Review Article

Biological and Non-biological Synthesis of Metallic Nanoparticles: Scope for Current Pharmaceutical Research

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Kiranmai Mandava: Scope of Metallic Nanoparticles in Pharma Research

Nanotechnology in pharmacy and medicine is going to have a major impact on the survival of the human race. The unique optical, catalytic, electronic and physical properties (melting point) of metallic nanoparticles have made them potential candidates in the field of nanotechnology. The synthesis of metallic nanoparticles is being carried out by various methods. Method of synthesis is one of the important factors, which largely influences their biological effectiveness. Moreover, conventional physical and chemical processes involve the use of expensive chemicals and these methods are non-ecofriendly. The present review outlined different non-biological and biological methods of synthesizing metallic nanoparticles for therapeutic applications including a good emphasis on green expertise in this field. Updated tools of characterization and potential applications of metallic nanoparticles in the field of pharmacy are also reviewed.

Key words: Metallic nanoparticles, green synthesis, characterization, silver nanoparticles, antimicrobial activity, pharmaceutical applications

"Nano" is the prefix word originating from the Latin word '*nanus*' meaning literally 'dwarf' and according to an International System of units (SI) it is used to indicate a reduction factor of 10^9 times. So nanosized materials are typically measured in terms of nanometers (1 nm is 10^{-9} m). Nanoscience can be defined as a study of the phenomenon and size reduction of materials at atomic or molecular scales. Pharmaceutical nanotechnology embraces applications of nanoscience to pharmacy as nanomaterial's and as devices like drug delivery, diagnostics, imaging and biosensors. The term nanomedicine refers to the application of nanotechnology to diagnosis, monitoring, control and treatment of diseases. Biologists are embracing nanotechnology as the engineering and manipulation of entities in 1-100 nm range and exploiting its potential to develop new therapeutics and diagnostics. Due to the advent of many modern and advanced analytical tools and capabilities to measure particle size in nanometres, particulate drug delivery systems research and development has been moving from macro to nano. It is an extremely large field ranging from *in vivo* and *in vitro* diagnostics to therapy, including targeted delivery and regenerative medicine[1]. Nanostructured materials brought about by the creation of functional materials with desired physicochemical properties.

Historically, India was probably the first country to maintain records of useful drugs. *Charaka Samhita* written by Acharya Charaka, the great Ayurvedic scholar of 1500 BC and later treatises describe the medicinal properties of various metals like gold, lead, mercury and silver. The metals used in Ayurvedic system of medicine includes copper, gold, iron, lead, mercury, silver and zinc[2-5]. The term metallic nanoparticles (MNPs) are used to describe nanosized metals with dimensions (length, width or thickness) with size ranges from 1-100 nm. The existence of MNPs in solution was first recognized by Faraday in 1857 and a qualitative explanation of their colour was given by Mie in 1908[6,7]. The current research in the field of MNPs is largely studied due to their special properties. Especially, from the last two decades, considerable

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attention has been devoted to the synthesis of MNPs because of their unusual properties and potential applications in optical, electronic, catalytic, magnetic materials and in medicine[8-11].

This review outlined the various terminologies and preparative approaches of MNPs. It mainly draws attention to the advantages in synthesizing MNPs using a green approach, including its database and scope and pharmaceutical applications of MNPs.

METHODS OF FABRICATION

Non-biological methods:

Broadly speaking, there are two fundamental approaches to fabricate nanomaterial's. The 'top-down' and 'bottom-up' approaches. The former method involves restructuring a bulk material in order to create a nanomaterial (larger size to nano level). The latter one represents the concept of constructing a nanomaterial from basic building blocks such as atoms or molecules. This approach illustrates the possibility of creating exact materials that are designed to have exactly the desired properties (atomic level)[12]. Top-down method is not very well suited to synthesize very-small sized particles. Bottom-up approaches are much better and suited for the generation of uniform particles often of distinct size, shape, and structure[13]. Various methods have been developed for the synthesis of metal nanoparticles includes chemical and physical methods. Chemical methods are based on the reduction of metal ions or decomposition of precursors to form atoms, followed by aggregation of atoms. MNPs produced by chemical methods usually have a narrow size distribution[14]. The mechanism involved in chemical synthesis of MNPs is reduction of metal ions with chemical reductants or decomposition of metal precursors with extra energy. In order to produce MNPs with a narrow size distribution, agents stabilizing colloidal dispersion of MNPs like sodium dodecyl sulphate (SDS), polyvinyl pyrrolidine (PVP), trisodium citrate and β-cyclodextrin are of vital importance. An explosion of reports and reviews appearing in the literature describing the chemical methods of synthesizing MNPs stand evidence to rising interest in this subject[15]. Some chemical agents can play a dual role as reducing and capping or stabilizing agents like plant constituents, β-cyclodextrin, dextrose and certain polymers. The physical methods are based on the subdivision of bulk metals including mechanical crushing or pulverization of bulk metal arc discharge between metal electrodes. MNPs produced by physical methods are usually larger in size and have wide size distribution (Table 1)[15-20].

