produce spherical particles with average size 10 nm (Biosynthesis of zinc oxide nanoparticles using leaf extract of *Calotropis gigantea*: characterization and its evaluation on tree seedling growth in nursery stage) and *Catharanthus roseus* leaf extracts can produce particles with an average size of 23 to 57 nm.

Bimetallic nanoparticles (BMNP)

BMNP are the 2 metals combination in the range of nanoscale size. This nano science region is gaining mounting awareness in the area of catalysis because of its effects of synergy. BMNP have 4 kinds of mixing prototypes: nanoparticles of core-shell, nanoparticles of sub- cluster, multi-shell nanoparticles as well as mixed (alloy) nanoparticles. Core-shell nanoparticles contain a shell of one atom type surrounding a core of another atom type as shown in Fig. 1.

Fig. Different Structures of bimetallic nanoparticles

Supriya Devarajan used N,N-[3-(trimethoxysilyl)propyl]diethylenetriamine (TPDT), tetraethoxysilane (TEOS), chloroauric acid, palladium chloride, silver nitrate, chloroplatinic acid, sodium borohydride, and methanol for the preparation of different structures of bimetallic nanoparticles. Double-distilled water was used in Brust process. Ethylene glycol was used as a solvent in case of polyol process.

Preparation of bimetallic nanoparticles

Burst et al. added 130 l of N,N_-[3

(trimethoxysilyl)propyl]diethylenetriamine (TPDT) to 3.8 ml of methanol followed by 50 l H2O and 50 l 0.1 M HCl. The mixture was shaken well for a couple of minutes. Different volumes of 0.01 MAuCl3 , AgNO3 , H2PtCl6 , and RuCl3 were added to the silica sol and mixed well until the solution became homogeneous. Sodium borohydride (2.5 mg) was thenaddedwith vigorous stirring. Instantaneous color changerangingfrom deepviolet ofAucolloidto brown color of Ru and Pt or yellowish brown in case ofAg colloid, depending on the composition, was observed. Various molar compositions of the two metal components such as 0.25:0.75, 0.43:0.57, 0.5:0.5, 0.57:0.43, 0.75:0.25, and 0.9:0.1 were prepared using the same protocol. The sols and the resulting solid monoliths of all the compositions were very stable over extended periods of several months.

Films of different thickness ranging from 0.1 to 10 m were cast on glass slides by a coating process [16]. Gels and monoliths of any desired shape were obtained by allowing the solvent to evaporate. The dried material was found to shrink considerably but slow evaporation of the solvent led to crack the free monoliths.

3. Pharmacological application of metallic nanoparticles

3.1 Anti-bactericidal activities of metallic nanoparticles

The AgNPs was effectively disrupting the polymer subunits of cell membrane in pathogenic organisms[17]. The reciprocal action of nanoparticles subsequently breaks the cell membrane and disturbs the protein synthesis mechanism in the bacterial system (Sondi et al., 2004). The increasing concentrations of silver nanoparticles have faster membrane permeability than the lower concentrations and consequently rupture the cell wall of bacteria (Kasthuri et al., 2009). The maximum conductivity was observed in *R. apiculata* reduced silver nanoparticles shown a low number of bacterial colony in the experimental plate compared with AgNO3 treated cells, which may due to the smaller size of the particles and larger surface area which leads to the increase of membrane permeability and cell destruction (Antony et al., 2011). The interactions of bacteria and the metallic silver and gold nanoparticles has been bind with active site of cell membrane to inhibit the cell cycle functions (Kim et al., 2007). The biosynthesized silver nanoparticles were achieved in a single step procedure by using *citrus sinensis* peel extract as a reducing and a capping agent. *C. sinensis* peel extract reduced silver nanoparticles effectively act against *Escherichia coli*, *Pseudomonas auroginosa* (gram-negative) and *Staphylococcus aureus* (gram-positive) has been proven (Kaviya et al., 2011). Similarly, Krishnanraj et al., (2010) reported that *A. indica* plant leaf synthesized silver nanoparticles effectively control water borne pathogenic bacteria with lower concentrations of 10μg/ml.

