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Review

Green nanotechnology – A new hope for medical biology



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ABSTRACT

The development of eco-friendly technologies in material synthesis is of considerable importance to expand their biological applications. Nowadays, a variety of green nanoparticles with well-defined chemical composition, size, and morphology have been synthesized by different methods and their applications in many cutting-edge technological areas have been explored. This review highlights the classification of nanoparticles giving special emphasis on biosynthesis of metal nanoparticle by viable organisms. It also focuses on the applications of these biosynthesized nanoparticles in a wide spectrum of potential areas of medical biology including catalysis, targeted drug delivery, cancer treatment, antibacterial agents and as biosensors.

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1. Introduction

Nanomaterials, with its characteristic dimension at the range of 1–100 nm, are at the leading edge of nanoscience and nanotechnology. In recent years nanomaterials, specifically metal nanoparticles, have received particular interest in diverse field of applied science ranging from material science to biotechnology (Guo et al., 2005; Daniel and Astruc, 2004; Huang et al., 2007). Although widespread interest in nanomaterials is recent, the concept was actually introduced over 40 years back. With the advancement of science and technology, the morphology of this material, which contains metallic nanoparticles, has been understood. Because of extremely small size and high surface volume ratio of nanoparticles, the physicochemical properties of nanoparticles-containing materials are quite different to those of the bulk materials (El-Sayed, 2001). Thus, nanomaterials have potential applications in electronics and photonics, catalysis, information storage, chemical sensing and imaging, environmental remediation, drug delivery and biological labelling (Guo et al., 2005; Daniel and Astruc, 2004; Huang et al., 2007). It is well known that the optical, electronic, and catalytic properties of metal nanoparticles are greatly influenced by their size, shape, and crystal structure. For example, silver (Ag) and gold (Au) nanocrystals of different shapes possess unique optical scattering responses (Daniel and Astruc, 2004; Roduner, 2006). Whereas highly symmetric spherical particles exhibit a single scattering peak, anisotropic shapes such as rods, triangular prisms, and cubes exhibit multiple scattering peaks in the visible wavelengths due to highly localized charge polarizations at corners and edges (Mie, 1908). Thus, synthesis of metal nanoparticles with defined morphology gained much interest. A variety of strategies have been developed for the synthesis of metal nanoparticles (MNPs) and nanomaterials.

Optimizing the nanomaterial synthesis has now become a prolific area of investigation. Metal nanoparticles are particularly unique in nanoscale system because of the ease in its

synthesis and chemical modifications. Hazardous substances such as sodium borohydride, tetrakis(hydroxymethyl)phosphonium chloride (THPC), poly-N-vinyl pyrrolidone (PVP), and hydroxylamine have been used for the synthesis of nanoparticles in the traditional wet methods. Other dry methods such as UV irradiation, aerosol and lithography are also not considered environment-friendly. The use of such toxic chemicals is still the subject of paramount concern because toxic chemicals on the surface of nanoparticles and non-polar solvents limit their applications in clinical fields. Therefore, the biosynthesis of clean, biocompatible, non-toxic and environment-friendly nanoparticles produced both extracellularly and intracellularly deserves merit (Karazhanov and Raveendran, 2003; Sharma et al., 2009; Narayanan and Sakthivel, 2010).

Despite significant private and public investment, progress moving nanomaterials from the laboratory to industrial production has been slow and difficult. Two challenges that have slowed the development, are the poor understanding of the new hazards introduced by nanotechnology (Senjen, 2007) and lack of appropriate policies to manage any new risks. Scientists, engineers and entrepreneurs, however, continue to move forward, grappling with challenges that range from the technical to the regulatory and everywhere in between. Just as the concepts of nanoscale invention have required new insights from scientists, they are also demanding new approaches to managing, producing, funding and deploying novel technologies into the larger chemical sector. In this case, there is an unusual opportunity to use science, engineering and policy knowledge to design novel products that are benign as possible to human and environmental health. Recognition of this opportunity has led to the development of the “green nanoscience” concept (McKenzie and Hutchison, 2004; Dahl et al., 2007).

Green nanotechnology has drawn on the field of green chemistry, and the framework of the Principles of Green Chemistry (Anastas and Warner, 1998) features significantly in work to design new nanotechnologies for joint economic,

social, and health/environmental benefit (Hutchison, 2008). These efforts have been aided by awareness throughout the nanotech community that they need to address the potential negative impacts of nano from the outset (Albrecht et al., 2006). Nanotechnology presents an opportunity to develop a new technology, and a new industry in a sustainable way from the outset. We are at a unique point where we have more understanding of how to go about this than at any time in the past. This new emerging science and associated technologies do not have to follow the path that has been typical of many past innovations in the chemical industry that, despite providing significant benefits, also turned out to have significant, unanticipated costs to human health and the environment. The development and commercialization of viable green nanotechnologies is difficult, and the barriers will require effort from the scientists, researchers, government and communities.

In the first part of this review, special emphasis is given on the classification of nanoparticles and different methodologies for the characterization of it, in the second part different strategies for the synthesis of MNPs have been discussed, with particular emphasis on biosynthesis by viable organisms. Lastly it focuses on the application of nanoparticles in different fields along with an idea of current state of green nano research.

2. Classification of nanoparticles

A broad library of nanoparticles consisting of different physical and chemical properties has been constructed. Due to new discoveries made in nanotechnology, however, classifications of nanoparticles are constantly changing. Currently nanoparticles can be separated into several different classes.

- There are the nanoclusters that are defined as semi crystalline nanostructures with dimensions within 1–10 nm and a narrow size distribution.
- There are the nanopowders that result from the aggregation of non-crystalline nanomaterials with dimensions between 10 and 100 nm.
- The nanocrystals that are single crystalline nanomaterials with dimensions between 100 and 1000 nm.

These examples are only the most basic classification of nanoparticles; others include nanorods, nanocups, nanospheres, nanodiamonds, nanostars and the quantum dots (Chakrabarti et al., 2004). Some examples of general and multi-functional classes of nanoparticles (Fig. 1) used in biotechnology and particularly in the area of nanomedicine are listed below.

2.1. Liposomes

An initial study on liposomes or lipid vesicles originated in the 1960s when there was a need to understand new types of polymer nanocontainers. Initially, liposomes were used as model systems to study biological membranes but by 1970 had been developed into a medium for the transportation of drugs (Graff et al., 2004). Liposomes, in general, had been reported

to be highly useful in biophysics as a good model system in understanding the properties of cell membrane and channels. In chemistry, they served as an excellent illustration of catalysis, energy conversion and photosynthesis while in biochemistry they improved the understanding of the biological function of proteins specifically in secretion, trafficking and signalling, gene delivery and other functions in cell biology (Graff et al., 2004). Liposomes have various extensive applications in the pharmaceutical industry as directed-delivery agent for drugs such as anticancer, anti-fungal and vaccines. They are also useful in cosmetics in the manufacturing of shampoos and other skin care products. They are very important tools in diagnostics as they are able to degrade in the cells after delivery (Graff et al., 2004; Salata, 2004). Liposomes were said to be the first synthesized nanoparticles (Fig. 1A) used for drug delivery but a major limitation was their tendency to fuse together in aqueous environments and release contents before getting to the target site. This has led to the search for either a replacement or a method of stabilization using newer substitute nanoparticles.

2.2. Superparamagnetic nanoparticles

Superparamagnetic nanoparticles (Fig. 1B) are a class of inorganic based particles having an iron oxide core [superparamagnetic iron oxide nanoparticles (SPION)] coated by either inorganic materials (silica, gold) or organic materials like phospholipids, fatty acids, polysaccharides, peptides, surfactants, polymers (Gupta and Curtis, 2004; Liu et al., 2007). An important property of SPIONs that makes them unique compared to other nanoparticles is their induced magnetization, i.e. they are able to attract to a magnetic field without retaining residual magnetism after the removal of the field. This property makes them attractive for many applications, ranging from various selective bio-separations and contrast enhancing agents for MRI in drug delivery systems, magnetic hyperthermia (local heat source in the case of tumour therapy) and magnetically assisted transfection of cells (Neuberger et al., 2005; Aptekar et al., 2009).