Researchers in the field of nanotechnology are turning towards 'nature' to gain inspiration to develop novel innovative methods for nanoparticles synthesis. Currently used physical and chemical methods of synthesis use hazardous chemicals in their protocols[21].

Green synthesis of MNPs (biological/bioreduction):

A lot of literature has been reported till date on the biological synthesis of MNPs using plants, microorganisms including bacteria and fungi because of their antioxidant/reducing properties typically responsible for reduction of metallic compounds to their respective MNPs (fig. 1). The ability of plant extracts to reduce MNPs has been known since early 19th century, although the nature of the reducing agents involved was not well understood[22]. In present days, green synthesis of MNPs has been an emerging research area in pharmacy. Advantages of this approach over physical and chemical methods are being eco-friendly, cost-effective, easy scale-up to synthesize large amounts of MNPs and devoid of using high temperature, pressure, energy and other toxic chemicals[23]. Plant extracts may act both as reducing and stabilizing agents in the synthesis of MNPs. The source of plant extract is known to influence the characteristics of nanoparticles (NPs)[24]. As different extracts contain different composition of phytoconstituents (organic reducing agents), the bioreduction process is relatively complex. Phytoconstituents like flavonoids, alkaloids,

TABLE 1: VARIOUS NON-BIOLOGICAL PREPARATIVE METHODS FOR THE SYNTHESIS OF MNPs[15-20]

Chemical methods (bottom-up approach)	Physical methods (top-down approach)
Chemical reductants: Molecular hydrogen, alcohol, hydrazine, sodiumtetrahydroborate, lithium aluminum hydrate, citrate, polyols, N,N-dimethyl formamide, ethyleneglycol, ß-cyclodextrin. Energy sources: Photoenergy like UV/Vis: light, γ-ray, electricity, thermal energy (heat), sonochemical energy.	Vapor phase: Chemical vapor condensation, arc discharge, hydrogen plasma, laser pyrolysis. Liquid phase: Microemulsion, hydrothermal, solgel, sonochemical, microbial Solid phase: Ball mill

polyphenols, vitamins, catechins, and enzymes, functional group containing compounds, tannins, plant pigments and polysaccharides are responsible for the reduction of metal salts to MNPs[25]. Typically a plant extract mediated bioreduction of MNPs involves simple mixing of an aqueous solution of extract with an aqueous solution of metallic salt. The reaction takes place at room temperature and is generally completed within few minutes.

In the biological methods of synthesis of MNPs, the

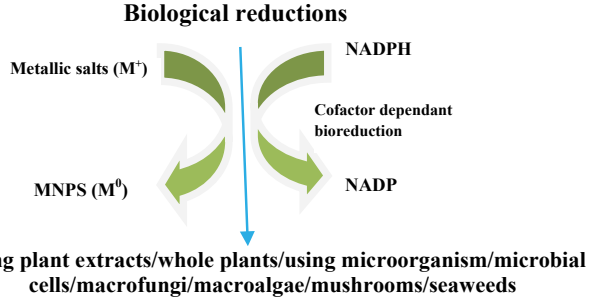

Fig. 1: Various sources for bioreduction of MNPs including cofactor dependant reduction

methods based on microorganisms (unicellular and multicellular) have been widely reported[26]. Microbial synthesis is considered as bottom-up approach where NP formation occurs due to reduction or oxidation of metal ions via biomolecules such as enzymes, sugars, proteins secreted by microorganisms[27]. However a complete mechanism is not well explored. This is due to the fact that the type of microorganism tends to behave and interacts differently with different metal ions. The interaction, biochemical processing activities of specific microorganism and the influence of environmental pH and temperature ultimately determines the formation of NP with a particular size and morphology[28,29]. Six main microbial routes employed for the synthesis of MNPs are actinomycetes[30-32], algae[33-35], bacteria[36-41], fungi[42-47], viruses[48-51] and yeast[52-56]. Microbial synthesis is of course readily scalable, environmentally benign and compatible with the use of product for medical applications but the production of microorganism is often more expensive than the production of plant extracts. Different plants