3.2 Anti-fungicidal activities of metallic nanoparticles

The fungicidal mechanism of biosynthesized metallic nanoparticles has more potent than commercial antibiotics like fluconazole and amphotericin. The plant derived Ag nanoparticles have clearly showed the membrane damage in *Candida* sp. and damage in fungal inter cellular components and finally cell function was destroyed (Logeswari et al., 2012). Most of the commercial antifungal agents have limited applications clinically and in addition, there are more adverse effect and less recovery from the microbial disease. Subsequently, the commercial drugs induces side effect such as renal failure, increased body temperature, nausea, liver damage, and diarrhoea after using the drugs. Nanoparticles were developed for novel and effective drug against microbes. The fungal cell wall is made up of high polymer of fatty acid and protein. The multifunctional AgNPs have a promising activity against spore producing fungus and effectively destroy the fungal growth (Mohankumar et al., 2012). The fungal cell membrane structure significant changes were observed by treating it with metallic nanoparticles (Gardea-Torresdey et al., 2002).

Antiplasmoidal activity of metallic nanoparticles

Currently, the most common diseases are spreading everywhere by vectors. Vector control is a serious requirement in epidemic disease situation. The advanced antiplasmoidal species specific control method is less effective. This method has been more economical but less effective to control the target organisms in the health care sector (Gnanadesigan et al., 2011). Hence, effective and affordable antimalarial drugs are urgently required to control the plasmoidal activity. In last few decades, plants have been used as traditional sources of natural products and having enough sources for drug development for antimalarial disease. The plant derived chemical constituents such as quinine, artemisinin and aromatic compound have been successfully used against resistant strains of malaria parasites (Jayaseelan et al., 2011). Due to that high resistance of parasites, the alternative drug is needed for control the resistance strains. Although, the plants developed metallic nanoparticles such as silver, platinum and palladium nanoparticles are effective in controlling the malarial replication was proved. The biogenic syntheses of silver nanoparticles mainly suppressed the number of malarial productions in an eco-friendly method.

Anti-inflammatory action of nanoparticles

Anti-inflammatory is an important in wound healing mechanism. Anti-inflammation is a cascade process that produce immune responsive compound such as inter leukines and cytokinins which can be produced by keratinocytes including T lymphocytes, B lymphocytes and macrophages (Jacob et al., 2012). Various inflammatory mediators such as enzymes, antibodies are secreted from the endocrine system. Other potential anti-inflammatory agents such as cytokines, IL-1, IL-2 are secreted from the primary immune organs. These anti-inflammatory mediators induce the healing process (Satyavani et al., 2011). Also, the inflammatory mediators are involved in biochemical pathways and control the expansion of diseases. Biosynthesized gold nanoparticles achieved positive wound repair mechanisms and tissue regeneration in inflammatory function (Gurunathan et al., 2009). The studies proved that biosynthesized gold and platinum nanoparticles are alternative sources for treating inflammation in a natural way.

Anticancer studies on plant mediated nanoparticles

Cancer is an uncontrolled cell proliferation with hysterical changes of biochemical and enzymatic parameters, which is universal property of tumour cells. The over expression of cellular growth will be arrested and regulated with systematic cell cycle mechanisms in cancerous cell by using bio-based nanoparticles as a novel controlling agents (Akhtar et al., 2013).

Antiviral effects of metallic nanoparticles

Biosynthesis of AgNPs nanoparticles can act as potent broad-spectrum antiviral agents to restrict virus cell functions. Suriyakalaa et al., (2013) studied the bio-AgNPs which have persuasive anti- HIV action at an early stage of reverse transcription mechanism. The metallic NPs are strong antiviral agents and inhibit the viral entry into the host system. The biosynthesized metallic nanoparticles have multiple binding sites to bind with gp120 of viral membrane to control the function of virus. The bio-based nanoparticles are acting as effective virucidal agent against cell-free virus and cell-associated virus (Sun et al., 2005). In addition, the silver and gold nanoparticles are constantly inhibiting post-entry stages of the HIV-1 life cycle. Therefore, the metallic nanoparticles will act as promising antiviral drug against retro viruses.