2.3. Fullerenes: buckyballs and carbon nanotubes

Fullerenes are molecules made exclusively of carbon and they exist in different forms such as hollow spheres, ellipsoids or tubes. The spherical forms of fullerenes are referred to as buckyballs, and tubular forms as carbon nanotubes (CNTs) or buckytubes. Fullerenes possess a structure similar to that of graphite that is composed of stacked sheets of graphene and often linked by hexagonal, pentagonal or heptagonal (not very common) rings (Theodore and Kunz, 2005; Kroto and Walton, 2011; Prasad and Jemmis, 2008). Discovery of fullerenes has increased the number of known allotropes of carbon, which was previously limited to graphite, diamond, and amorphous carbon.

Due to their novel characteristics, a great deal of research on buckyballs and CNTs has been carried out especially in the various technological fields of material sciences, nanotechnology and electronics. Bulky ball, also known as, Buckminsterfullerene or C60 is the smallest form of fullerenes and the most abundant in nature, as it is mostly found in

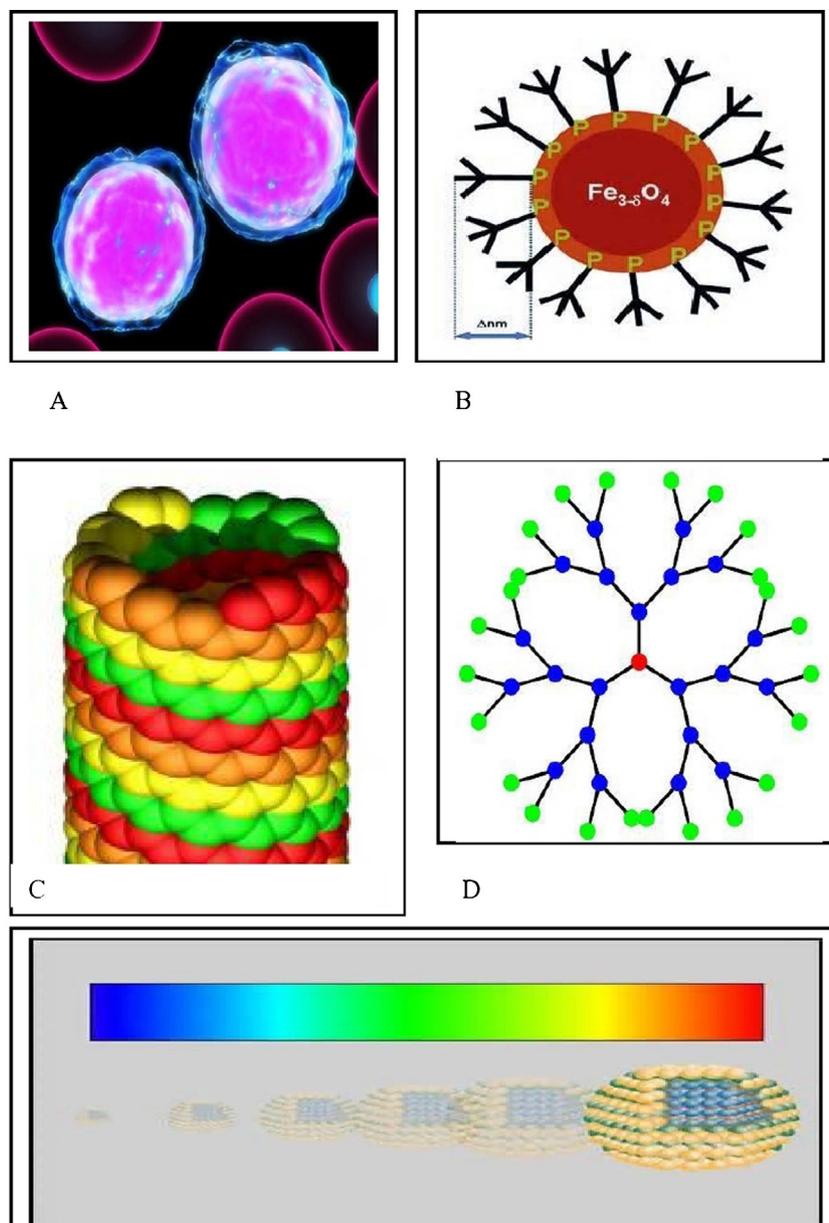


Fig. 1 – Different classes of nanoparticles. (A) Nanoparticle in liposomes; (B) superparamagnetic nanoparticle; (C) nanotube; (D) dendrimer; (E) quantum dots with changing optical properties. (For interpretation of the references to colour in text, the reader is referred to the web version of the article.)

soot, though a second type of buckyball composed of boron atoms (i.e. boron bulky ball or B80) instead of carbon has been described (Gopakumar et al., 2008) in which each boron atom that makes up the B80 structure forms about 5–6 bonds and is believed to make the structure more stable than the C60. CNTs are also allotropes of carbon that, as mentioned earlier, are cylindrical in structure. Nanotubes with length-to-diameter ratio of 132 000 000:1 have been fabricated and this makes them much larger than any other material. CNT have unique properties that make them important to nanoscience/nanotechnology and other fields of science like material science, optics and even architecture. A possible use of them in the construction of body armour has been reported (Mintmire et al., 1992). They display exceptional strength

and peculiar electrical properties. In addition to this, CNTs have also been found to be excellent conductors of heat and are referred to as thermal conductors. The major drawback, however, in their widespread application is their potential to possess some toxic properties. CNTs (Fig. 1C) are classified into various forms including single walled carbon nanotubes (SWCNT), double walled carbon nanotubes (DWCNT) and multi walled carbon nanotubes (MWCNT) (Konishi et al., 1995; Jian et al., 2006; Clourier et al., 2006; Langmuir et al., 2009). The uniqueness in the properties of each type of CNTs is what determines their applications in different scientific areas. For example, the SWNT which is the most studied of all the CNTs have particularly strong electric properties which is lacking in the other types (Martel et al., 2001; Theodore and Kunz, 2005).

2.4. Dendrimer

Dendrimers are highly branched structures with uniform size, radial symmetry and assume a circular shape in solution (Graff et al., 2004). Dendrimers are built layer-by-layer from core to periphery by repetitive covalent bond-forming reactions. The density of the dendrimers increased for every layer formed in each step as a result of the geometric growth at each branching point (Tomalia, 2005). By choosing the final reagent, it was possible to design dendritic molecules with different active surface groups (Fig. 1D).

The first dendritic molecule was synthesized in about 1980, but interest in them only developed during the 2000s due to increased discovery of various applications especially in the biotechnological areas. In nanomedicine, dendrimers had been found to be an invaluable tool in attaching fluorescent dyes, enzymes cell identification tags and other molecules because of the many molecular “hooks” present on their surface. Production of these molecules, however, can be quite challenging and expensive and a drawback for their large scale application. Nevertheless, their high stability and the possibility of functionalizing them with biomolecules like antibodies and receptors, makes them a very important medium in target drug delivery (Smith and Diederich, 2000).

2.5. Quantum dots

Quantum dots (QDs) or nanocrystals are semiconductor nanoparticles that can emit light in all colours of the spectrum depending on their size (Fig. 1E). The size of QDs decreases as they get closer to the blue-end of the spectrum, and increase as they proceed to the red end.

They have unique properties such that they can even be tuned beyond visible light, into the infra-red or into the ultra-violet spectrum and were able to confine conduction band electrons, valence band holes, or excitations in all three spatial directions (Murray et al., 2000). QDs are valuable tools in biotechnology most especially in cellular imaging and labelling as they are believed to be an excellent alternative to conventional fluorescent dyes used in imaging.

2.6. Liquid crystals

These are pharmaceuticals made from liquid organic crystalline materials and are designed to mimic naturally occurring biomolecules like proteins or lipids. They are regarded as a very safe and specific vehicle of drug delivery as they can target a particular area of the body where tissues are inflamed and are capable of detecting tumours.