TABLE 2: GREEN SYNTHESIS OF METALLIC NANOPARTICLES FROM PLANT SOURCES

Plant	MNP	Size, nm	Shape	References
Vitex negundo	Ag;Au	5; 10-30	Spherical; face centered cubic	[57-58]
Melia dubia	Ag	35	Spherical	[59]
Portulaca oleracea	Ag	<60	--	[60]
Thevetia peruviana	Ag	10-30	Spherical	[61]
Pogostemon benghalensis	Ag	>80	--	[62]
Trachyspermum ammi	Ag	87, 99.8	--	[63]
Swietenia mahogany	Ag	50;100 at pH 12.5	spherical	[64]
Musa paradisiaca	Ag	20	--	[65]
Moringa oleifera	Ag	57	--	[66]
Garcinia mangostana	Ag	35	--	[67]
Eclipta prostrate	Ag	35-60	Triangular, pentagon, hexagon	[68]
Nelumbo nucifera	Ag	25-80	Spherical, triangular	[69]
Acalypha indica	Ag	25-80	Spherical	[70]
Allium sativum	Ag	4-22	Spherical	[71]
Aloe vera	Ag, Au, In_2O_3	50-350; 5-50	spherical, triangular	[72-73]
Citrus sinensis	Ag	10-35	Spherical	[74]
Eucalyptus hybrid	Ag	50-150	--	[75]
Memecylon edule	Ag	20-50	Triangular, circular hexagon	[76]
Nelumbo nucifera	Ag	25-80	Spherical, triangular	[69]
Datura metel	Ag	16-40	Quasilinear suprastructures	[77]
Carica papaya	Ag	25-50	--	[78]
Vitis vinifera	Ag	30-40	--	[79]
Alternanthera dentate	Ag	50-100	Spherical	[80]
Acorus calamus	Ag	31.83	Spherical	[81]
Boerhaavia diffusa	Ag	25	Spherical	[82]
Tea extract	Ag	20-90	Spherical	[83]
Tribulus terrestris	Ag	16-28	Spherical	[84]
Cocous nucifera	Ag	22	Spherical	[85]

Abutilon indicum	Ag	7-17	Spherical	[86]
Pistacia atlantica	Ag	10-50	Spherical	[87]
Ziziphora tenuior	Ag	8-40	Spherical	[88]
Ficus carica	Ag	13	--	[89]
Cymbopogan citrates	Ag	32	--	[90]
Acalypha indica	Ag;Au	0.5; 20-30	Spherical	[70]
Premna herbacea	Ag	10-30	Spherical	[91]
Calotropis procera	Ag	19-45	Spherical	[92]
Centella asiatica	Ag	30-50	Spherical	[93]
Argyreia nervosa	Ag	20-50	--	[94]
Psoralea corylifolia	Ag	100-110	--	[95]
Brassica rapa	Ag	16.4	--	[96]
Coccinia indica	Ag	10-20	--	[97]
Alternanthera sessilis	Ag	40	Spherical	[98]
Andrographis paniculata	Ag	67-88	Spherical	[99]
Allium cepa	Ag	33.6	--	[100]
Curcuma longa	Ag; Pd	10-15	Spherical	[101]
Withania somnifera leaves	Ag	5-40	Irregular, spherical	[102]
Ocimum sanctum L.	Ag	4-30	--	[103]
Syzygium cumini L	Ag	93	--	[104]
Euphorbiaceae latex	Ag; Cu	18; 10.5	--	[105]
Trigonella-foenum graecum seed	Au	15-25	Spherical	[106]
Anacardium occidentale	Ag; Au	~6 at 27°; 17 at 100°	--	[107]
Apiin extracted from henna *(Lawsonia inermis)* leaves	Au	7.5-65	spherical, triangular, quasispherical	[108]
Azadirachta indica (neem)	Ag; Au	50-100	--	[109]
Camelia sinensis (Green tea)	Ag; Au; ZnO	30-40; 16	hexagonal wurtzite structure for ZnO	[110-111]
Chenopodium album	Ag; Au	10-30	quasi-spherical shape	[112]
Cinnamomum camphora	Ag; Au; Pd	55-80	Cubic, hexagonal, crystalline	[113]
Cymbopogon sp. (lemon grass)	Au	200-500	spherical, triangular	[114]
Dioscorea bulbifera	Au	11-30	spheres	[115]
Emblica officinalis	Ag; Au	10-20; 15-25	--	[116]
Geranium leaf	Au	16-40	--	[117]
Memecylon edule	Au	20-50	triangular, circular, hexagonal	[118]
Mentha piperita (peppermint)	Ag; Au	5-150	spherical	[119]
Mucuna pruriens	Au	6-17. 5	spherical	[120]
Parthenium leaf	Au	50	face-centered cubic	[119]
Psidium guajava	Ag; Au	25-30; 2-10	spherical	[121-122]
Tagetes erecta	Ag	10-90	-	[123]
Zingiber officinale Rosc.		10	--	[124]
Pyrus sp. (pear fruit extract)	Au	200-500	triangular, hexagonal	[125)
Rosa rugosa	Ag; Au	30-60; 50-250	--	[126]
Swietenia mahogani (mahogany)	Au	100 at pH 12.5	spherical	[64]
Tanacetum vulgare (tansy fruit)	Ag; Au	16; 11	--	[127]
Terminalia catappa	Au	10-35	--	[128]
Eucalyptus macrocarpa	Au	20-100	Spherical, triangular, hexagonal	[129]
Diopyros kaki	Pt	15-19	--	[130]
Jatropha curcas L. latex	Pb	10-12	--	[131]