Antidiabetic management of metallic nanoparticles

Diabetes Mellitus (DM) is a metabolic dysfunction group in which an individual has uncontrolled sugar level in blood. Whilst taking the insulin/pills, certain food items as well as a balanced diet could avoid at certain levels. Even though the DM complete recovery is a big challenge. However, the nanomaterials that are biosynthesized could get alternative drug for cure the diabetes mellitus. The results by Daisy et al. (2012) have declared that gold nanoparticles have better therapeutic effects against diabetic models. Significantly gold nanoparticles would be reducing the liver enzymes level like transaminase of alanine, alkaline phosphatase, serum creatinine, as well as uric acid in treated diabetes mice. The gold nanoparticles have treated diabetic model shown a reduction of HbA (glycosylated heamoglobin) level which has been maintaining the normal range. Swarnalatha et al., (2012) explored the *Sphaeranthus amaranthoides* biosynthesized silver nanoparticles inhibited _-amylase as well as the acarbose sugar in diabetes which has been induced animal model. It is primarily _-amylase inhibitory components are available in ethanolic extract of *S. amaranthoides* (Manikanth et al., 2010). Similarly, Pickup et al., (2011) researched that the nanoparticles are potent therapeutic agent for controlling diabetes along with few side effects. The clinical researches in mice successfully control the sugar level of 140mg/dl in silver nanoparticles treated group.

Antioxidant mechanisms of plants derived nanoparticles:

Antioxidant agents including enzymatic and non-enzymatic substances regulate the free radical formation [18]. Free radicals are causing cellular damage including brain damage, atherosclerosis and cancer. The free radicals are generated by ROS (reactive oxygen species) such as superoxide dismutase, hydrogen peroxides and hydrogen radicals. Biomolecules such as proteins, glycoprotein, lipids, fatty acids, phenolics, flavonoids and sugars are strongly controlled the free radical formation (Marambio-Jones et al., 2010). The scavenging power of enzymatic and nonenzymatic antioxidants is useful for the management of various chronic diseases such as diabetes, cancer, AIDS, nephritis, metabolic disorders and neurodegenerative. The antioxidant effect of silver nanoparticles was stronger than other synthetic commercial standards e.g. ascorbic acid and so on. The nanoparticles showed higher antioxidant activity whereas the tea leaf extract possess higher phenolic and flavonoids content in the extract (Reichelt et al., 2012)

Table 1 Overview of nanoparticle based pharmaceutical drugs and their clinical trial status

Nanoparticle based drugs	Company	Trade name/generic name/brand name	Therapeutic use	Clinical trial status/approval/ indication
Liposomal as nanocarriers Annamycin	Callisto	L-Annamycin	Acute lymphocytic leukemia, acute myeloid leukemia	Phase I
Cisplatin	Transave	SLIT Cisplatin	Progressive osteogenic sarcoma metastatic to the lung	Phase II
Vincristine	Inex, Enzon	nco TCS	Non-Hodgkin's lymphoma	Phase II/II
Doxorubicin	GP-Pharm	Sarcodoxome	Soft tissue sarcoma	Phase II
Fentanyl	Delux Therapeutics	aeroLEF	Postperative analgesic	Phase II
AmBisome®	Gilead Sciences, Inc.	Amphotericin B	Treatment of Cryptococcal Meningitis in HIV-infected patients, Treatment of visceral leishmaniasis	FDA 1997