3. Metal nanoparticles and characterization methods

Nanoparticles of metallic origin have been shown to exhibit unusual properties that they normally will not display in their bulk form (Elechiguerra et al., 2005; Blackman, 2009). Due to their huge potential and benefits to nanotechnology, they have come under intense scrutiny as far as applications across various disciplines are concerned. In biochemistry, for

example, they are considered to be better catalysts (Astruc, 2008) and good biological and chemical sensors (Nam et al., 2003; Nie et al., 2007); in information systems, their size and magnetic properties are being explored in the production of data storage devices where the issue of miniaturization is posing an overwhelming challenge (Mayes and Mann, 2004); in medicine their potential as drug delivery agents has being reported (Nie et al., 2007).

Nanotechnology, being an interdisciplinary field of science, will have many characterization and analytical techniques available (Table 1) in the elucidation of nanomaterials (Gabor et al., 2008). These characterization methods are based on two physical processes: the first being primary (1°) analytical probes such as photons, neutrons, ions and electrons, which may be combined with input stresses like magnetic and electric fields and mechanical stress.

Second, the measurable secondary (2°) effect obtained e.g. the release or absorption of electrons, electromagnetic radiation, volume change, mechanical distortion and third, the choice of the investigating medium, energy, temperature, time, intensity, phase or angle. During characterization, the 1° probe, which may be either a beam of electron or a photon of light, interacts with the analyte or matter causing a change in its equilibrium and responds in order to gain its previous state of equilibrium thus modifying the 1° probe. Examples of alteration produced as a result of interaction of 1° probe with matter are excitation of electrons, phonons, excitons or plasmons. Modification of the 1° probe as a result of this produces a 2° effect which is the measured signal (Kelsall et al., 2005).

4. Synthesis of metal nanoparticles by traditional physical and chemical methods

Synthesis of MNPs is carried out by several physical and chemical methods that include laser ablation (Mafuné et al., 2001), ion sputtering (Raffi et al., 2007), solvothermal synthesis (Rosemary and Pradeep, 2003), chemical reduction (Chaki et al., 2002), and sol-gel (Shukla and Seal, 1999) method. Basically, there are two approaches for nanoparticle synthesis, the top-down and bottom-up. Top-down approaches seek to create nanoscale objects by using larger, externally controlled microscopic devices to direct their assembly, while bottom-up approaches adopt molecular components that are built up into more complex assemblies. The top-down approach often uses microfabrication techniques where externally controlled tools are used to cut, mill, and shape materials into the desired shape and size. Micropatterning techniques, such as photolithography and inkjet printing are well known examples of top-down approach. On the other hand, bottom-up approaches use the self-assembled properties of single molecules into some useful conformation.

4.1. Laser ablation

Laser ablation (Mafuné et al., 2001) enables to obtain colloidal nanoparticles solutions in a variety of solvents. Nanoparticles are formed during the condensation of a plasma plume produced by the laser ablation of a bulk metal plate dipped in a liquid solution. This technique is considered as a ‘green

Table 1 – Characterization of metal nanoparticles.

Characterization of size, shape, and surface properties of nanoparticle		Characterization of chemical properties of nanoparticle	
Single-particle techniques	Ensemble analytical techniques	Single-particle techniques	Ensemble analytical techniques
1. Scanning Electron Microscopy (SEM)	1. Dynamic Light Scattering (DLS)	1. Surface composition 1.1. Electron spectroscopy for Chemical Analysis (ESCA) or X-ray photoelectron spectroscopy (XPS)	1. Atomic/chemical structure 1.1. Fourier Transform Infrared Spectroscopy 1.2. Raman Scattering (RS) 1.3. X-ray Absorption Spectroscopy (XAS) 1.4. Circular dichroism
2. Transmission Electron Microscopy (TEM)	2. Laser Diffraction/Static Light Scattering		2. Surface charge 2.1. Zeta potential
3. Atomic Force Microscopy (AFM)	3. Field Flow Fractionation (FFF)		3. Surface reactivity 3.1. Comparative microcalorimetry
	4. Centrifugal sedimentation 5. Specific Surface Area (BET) 6. Time of Flight Mass Spectroscopy		

technique' alternative to the chemical reduction method for obtaining noble MNPs. However, the main drawbacks of this methodology are the high energy required per unit of MNPs produced and the little control over the growth rate of the MNPs.

4.2. Inert gas condensation

Inert gas condensation (IGC) is the most widely used methods for MNPs synthesis at laboratory-scale. Gleiter (1989) introduced the IGC technique in nanotechnology by synthesizing iron nanoparticles. In IGC, metals are evaporated in ultra high vacuum chamber filled with helium or argon gas at typical pressure of few hundreds Pascal's. The evaporated metal atoms lose their kinetic energy by collisions with the gas, and condense into small particles. These particles then grow by Brownian coagulation and coalescence and finally form nano-crystals. Recent application of this technique includes size-controlled synthesis of Au/Pd NPs (Pérez-Tijerina et al., 2008) and hetero-sized Au nanoclusters for non-volatile memory cell applications (Kang et al., 2011).

4.3. Sol-gel method

The sol-gel process is a wet-chemical technique developed recently in nanomaterial synthesis. The inorganic nanostructures are formed by the sol-gel process through formation of colloidal suspension (sol) and gelation of the sol to integrated network in continuous liquid phase (gel). Size and stability control quantum-confined semiconductor, metal, and metal oxide nanoparticles has been achieved by inverted micelles (Gacoin et al., 1997), polymer blends (Yuan et al., 1992), block copolymers (Sankaran et al., 1993), porous glasses (Justus et al., 1992), and ex situ particle-capping techniques (Olshavsky and Allcock, 1997). However, the fundamental problem of aqueous sol-gel chemistry is the complexity of process and the fact

that the as-synthesized precipitates are generally amorphous. In non-aqueous sol-gel chemistry the transformation of the precursor takes place in an organic solvent. The nonaqueous (or non-hydrolytic) processes are able to overcome some of the major limitations of aqueous systems, and thus represent a powerful and versatile alternative. The advantages are a direct consequence of the manifold role of the organic components in the reaction system (e.g., solvent, organic ligand of the precursor molecule, surfactants, or in situ formed organic condensation products). Nowadays, the family of metal oxide nanoparticles is synthesized by non-aqueous processes and ranges from simple binary metal oxides to more complex ternary, multi-metal and doped systems.

4.4. Hydrothermal and solvothermal synthesis

The hydrothermal and solvothermal synthesis of inorganic materials is an important methodology in nanomaterial synthesis. In hydrothermal method, the synthetic process occurs in aqueous solution above the boiling point of water, whereas in solvothermal method the reaction is carried out in organic solvents at temperatures (200–300 °C) higher than their boiling points. Though development of hydrothermal and solvothermal synthesis has a history of 100 years, recently this technique has been applied in material synthesis process. Normally, hydrothermal and solvothermal reactions are conducted in a specially sealed container or high pressure autoclave under subcritical or supercritical solvent conditions. Under such conditions, the solubility of reactants increases significantly, enabling reaction to take place at lower temperature. Among numerous examples, TiO₂ photocatalysts were synthesized through hydrothermal process (Ren et al., 2007). Because low cost and energy consumption, hydrothermal process can be scale-up for industrial production. Solvothermal process enables to choose among numerous solvents or mixture thereof, thus increasing the versatility of the

synthesis. For example, well-faceted nanocrystals of TiO₂ with high reactivity were synthesized in a mixture of the solvents hydrogen fluoride (HF) and 2-propanol (Yang et al., 2008).

4.5. Colloidal methods

The crystallographic control over the nucleation and growth of noble-metal nanoparticles has most widely been achieved using colloidal methods (Tao et al., 2008; Turkevitch et al., 1951; Frens, 1972; Brust and Kiely, 2002). In general, metal nanoparticles are synthesized by reducing metal salt with chemical reducing agents like borohydride, hydrazine, citrate, etc., followed by surface modification with suitable capping ligands to prevent aggregation and confer additional surface properties. Occasional use of organic solvents in this synthetic process often raises environmental questions. At the same time, these approaches produce multi-shaped nanoparticles requiring purification by differential centrifugation and consequently have low yield. Thus, the development of reliable experimental protocols for the synthesis of nanomaterials over a range of chemical compositions, sizes, and high monodispersity is one of the challenging issues in current nanotechnology. In this context, current drive is focused on the development of green and biosynthetic technologies for production of nanocrystals with desired size and shape.