used for the synthesis of MNPS of different size and shape are given in Table 2[57-131].

Factors influencing biological synthesis of MNPs:

During the course of biological synthesis of MNPs a number of controlling factors are involved in the nucleation and subsequent formation of stabilized NP. These factors include pH, reactants concentration, reaction time and temperature and details were given in Table 3[132-136].

Characterization of MNPs:

After green synthesis of NP, characterization is an important step to identify NP by their shape, size, surface area and dispersity[57]. For this purpose, various characterization techniques have been developed as analytical tools (fig. 2), like UV/Vis for identification, characterization and analysis; dynamic light scattering (DLS) for surface charge, size distribution and quality; scanning electron microscopy (SEM) and transmission electron microscopy (TEM) for surface and morphological characters; zeta potential (ZP) for indirect determination of surface charge; Fourier transform infrared spectroscopy (FTIR) for identification; X-ray diffraction (XRD) for crystal structure of NP; energy dispersive X-ray spectroscopy (EDS) for elemental composition; Auger electron microscopy (AEM), scanning probe electron microscopy (SPM), X-ray photo electron microscopy (XPS), time of flight-secondary ion mass spectroscopy (TOF-SIMS) for primary surface analysis; low energy ion scattering (LEIS) for identification of elements present in the outer most surface of the material under examination; scanning tunneling microscopy (STM), atomic force microscopy (AFM) for surface characterization at atomic scale; inductively coupled plasma-optical emission spectroscopy (ICP-OES) for optical properties; surface enhanced Raman scattering (SERS) for single molecular attachments to the surface of NP.

Pharmaceutical applications of MNPs:

Various applications of MNPs are given in fig. 3. Antimicrobial activities of MNPs were well studied. Silver nanoparticles (AgNPs) and gold nanoparticles (AuNPs) have been reported to have a broad spectrum of antimicrobial activity against human and animal pathogens[137,138]. This is due to effective disruption of polymer subunits of cell membrane in a pathological organism, which in turn results in disturbance in

TABLE 3: FACTORS INFLUENCING THE BIOLOGICAL SYNTHESIS OF MNPs

Controlling factors	Influence on biological synthesis of MNPs	References
pH	Variability in size and shape	[132]
Reactants concentration	Variability in shape	[133]
Reaction time	Increase in reaction time increases the size of MNPs	[134]
Reaction temperature	Size, shape, yield and stability	[135-136]