DaunoXome®	Galen Limited, Seagoe Industrial Estate.		Treatment of advanced HIVrelated Kaposi's Sarcoma	FDA 1996
DepoCyt®	SkyePharma Inc.	Daunorubicin citrate	Leukemias, lymphomas, and other hematologic cancers	FDA 1999/2007
DepoDur®	Flynn Pharma	Morphine sulfate extended-release liposome injection	For treatment of chronic pain in patients requiring a long-term daily around-the-clock opioid analgesic	FDA 2004
Doxil®	GlaxoSmithKline Manufacturing S.p.A. Parma, Italy	Doxorubicin HCl	AIDS-related KS, multiple myeloma, ovarian cancer (IV)	FDA 1995
Marqibo®	Talon Therapeutics, Inc.	VinCRIStine sulfate	Treatment of adult patients with Philadelphia chromosomenegative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more antileukemia therapies	FDA 2012
Mepact™	Takeda Austria GmbH	Mifamurtide	It boosts the immune system to kill cancer cells by making it produce certain types of white blood cells called monocytes and macrophages	Europe 2009
Myocet®	TEVA B.V. Swensweg 5 2031 GA Haarlem Netherlands	Doxorubicin	Metastatic breast cancer (IV)	Europe 2000
Visudyne®	Valeant Pharmaceuticals, Inc	Nvartis AG	Photodynamic therapy of wet agerelated macular degeneration, pathological myopia, ocular histoplasmosis syndrome (IV)	FDA 2000
Abelcet®	Sigma-Tau PharmaSource, Inc.	Amphotericin B	Systemic fungal infections (IV)	FDA 1995 and 1996
Amphotec®	Alkopharma USA, Inc.	Amphotericin b	Prescribed for life-threatening fungal infections. It is also effective in treating leishmaniasis	-
Pegylated proteins and polypeptides as nanopharmaceuticals Adagen®	Sigma-Tau Pharmaceuticals, Inc.	Pegademase bovine	Adenosine deaminase deficiency—severe combined immunodeficiency disease	FDA 1990
Cimzia	-	Certolizumab pegol	Crohn's disease, rheumatoid arthritis	FDA 2008
Neulasta	Amgen	Pegfilgrastim	Febrile neutropenia, In patients with nonmyeloid malignancies; prophylaxis (SC)	FDA 2002
Oncaspar	Sigma-Tau Pharmaceuticals, Inc	Pegaspargase	Acute lymphoblastic leukemia	FDA 1994
Pegasys	Roche Ltd	PEGINTERFERON ALFA-2A	Hepatitis B and C	FDA 2002
Peglntron	Roche Ltd	PEGINTERFERON ALFA-	2B Hepatitis C	FDA 2001
Somavert	Pharmacia & Upjohn	Pegvisomant	Acromegaly, second-line therapy	FDA 2003
Macugen	Valeant Pharms LIc	Pegaptanib sodium	Intravitreal Neovascular age-related macular degeneration	FDA 2004
Micera	Roche Ltd	Epoetin beta and Methoxy polyethylene glycol	Anemia associated with chronic renal failure in adults	FDA 2007
Polymer-based nanoformulations as pharmaceuticals l-Leucine, L-glutamate copolymer and Insulin	Flamel Technologies	Basulin	Type I Diabetes	Phase II
Polyglutamate camptothecin	Cell Therapeutics	CT-2106	Colorectal and Ovarian cancers	Phase I/II

IV. CONCLUSION

Metal nanoparticles will be considered as one of the most attractive study regions along with numerous applications such as textiles, electronics, bioremediation, antimicrobial, catalytic and various biomedical applications. The current review would be summarizing the literature to understand the biosynthesis of metal nanoparticles utilizing the extracts of plant as well as their applications of pharmacology. The process of nanoparticles plant extract would act as a reducing agents as well as stabilizing agents also in biosynthesis. There are primarily 2 reasons to be explored in the metallic nanoparticles biosynthesis, they are as follows: Firstly for identifying the active metabolites of plants which is involved partially/ fully in the metal reduction reaction and the second is laboratory scale production of metallic nanoparticles to extent their production of large-scale and enlarge their functional mechanism against a broad pathogenic range of organisms.

A comprehensive study is needed for providing definite biosynthesis mechanism of metal nanoparticles utilizing bio-molecules available in dissimilar extracts of plant that would be precious for enhancing the metallic nanoparticles properties. The most of biosynthesis methods have reported earlier are committed only to silver & gold nanoparticles which might be because of their helpfulness specifically in biomedical sciences in the science of disinfection. These reports should get concerned to the many other metals & their oxide nanoparticles such as Pb, Pd, Ru, CeO_2, CuO, MgO, FeO, TiO_2 and ZnO nanoparticles synthesized through methods of biology which also have vital roles in human benefits. The other considerable efforts are also needed for obtaining the secondary metabolites from the natural resources so that it could be utilized as stabilizing, reducing, and capping agents in the biosynthesis nanoparticles procedures. The most of these studies have been executed in laboratories of research at level of small scale but exploration and nanoparticles utilize at large-scale level in the field of environment, agriculture, medical sciences, catalysis and other area of sciences for achieving the future demands of growing population in the world is essential.

V. REFERENCES

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