5. Bio-inspired green nanomaterial synthesis

Nature has devised various processes for the synthesis of nano- and micro-length scaled inorganic materials which have contributed to the development of relatively new (Fig. 2) and largely unexplored area of research based on the biosynthesis of nanomaterials (Mohanpuria et al., 2008). Biosynthesis of nanoparticles is a kind of bottom up approach where the main reaction is reduction/oxidation (Durán et al., 2011). The microbial enzymes or the plant phytochemicals with anti oxidant or reducing properties are usually responsible for reduction of metal compounds into their respective nanoparticles.

5.1. Use of bacteria to synthesize nanoparticles

Bacteria play a crucial role in metal biogeochemical cycling and mineral formation in surface and subsurface environments (Lowenstam, 1981; Southam and Saunders, 2005). The use of microbial cells for the synthesis of nanosized materials (Fig. 3) has emerged as a novel approach for the synthesis of metal nanoparticles. Although the efforts directed towards the biosynthesis of nanomaterials are recent, the interactions between microorganisms and metals have been well documented and the ability of microorganisms to extract and/or accumulate metals is employed in commercial biotechnological processes such as bioleaching and bioremediation (Gericke and Pinches, 2006). Bacteria are known to produce inorganic materials either intra cellularly or extra cellularly. Microorganisms are considered as a potential biofactory for the synthesis of nanoparticles like gold, silver and cadmium sulphide.

Among the microorganisms, prokaryotic bacteria have received the most attention in the area of metal nanoparticle biosynthesis. The formation of extracellular and intracellular metal nanoparticles by bacteria like *Escherichia coli*, *Pseudomonas stutzeri*, *Pseudomonas aeruginosa*, *Plectonema boryanum*, *Salmonella typhi*, *Staphylococcus aureus*, *Vibrio cholerae*, etc., have been reported (Klaus et al., 1999; Beveridge and Murray, 1976; Southam and Beveridge, 1994).

Some well known examples of bacteria synthesizing inorganic materials include magnetotactic bacteria (synthesizing magnetic nanoparticles) and S layer bacteria which produce gypsum and calcium carbonate layers (Shankar et al., 2004). Some microorganisms can survive and grow even at high metal ion concentration due to their resistance to the metal. The mechanisms involve: efflux systems, alteration of solubility and toxicity via reduction or oxidation, biosorption, bioaccumulation, extra cellular complexation or precipitation of metals and lack of specific metal transport systems (Husseiny et al., 2007). For e.g. *P. stutzeri* AG 259 isolated from silver mines has been shown to produce silver nanoparticles (Mohanpuria et al., 2008).

Many microorganisms are known to produce nanostructured mineral crystals and metallic nanoparticles with properties similar to chemically synthesized materials, while exercising strict control over size, shape and composition of the particles. Examples include the formation of magnetic nanoparticles by magnetotactic bacteria, the production of silver nanoparticles within the periplasmic space of *P. stutzeri* and the formation of palladium nanoparticles using sulphate reducing bacteria in the presence of an exogenous electron donor (Gericke and Pinches, 2006).

Though it is widely believed that the enzymes of the organisms play a major role in the bioreduction process, some studies have indicated it otherwise. Studies indicate that some microorganisms could reduce silver ions where the processes of bioreduction were probably non enzymatic. For e.g. dried cells of *Bacillus megaterium* D01, *Lactobacillus* sp. A09 were shown to reduce silver ions by the interaction of the silver ions with the groups on the microbial cell wall (Fu et al., 2000, 2006).

Silver nanoparticles in the size range of 10–15 nm were produced by treating dried cells of *Corynebacterium* sp. SH09 with diamine silver complex. The ionized carboxyl group of amino acid residues and the amide of peptide chains were the main groups trapping [Ag(NH₃)²⁺] onto the cell wall and some reducing groups such as aldehyde and ketone were involved in subsequent bioreduction. But it was found that the reaction progressed slowly and could be accelerated in the presence of OH⁻ (Fu et al., 2006).

The supernatant of gram positive, thermophilic bacterium *Bacillus licheniformis* synthesized AgNPs in the range of 50 nm (Kalishwaralal et al., 2008). Formation of nanoscale elemental silver particles through enzymatic reduction was reported in *Geobacter sulfurreducens* (Law et al., 2008).

Kalimuthu et al. (2008) studied AgNPs synthesis using bacteria *B. licheniformis*, isolated from sewage collected from municipal wastes, and ultrasonically lysed bacterial cell. The synthesized AgNPs had average particle size of around 50 nm. Recently, a rapid method for synthesizing small (1–7 nm) monodisperse AgNPs has been described by electrochemically

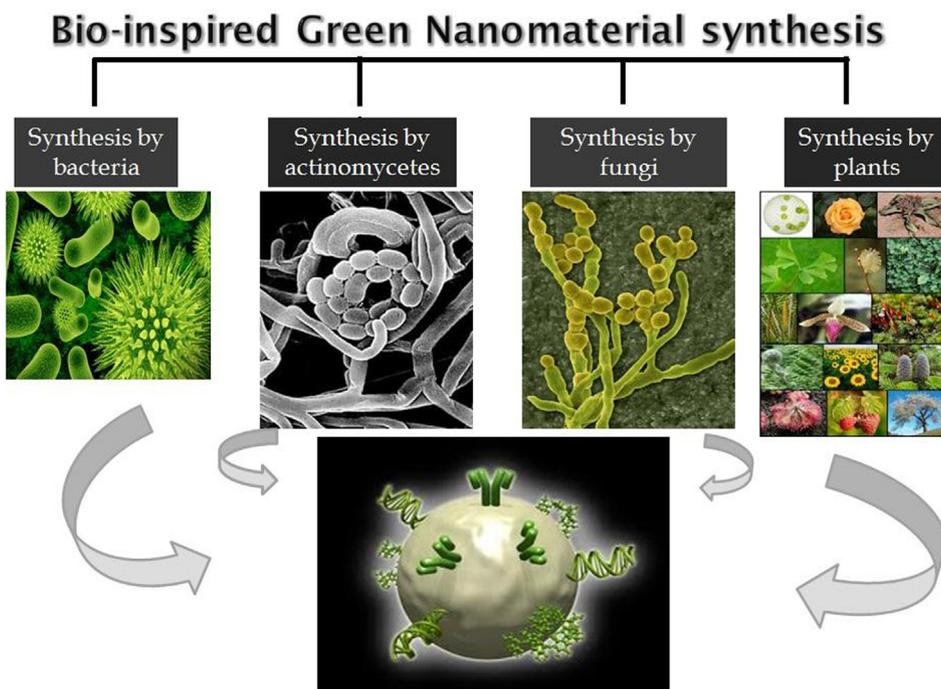


Fig. 2 – A schematic representation of bioinspired green nanomaterial synthesis.

active biofilm (EAB) using sodium acetate as an electron donor (Kalathil et al., 2011).

The formation of AuNP was indicated by the change in reaction mixture, which turned to light yellow after 1 h. The AuNPs were synthesized adopting similar procedure using two *P. aeruginosa* isolates (Husseiny et al., 2007). The synthesis of stable gold nanocubes by the reduction of aqueous $AgCl_4^-$ solution by *B. licheniformis* was reported by Kalishwaralal et al. (2009). Biofilm formation of gram-negative β -proteobacterium *Cupriavidus metallidurans* is very common on Au grains. The isolated *C. metallidurans* from soils and sediments from temperate and tropical Australian sites interacted with Au^{3+} ions and form AuNPs distributed homogenously throughout cell wall (Reith et al., 2009). The AuNPs were also synthesized on

the surface of *Rhodopseudomonas capsulate* by interaction bacterial cells with $HAuCl_4$ solution (He et al., 2007). The aqueous chloroaurate ions were reduced after 48 h of incubation and transformed to AuNPs. The pH value of the solution controlled the shape of AuNPs.

In the case of bacteria, most metal ions are toxic and therefore the reduction of ions or the formation of water insoluble complexes is a defense mechanism developed by the bacteria to overcome such toxicity (Sastri et al., 2003).