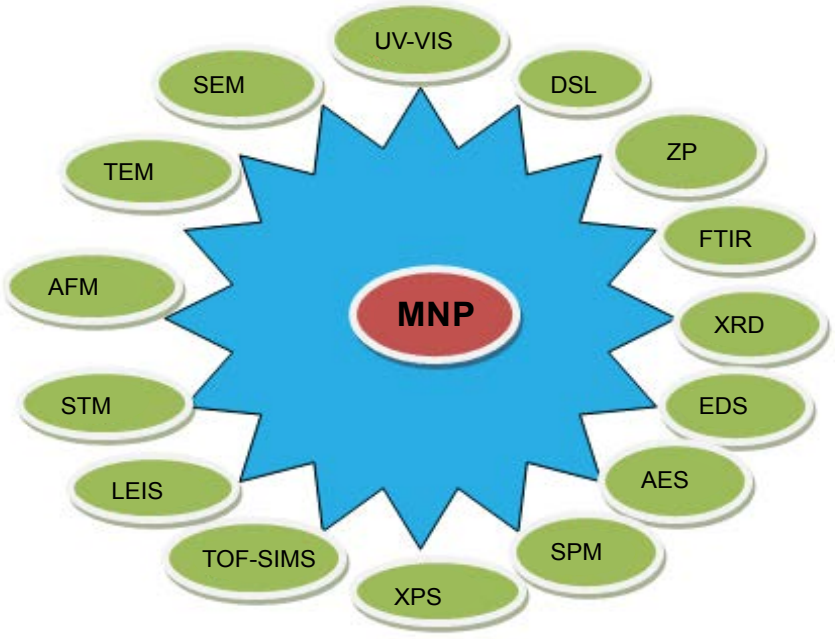

Fig. 2: Summary of characterization techniques of MNPs

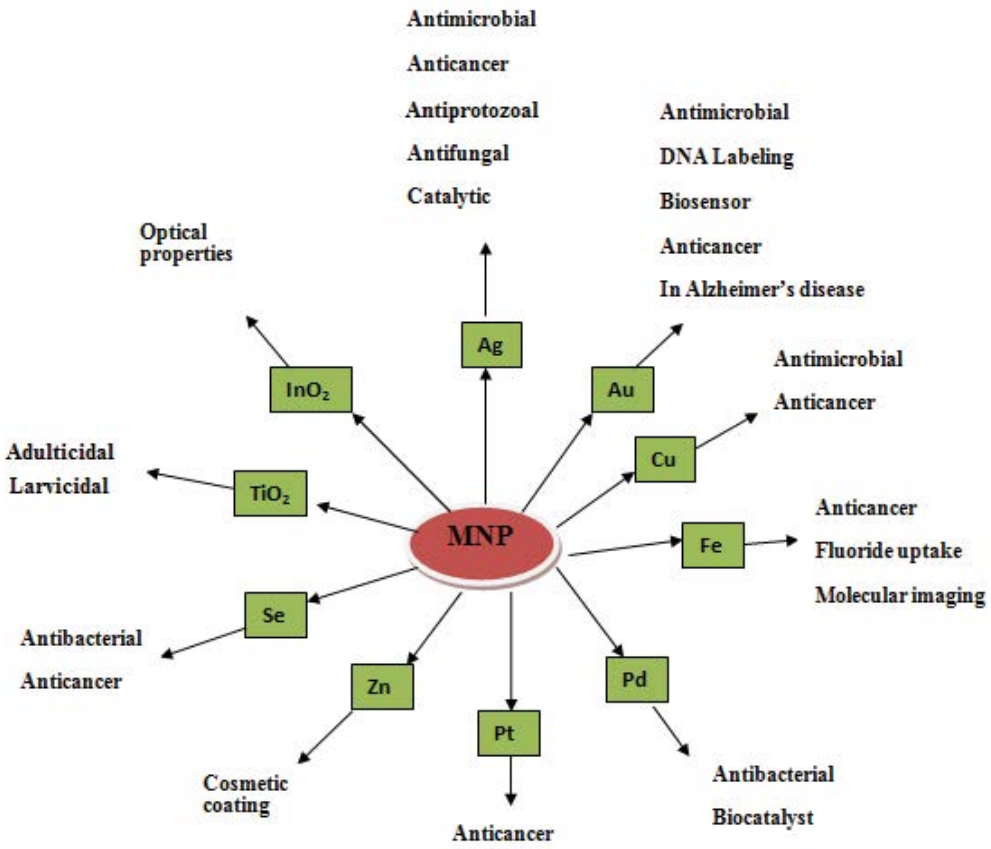

Fig. 3: Various pharmaceutical applications of MNPs

bacterial system[139]. Membrane permeability of AgNPs can be increased by increasing the concentration and consequent rupture of cell wall can be achieved[140]. The interaction between silver and gold MNPs with cell membrane via binding to the active site is demonstrated[141]. Copper and copper oxide nanoparticles (CuNPs) were found to be effective antimicrobial agents[142]. CuNPs were found as strain specific antibacterial agents against *Bacillus subtilis*[143]. Antiinflammatory activity of AgNPs was explored previously and it was due to inhibition of interferon-γ, tumor necrosis factor alpha (TNF-α); reducing matrix metallo proteinase (MMP) and proinflammatory cytokines[144,145]. Biosynthesized MNPs was proved to be having wound healing and tissue regeneration activity in inflammatory mechanism[146]. AgNPs were demonstrated to have antifungal activity[147] and fungicidal properties were explored against *Candida* sp. and results were found to be significant to that of fluconazole and amphotericin. This activity is may be due to damage to fungal intracellular components[148]. As commercially available antifungal products are had various side effects, developing and exploring multifunctional MNPs to combat fungal infections is recommended. AgNPs were active against malarial vectors and reported to have a larvicidal effect[149,150]. Green synthesized MNPs of silver, platinum, palladium are effective in controlling malarial population. There is an urgent need to search for an alternative against vectors that are responsible for spreading the most common plasmodial diseases[151,152]. Recently, many investigators reported that green synthesized MNPs have potential to control tumor cell growth. This activity is due to presence of secondary metabolites in plant extracts[153,154]. AgNPs and AuNPs were found to be effective against malignant cells[155]. AntiHIV activity of AgNPs was studied at an early stage of reverse transcription mechanism[156]. Biosynthesized MNPs significantly reduce the level of hepatic enzymes like alanine transaminase, alkaline phophatase, serum creatinine and uric acid in diabetes-induced mice[157]. AgNPs were potent inhibitors of α-amylase at 140 mg/dl[158,159]. Secondary metabolites present in plant derived MNPs are responsible for antioxidant activity[160].

MNPs in drug delivery:

In recent years, interest has been generated in the capability of MNPs to bind a wide range of organic

molecules, their low toxicity and their strong and tunable absorption. Unique chemical, physical and photo-physical properties of MNPs paved innovative ways in drug delivery systems to achieve controlled transport, controlled release and specific targeting of drugs[161-164]. It has been shown that conjugates of MNPs with antibiotics provide promising results in antimicrobial therapy[163]. Combination of antibiotic with MNPs would be helpful to improve antibiotic