5.2. Use of actinomycetes to synthesize nanoparticles

Actinomycetes are microorganisms that share important characteristics of fungi and prokaryotes such as bacteria. Even

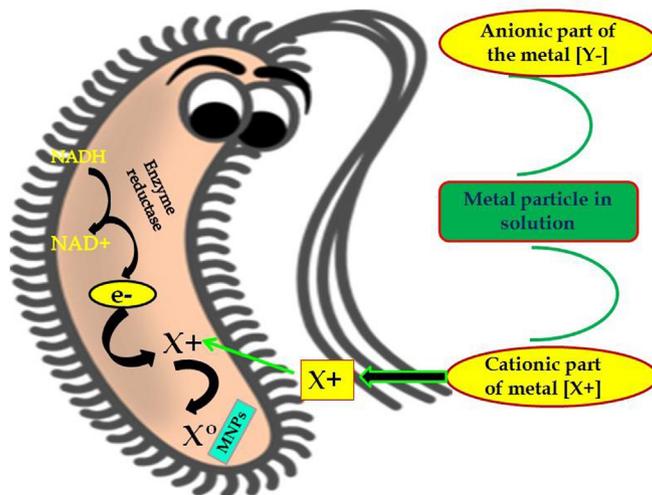


Fig. 3 – Hypothetical diagram of possible mechanism of synthesis of metal nanoparticles by bacteria.

though they are classified as prokaryotes, they were originally designated as ray fungi. Focus on actinomycetes has primarily centred on their exceptional ability to produce secondary metabolites such as antibiotics. It has been observed that a novel alkalothermophilic actinomycete, *Thermomonospora* sp. synthesized gold nanoparticles extracellularly when exposed to gold ions under alkaline conditions (Sastry et al., 2003). In an effort to elucidate the mechanism or the processes favouring the formation of nanoparticles with desired features, Ahmad et al. (2003), studied the formation of monodisperse gold nanoparticles by *Thermomonospora* sp. and concluded that extreme biological conditions such as alkaline and slightly elevated temperature conditions were favourable for the formation of monodisperse particles. Based on this hypothesis, alkalotolerant actinomycete *Rhodococcus* sp. has been used for the intracellular synthesis of monodisperse gold nanoparticles by Ahmad et al. (2003). In this study it was observed that the concentration of nanoparticles were more on the cytoplasmic membrane. This could have been due to the reduction of metal ions by the enzymes present in the cell wall and on the cytoplasmic membrane but not in the cytosol. The metal ions were also found to be non toxic to the cells which continued to multiply even after the formation of the nanoparticles.

It has been observed that a novel alkalothermophilic actinomycete, *Thermomonospora* sp. synthesized golden nanoparticles extracellularly when exposed to gold ions under alkaline conditions (Sastry et al., 2003). The use of algae for the biosynthesis of nanoparticles is a largely unexplored area. There is very little literature supporting its use in nanoparticle formation. Recently stable gold nanoparticles have been synthesized using the marine alga *Sargassum wightii*. Nanoparticles with a size range between 8 nm and 12 nm were obtained using the seaweed. An important potential benefit of the method of synthesis was that the nanoparticles were quite stable in solution (Singaravelu et al., 2007).

5.3. Use of fungi to synthesize nanoparticles

The fungal mediated MNP synthesis is a relatively recent research area. Fungi have been widely used for the biosynthesis of nanoparticles and the mechanistic aspects governing the nanoparticle formation have also been documented for a few of them. In addition to monodispersity, nanoparticles with well defined dimensions can be obtained using fungi. Compared to bacteria, fungi could be used as a source for the production of large amount of nanoparticles. This is due to the fact that fungi secrete more amounts of proteins which directly translate to higher productivity of nanoparticle formation (Mohanpuria et al., 2008).

Yeast, belonging to the class ascomycetes of fungi has shown to have good potential for the synthesis of nanoparticles. Gold nanoparticles have been synthesized intracellularly using the fungi *Verticillium luteoalbum*. The rate of particle formation and the size of the nanoparticles could to an extent be manipulated by controlling physical parameters such as pH, temperature, concentration of metal (gold) and exposure time. A biological process with this ability to strictly control the shape of the particles would be a considerable advantage (Gericke and Pinches, 2006). Yeast, belonging to the

class ascomycetes has shown to have good potential for the synthesis of nanoparticles. Cells of *Schizosaccharomyces pombe* were found to synthesize semiconductor CdS nanocrystals and the productivity was maximum during the mid log phase of growth. Addition of Cd in the initial exponential phase of yeast growth affected the metabolism of the organism (Kaushik and Dhiman, 2002). Baker's yeast (*Saccharomyces cerevisiae*) has been reported to be a potential candidate for the transformation of Sb_2O_3 nanoparticles and the tolerance of the organism towards Sb_2O_3 has also been assessed. Particles with a size range of 2–10 nm were obtained in this condition.

Extracellular secretion of the microorganisms offers the advantage of obtaining large quantities of materials in a relatively pure state, free from other cellular proteins associated with the organism with relatively simpler downstream processing. Mycelia free spent medium of the fungus, *Cladosporium cladosporioides* was used to synthesize silver nanoparticles extracellularly. It was hypothesized that proteins, polysaccharides and organic acids released by the fungus were able to differentiate different crystal shapes and were able to direct their growth into extended spherical crystals (Balaji et al., 2009). The extracellular synthesis of AgNPs by a marine fungus *Penicillium fellutanum*, isolated from coastal mangrove sediment, has been described by Kathiresan et al. (2009). The extracellular synthesis of stable AgNPs using the fungus *Penicillium brevicompactum* WA 2315 was demonstrated by Shaligram et al. (2009). A single pot green chemical synthesis of AuNP by fungal strain *Rhizopus oryzae* has been reported by Das et al. (2009).

Fusarium oxysporum has been reported to synthesize silver nanoparticles extracellularly. Studies indicate that a nitrate reductase was responsible for the reduction of silver ions and the corresponding formation of silver nanoparticles. However *Fusarium moniliformae* did not produce nanoparticles either intracellularly or extracellularly even though they had intracellular and extracellular reductases in the same fashion as *F. oxysporum*. This indicates that probably the reductases in *F. moniliformae* were necessary for the reduction of Fe(III) to Fe(II) and not for Ag(I) to Ag(0) (Duran et al., 2005). *Aspergillus flavus* has been found to accumulate silver nanoparticles on the surface of its cell wall when challenged with silver nitrate solution. Monodisperse silver nanoparticles with a size range of 8.92 ± 1.61 nm were obtained and it was also found that a protein from the fungi acted as a capping agent on the nanoparticles (Vigneshwaran et al., 2007).

Aspergillus fumigatus has been studied as a potential candidate for the extracellular biosynthesis of silver nanoparticles. The advantage of using this organism was that the synthesis process was quite rapid with the nanoparticles being formed within minutes of the silver ion coming in contact with the cell filtrate. Particles with a size range of 5–25 nm could be obtained using this organism (Bhainsa and D'Souza, 2006).

In addition to the synthesis of silver nanoparticles, *F. oxysporum* has also been used to synthesize zirconia nanoparticles. It has been reported that cationic proteins with a molecular weight of 24–28 kDa (similar in nature to silicatein) were responsible for the synthesis of the nanoparticles (Bansal et al., 2004).

Instead of fungi culture, isolated proteins from them have also been used successfully in nanoparticles production.

Nanocrystalline zirconia was produced at room temperature by cationic proteins while were similar to silicatein secreted by *F. oxysporum* (Mohanpuria et al., 2008).

The use of specific enzymes secreted by fungi in the synthesis of nanoparticles appears to be promising. Understanding the nature of the biogenic nanoparticle would be equally important. This would lead to the possibility of genetically engineering microorganisms to over express specific reducing molecules and capping agents and thereby control the size and shape of the biogenic nanoparticles (Balaji et al., 2009).