efficacy. This conjugation can be via covalent, ionic or physical absorption[165,166]. Cisplatin conjugation to MNPs has shown a significant cytotoxic effect, which is seven times higher than that of cisplatin alone. Conjugation of methotrexate to AuNPs, which involves the interaction of carboxylic group of drug with the metal surface found to have high concentrations of drug in Lewis lung carcinoma cells[167]. Conjugation of tamoxifen and AuNPs has been reported[168]. MNPs surfaces have to be modified in order to avoid aggregation and to improve the efficiency of MNPs drug delivery systems[169]. Doxorubicin in combination with surface modified AuNPs reported to have significant cytotoxicity when compared to the free form of doxorubicin[170]. Polyethylene glycol (PEG) can be used to modify the surface of MNPs so that the cellular uptake of nanoparticles can be improved[171].

AntiHER antibody-targeted gold/silicon nanoparticles in the form of nanoshells to treat metastatic breast cancer[172], aminosilane coated iron oxide nanoparticles to treat brain tumors[173] and starch coated iron oxide nanoparticles in the form of magnetically guided mitoxantrone to treat tumor angiogenesis[174] have been reported. Calcium phosphate nanoparticles as vaccine adjuvant (Biovant) is developed by Biosante for subcutaneous administration has entered into phase I trials[175]. Author previously reported a simple, cost effective and eco-friendly method for the synthesis of water soluble AgNPs using root bark extract of *Azadirachta indica* (RBAI). Clinical ultrasound gel prepared from these NPs proved to be effective with significant antibacterial activity[176].

Drawbacks of MNPs:

Few of the disadvantages of MNPs are the exact mechanism for synthesis of NPs needs to be elucidated, limitations to scale up production processes and reproducibility of the processes[177]. Chronic exposure to silver NPs causes adverse effects like argyria and argyrosis, soluble silver may cause organ damage[178].

Biological synthesis of MNPs has been always beneficial. Especially green synthesis of MNPs using plants and their extracts is more economical, energy efficient and eco-friendly approach, which is free of toxic contaminates as required in therapeutic applications. Microbes are regarded as potential biofactories for MNPs synthesis and serve a new generation antimicrobial agents with their unique physicochemical properties. The MNPs have found diverse applications in the field of pharmacy as direct therapeutic agents to treat ailments and also as carriers for drug delivery systems. In both the cases, stability and surface activity of MNPs are the vital areas where researchers have to concentrate. In particular, the development of rational protocol for green synthesis of MNPs in keeping view of the advantages of this approach; application of these particles to resolve problem of antibiotic resistance and in the target specific drug delivery systems to treat microbial infections including HIV and cancer should be highly focused in the future.

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