The exposure of *Verticillium* sp. to silver ions resulted in a similar intracellular growth of silver nanoparticles (AgNPs) (Mukherjee et al., 2001). The intracellular formation mechanism of AuNPs and AgNPs has not been understood. However, it has been postulated that the gold and silver ions initially bind on the fungal cell surface through electrostatic interaction. The adsorbed metal ions are then reduced by enzymes present in the cell wall, leading to the formation of the metal nuclei, which subsequently grow through further reduction of metal ions. Absar et al. (2005) reported the extra- and intracellular biosynthesis of AuNPs by fungus *Trichothecium* sp. They observed that *Trichothecium* sp. reacted with gold ions during stationary phase and forms extracellular AuNPs of various morphologies, such as spherical, rod-like and triangular. However, under shaking conditions, the same fungal biomass forms intracellular AuNPs under shaking conditions. It was postulated that under shaking condition fungi secretes enzymes and proteins into the medium, however in shaking conditions these enzymes and proteins are not being released, thus resulting in the formation of extracellular or intracellular AuNP, respectively. Fungal templates have been used for noble-MNP synthesis (Bigall et al., 2008). Fungal cells were grown in presence of AuNP. Growth of a variety of fungi, such as *Penicillium citreonigrum*, *Trametes versicolor*, *Fusarium* sp., *Phanaerochaete crysosporium*, *Trichoderma viride*, *Neurospora crassa*, *Nematolona frowardii*, and *Bjerkandera adusta* was tested in citrate-stabilized colloidal medium containing different noble-metal nanoparticles.

Thermomonos sp. reduced the gold ions extracellularly, yielding ANPs (Sastri et al., 2003). Even the edible mushroom *Volvariella volvacea* can produce Au and Ag NPs through metal reducing compounds. The mushroom was boiled initially in water and then filtered. The filtrate was cooled to room temperature and used as reducing agent for AuNPs synthesis. Following reduction purple coloured AuNPs was formed. The mushroom biomass also prevents NPs aggregation after their formation (Philip, 2009).

Microbiological methods generate nanoparticles at a much slower rate than that observed when plant extracts are used. This is one of the major drawbacks of biological synthesis of nanoparticles using microorganisms and must be corrected if it must compete with other methods. Different microorganisms that are capable of synthesizing different nanoparticles are listed in Table 2.

5.4. Use of plants to synthesize nanoparticles

The advantage of using plants for the synthesis of nanoparticles is that they are easily available, safe to handle and possess a broad variability of metabolites that may aid in reduction.

A number of plants (Fig. 4) are being currently investigated for their role in the synthesis of nanoparticles. Gold nanoparticles with a size range of 2–20 nm have been synthesized using the live alfalfa plants (Torresday et al., 2002). Nanoparticles of silver, nickel, cobalt, zinc and copper have also been synthesized inside the live plants of *Brassica juncea* (Indian mustard), *Medicago sativa* (Alfa lfa) and *Heliantus annus* (Sunflower). Certain plants are known to accumulate higher concentrations of metals compared to others and such plants are termed as hyperaccumulators. Of the plants investigated, *B. juncea* had better metal accumulating ability and later assimilating it as nanoparticles (Bali et al., 2006).

Recently much work has been done with regard to plant assisted reduction of metal nanoparticles and the respective role of phytochemicals. The main phytochemicals responsible have been identified as terpenoids, flavones, ketones, aldehydes, amides and carboxylic acids in the light of IR spectroscopic studies. The main water soluble phytochemicals are flavones, organic acids and quinones which are responsible for immediate reduction. The phytochemicals present in *Bryophyllum* sp. (Xerophytes), *Cyprus* sp. (Mesophytes) and *Hydrilla* sp. (Hydrophytes) were studied for their role in the synthesis of silver nanoparticles. The Xerophytes were found to contain emodin, an anthraquinone which could undergo redial tautomerization leading to the formation of silver nanoparticles.

The Mesophytes contain three types of benzoquinones, namely, cyperoquinone, dietchequinone and remirin. It was suggested that gentle warming followed by subsequent incubation resulted in the activation of quinones leading to particle size reduction. Catechol and protocatechaldehyde were reported in the hydrophytes studied along with other phytochemicals. It was reported that catechol under alkaline conditions gets transformed into protocatechaldehyde and finally into protocatecheuic acid. Both these processes liberated hydrogen and it was suggested that it played a role in the synthesis of the nanoparticles. The size of the nanoparticles synthesized using xerophytes, mesophytes and hydrophytes were in the range of 2–5 nm (Jha and Prasad, 2009).

Recently gold nanoparticles have been synthesized using the extracts of *Magnolia kobus* and *Diopyros kaki* leaf extracts. The effect of temperature on nanoparticle formation was investigated and it was reported that polydispersed particles with a size range of 5–300 nm was obtained at lower temperature while a higher temperature supported the formation of smaller and spherical particles (Song et al., 2009). Name of some plants and synthesized nanoparticles are listed in Table 3.

While fungi and bacteria require a comparatively longer incubation time for the reduction of metal ions, water soluble phytochemicals do it in a much lesser time. Therefore compared to bacteria and fungi, plants are better candidates for the synthesis of nanoparticles. Recently, Fahmy et al. introduced fully green nanotechnology as a gateway to beneficiation of natural cellulose fibres (Fahmy and Mobarak, 2008, 2011). Taking use of plant tissue culture techniques and downstream processing procedures, it is possible to synthesize metallic as well as oxide nanoparticles on an industrial

Table 2 – List of microorganisms and synthesized metal nanoparticles.

Microorganisms	Products	Size (nm)	Shape
<i>Sargassum wightii</i>	Au	8–12	Planar
<i>Rhodococcus</i> sp.	Au	5–15	Spherical
<i>Shewanella oneidensis</i>	Au	12 ± 5	Spherical
<i>Plectonemaboryanum</i>	Au	<10–25	Cubic
<i>Plectonema boryanum</i> UTEX 485	Au	10 nm to 6 μm	Octahedral
<i>Candida utilis</i>	Au	Not available	Not available
<i>V. luteoalbum</i>	Au	Not available	Not available
<i>Escherichia coli</i>	Au	20–30	Triangles, hexagons
<i>Yarrowia lipolytica</i>	Au	15	Triangles
<i>Pseudomonas aeruginosa</i>	Au	15–30	Not available
<i>Rhodopseudomonas capsulate</i>	Au	10–20	Spherical
<i>Shewanella algae</i>	Au	10–20	Not available
<i>Brevibacterium casei</i>	Au, Ag	10–50	Spherical
<i>Trichoderma viride</i>	Ag	5–40	Spherical
<i>Phaenerochaete chrysosporium</i>	Ag	50–200	Pyramidal
<i>Bacillus licheniformis</i>	Ag	50	Not available
<i>Escherichia coli</i>	Ag	50	Not available
<i>Corynebacterium glutamicum</i>	Ag	5–50	Irregular
<i>Trichoderma viride</i>	Ag	2–4	Not available
<i>Ureibacillus thermosphaericus</i>	Au	50–70	Not available
<i>Bacillus cereus</i>	Ag	4–5	Spherical
<i>Aspergillus flavus</i>	Ag	8.92 ± 1.61	Spherical
<i>Aspergillus fumigatus</i>	Ag	5–25	Spherical
<i>Verticillium</i> sp.	Ag	25 ± 8	Spherical
<i>Fusarium oxysporum</i>	Ag	5–50	Spherical
<i>Neurospora crassa</i>	Au, Au/Ag	32, 20–50	Spherical
<i>Shewanella algae</i>	Pt	5	Not available
<i>Enterobacter</i> sp.	Hg	2–5	Spherical
<i>Shewanella</i> sp.	Se	181 ± 40	Spherical
<i>Escherichia coli</i>	Cd/Te	2.0–3.2	Spherical
Yeast	Au/Ag	9–25	Irregular polygonal
<i>Fusarium oxysporum</i>	Au-Ag alloy	8–14	Spherical
<i>Pyrobaculum Islandicum</i>	U(VI), Tc(VII), Cr(VI), Co(III), Mn(IV)	N/A	Spherical
<i>Desulfovibrio desulfuricans</i>	Pd	50	Spherical

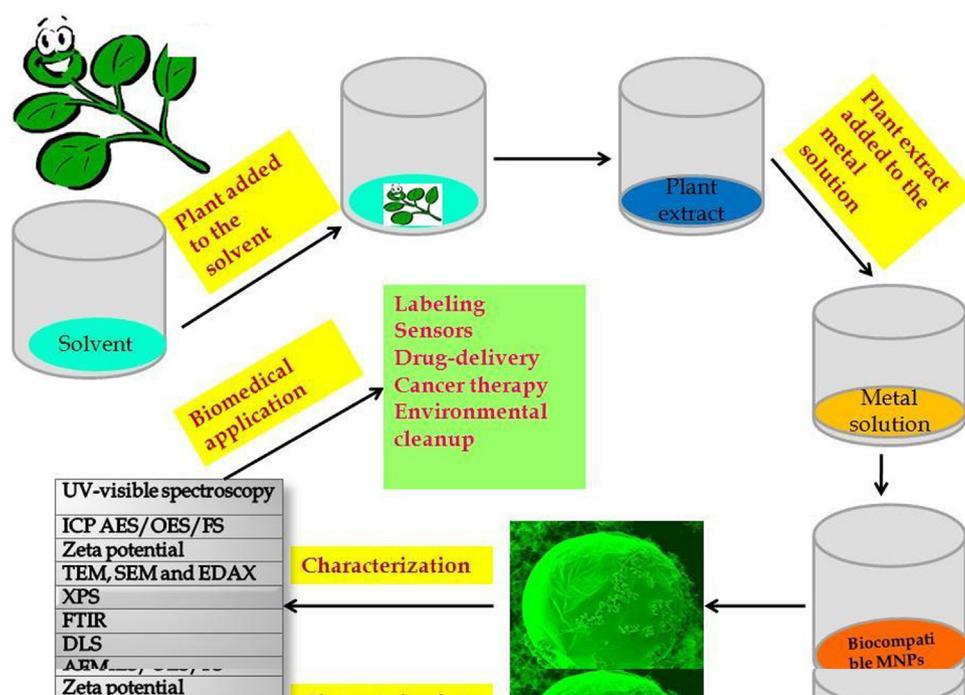
**Fig. 4 – A schematic representation of plant as a source of green nanosynthesis, its characterization and biomedical application.**

Table 3 – Name of some plants and synthesized nanoparticles.

Plants	Nanoparticles	Shape	Size
Alfalfa plant (<i>Medicago sativa</i>)	Au and Ag	Spherical and triangular	20–40 nm
<i>Avena sativa</i>	Au	Spherical	25–85 nm
<i>Azadirachta indica</i>	Ag, Au and Ag/Au bimetallic	Spherical	50–100 nm
<i>Aloe vera</i>	Ag	Spherical	15–15.6 nm
<i>Emblica officinalis</i>	Ag & Au	Mainly spherical	10–20 nm and 15–25 nm respectively
<i>Cinnamomum camphora</i>	Au & Ag	Mainly spherical	55–80 nm
Tamarind leaf extract	Au nanotriangles	Mainly spherical	20–40 nm
<i>Capsicum annum</i>	Ag Nanoparticles	Mainly spherical	16–40 nm
<i>Medicago sativa</i>	Ti/Ni bimetallic	Mainly spherical	2–6 nm
<i>Medicago sativa</i>	Zn	Spherical	2–5.6 nm

scale once issues like the metabolic status of the plant etc. are properly addressed.

Recently, scientists in India have reported the green synthesis of silver nanoparticles using the leaves of the obnoxious weed, *Parthenium hysterophorus*. Particles in the size range of 30–80 nm were obtained after 10 min of reaction. The use of this noxious weed has an added advantage in that it can be used by nanotechnology processing industries (Parasar et al., 2009). *Mentha piperita* leaf extract has also been used recently for the synthesis of silver nanoparticles. Nanoparticles in the size range of 10–25 nm were obtained within 15 min of the reaction (Parasar et al., 2009). *Azadirachta indica* leaf extract has also been used for the synthesis of silver, gold and bimetallic (silver and gold) nanoparticles (Tripathi et al., 2009). Studies indicated that the reducing phytochemicals in the neem leaf consisted mainly of terpenoids. It was found that these reducing components also served as capping and stabilizing agents in addition to reduction as revealed from FT IR studies. The major advantage of using the neem leaves is that it is a commonly available medicinal plant and the antibacterial activity of the biosynthesized silver nanoparticle might have been enhanced as it was capped with the neem leaf extract. The major chemical constituents in the extract were identified as nimbin and quercetin (Shankar et al., 2004; Tripathi et al., 2009).

6. Bio-inspired green nanoparticles over chemically synthesized nanoparticles

In keeping with global efforts to reduce generation of hazardous waste and to develop energy-effective production routes, 'green' chemistry and biochemical processes are progressively integrating with modern developments in science and technology. Hence, any synthetic route or chemical process should address the fundamental principles of 'green chemistry' by using environmentally benign solvents and nontoxic chemicals (Anastas and Warner, 1998). The green synthesis of MNPs should involve three main steps based on green chemistry perspectives, namely (1) the selection of a biocompatible and nontoxic solvent medium, (2) the selection of environmentally benign reducing agents, and (3) the selection of nontoxic substances for stabilization of the nanoparticles. Employing these principles in nanoscience will facilitate the production and processing of inherently safer

nanomaterials and nanostructured devices. Green nanotechnology (Dahl et al., 2007) thus aims to the application of green chemistry principles in designing nanoscale products, and the development of nanomaterial production methods with reduced hazardous waste generation and safer applications.

Further, biochemical processes can occur at low temperatures, because of the high specificity of the biocatalysts. Hence, a synthetic route that include one or more biological steps will result in consistent energy saving and lower environmental impact with respect to conventional methods. To optimize safer nanoparticle production, it would be desirable to employ bio-based methods, which could minimize the hazardous conditions of material fabrication. Taking inspiration from nature, where living organisms produce inorganic materials through biologically guided process known as biomineralization, should be adopted as a superior approach to nanomaterials assembly (Mann, 1993). The biomineralization processes exploit biomolecular templates that interact with the inorganic material at nanoscale, resulting in extremely efficient and highly controlled syntheses. The structures of these biocomposite materials are highly controlled both at nano- and macroscale level, resulting in complex architectures that provide multifunctional properties.

Simpler organisms, such as bacteria, algae, and fungi, have also developed highly specialized strategies for biominerals synthesis through hundreds of millions of years of evolution. The role of the templating molecule in biomineralization is to provide a synthetic microenvironment in which the inorganic phase morphology is tightly controlled by a range of low-range interactions.

7. Applications of metal nanoparticles in medical biology

The reason why these nanoparticles are attractive for medical purposes is based on their important and unique features such as surface to mass ratio that is much larger than that of other particles, their quantum properties and their abilities to adsorb and carry other compounds such as drugs, probes and protein. In the ever expanding field of nanomaterial research, metal nanoparticle received particular attention due to their wide application (Fig. 5) in catalysis, electronics, sensing, photonics, environmental cleanup, imaging, and drug delivery (Guo et al., 2005; Daniel and Astruc, 2004; Huang et al., 2007).

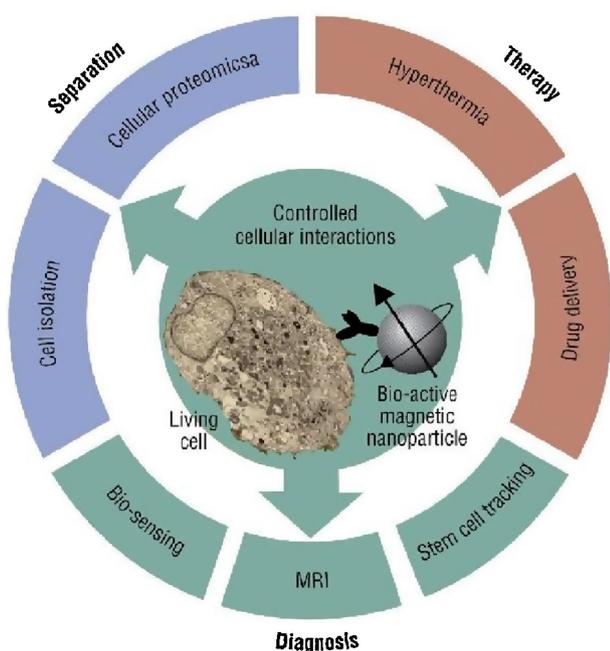


Fig. 5 – A schematic representation on biological application of green nanomaterials.

7.1. Catalysis

The application of nanoparticles as catalysts is a rapidly growing field in nanoscience and technology. The properties of noble metal nanoparticles make them ideal materials for nanocatalysis, where reaction yield and selectivity are dependent on the nature of the catalyst surface. Compared to bulk materials, nanoparticles have high surface-area-to-volume ratio and thus found to exhibit higher turnover frequencies. The catalytic activity of Au, Ag and Pt in the decomposition of H_2O_2 to oxygen is well known. Additionally they also catalyze luminal- H_2O_2 systems. It was observed that the chemiluminescence emission from the luminal- H_2O_2 system was greatly enhanced by addition of Ag colloid (Guo et al., 2008). The catalytic application of Ag in oxidation of ethylene to ethylene oxide and methanol to formaldehyde is also the most popular.

More interestingly, the nanoparticles shows shaped controlled catalytic activity. The shape-controlled catalytic properties have recently been observed in benzene hydrogenation by Pt catalyst (Brown and Hutchison, 1997). Among different Pt nanocrystals (cubes, tetrahedral, and spheres) tetrahedral nanocrystals, completely bound by crystal facets, exhibited highest catalytic activity whereas cubic nanocrystals exhibit the lowest activity. However, it is not clearly understood whether this observation is truly a shape-dependent effect, as in solution the surface reconstruction and shape changes of NPs is evident. To study the dynamics of adsorbents on solution phase nanocrystalline structures is required for direct surface measurements analogous to those commonly used for single-crystalline studies.

Among other metal catalysts, Au has potentially more advantages due to its lower cost and greater stability. Au

is substantially cheaper and more plentiful than Pt. AuNP, less than 5 nm supported on base metal oxide or carbon demonstrated very high activity (Hvolbek et al., 2007). High activity of AuNP for the oxidation of many compounds, particularly CO and trimethylamine are also observed. AuNP based gas sensors have recently been developed for detecting a number of gases, including CO and NOx (Thompson, 2007). Very recently Zeng et al. (2010) also demonstrated shape controlled catalytic activity of AuNPs for well known p-nitro phenol reduction in presence of sodium borohydride. Gold nanoboxes among other nanostructure (nanocages, and solid nanoparticles) have highest catalytic activity. The good intrinsic electrical connection across the entire surface of an Au nanocage makes it a much better catalyst than small Au solid nanoparticles for the redox reaction.

7.2. Biological application of metal nanoparticles

The application of metal nanoparticles in biological science showed very rapid progress in the area of labelling, delivery, heating, and sensing in the past decades. The SPER optical properties of colloidal AuNPs directed towards recent biomedical applications with an emphasis on cancer diagnostics and therapeutics.

7.2.1. Labelling

For labelling, electron absorbing properties of the metal nanoparticles are exploited to generate contrast. The AuNPs strongly absorb electrons, thus make them suitable as a contrasting agent in TEM. Besides, nanoparticles have the same size domain as proteins that make nanomaterials suitable for bio tagging or labelling (Sperling et al., 2008). Due to their small size and functionalising properties, i.e. with antibodies (immunostaining), AuNPs provide extremely high spatial resolution and applied in many labelling applications (Salata, 2004). Additionally optical detection techniques are wide spread in biological research because of change of their optical or fluorescence properties. Similarly, the particles' optical properties – strong absorption, scattering and especially plasmon resonance – make them of value for a large variety of light-based techniques including combined schemes such as photothermal or photo-acoustic imaging. In addition, AuNP can be radioactively labelled by neutron activation, which allows for very sensitive detection, and used as an X-ray contrast agent.

7.2.2. Sensors

Metal nanoparticles can also be used as sensors. The optical and electronic sensing of biomaterials on surfaces is a common practice in analytical biochemistry. Thus, the immobilization of biomolecule-NP conjugates on surfaces provides a general route for the development of optical or electronic biosensors. Metal NPs such as Au or Ag NPs exhibit plasmon absorbance bands in the visible spectral region that are controlled by the size of the respective particles. Their optical properties can change upon binding to certain molecules, allowing the detection and quantification of analytes (Huo, 2007). The absorption spectra of AuNP change drastically when several particles come close to each other. Numerous studies on the labelling of bioassays and the staining of

biological tissues by metal particles as a means to image and visualize biological processes have been reported. The spectral shifts which originate from adjacent or aggregated metal nanoparticles, such as Au NPs, are of increasing interest in the development of optical biosensors based on biomolecule–NP hybrid systems. As an example, NPs that were functionalized with two kinds of nucleic acid, which were complementary to two segments of an analyzed DNA, were hybridized with the analyzed DNA. This led to the aggregation of the NPs and to the detection of a red shifted interparticle plasmon absorbance of the nanoparticle aggregate.

7.2.3. Drug delivery

Because of nontoxicity and nonimmunogenicity AuNPs is ideal for preparation of drug delivery scaffold. Functionalization property of AuNP also makes it an excellent potential vehicle for the drug delivery. Functionalized AuNP represent highly attractive and promising candidates in the applications of drug delivery. [Aubin-Tam and Hamad-Schifferli \(2008\)](#) recently developed drug delivery system with AuNPs and infrared light. This delivery system released multiple drugs in a controlled fashion. They demonstrated that nanoparticles of different shapes respond to different infrared wavelengths. For example, nanobones and nanocapsules melt at light wavelengths of 1100 and 800 nm, respectively. Thus excitation at one wavelength could selectively melt one type of Au nanorods and selectively release one type of DNA strand. [Brown et al. \(2010\)](#) also reported AuNPs for the improved anticancer drug delivery of the active component of oxaliplatin. Naked AuNPs were functionalized with a thiolated poly(ethylene glycol) (PEG) monolayer capped with a carboxylate group. $[\text{Pt}(\text{1R},\text{2Rdiaminocyclohexane})(\text{H}_2\text{O})_2]\text{2NO}_3$ was added to the PEG surface and yielding a supramolecular complex with drug molecules. The cytotoxicity, drug uptake, and localization in the A549 lung epithelial cancer cell line and the colon cancer cell lines HCT116, HCT15, HT29, and RKO were examined for platinum-tethered nanoparticles. The platinum-tethered nanoparticles showed significant improvement in cytotoxicity than oxaliplatin alone in all of the cell lines and an unusual ability to penetrate the nucleus in the lung cancer cells.

7.2.4. Cancer therapy

Nanotechnology is one of the most popular research areas, especially with regard to biomedical applications. Nanoparticles have very good opportunity in the form of targeted drug therapies ([Ghosh et al., 2008](#)). Nanoparticles also carry the potential for targeted and time-release drugs. A potent dose of drugs could be delivered to a specific area but engineered to release over a planned period to ensure maximum effectiveness and the patient's safety. The strong light absorbing properties of AuNPs makes it suitable as heat mediating objects; the absorbed light energy is dissipated into the surroundings of the particles', generating an elevated temperature in their vicinity. This effect can be used to open polymer microcapsules, for example, for drug delivery purposes and even destroys the cancerous cells. The nanoparticles are functionalized with antibody specific to the cancerous cells. The functionalized nanoparticles specifically bind with the targeting cells, which was then killed by hyper thermal therapy

through heating the particle-loaded tissue. However, for such in vivo applications, the potential cytotoxicity of the nanoparticles might become an issue and should be investigated with care. Due to biocompatibility, hyper thermal activity AuNPs find wide application now-a-days in killing of malignant cancerous cells ([Dickerson et al., 2008](#)). Recently, [Melancon et al. \(2008\)](#) demonstrated destruction of cancerous cell by photothermal effect of AuNPs. The hollow gold nanoshells (HAuNS; average diameter, ~30 nm) were covalently attached to monoclonal antibody directed to the epidermal growth factor receptor (EGFR). The resulting anti-EGFR-HAuNS exhibited excellent colloidal stability and efficient photothermal effect in the near-infrared region. Anti-EGFR-HAuNS then bound in EGFR-positive A431 tumour cells. Irradiation of A431 cells treated with anti-EGFR-HAuNS with near-infrared laser resulted in selective destruction of these cells.

AuNPs has also been applied to amplify the biorecognition of the anticancer drug ([Shen et al., 2008](#)). Dacarbazine [5-(3,3-dimethyl-1-triazenyl) imidazole-4-carboxamide; DTIC] is a commonly used anticancer drug. AuNPs were stabilized by PPh3 with negative charge. The oxidized DTIC is positive charged. Thus, DTIC could be easily assembled onto the surface of AuNPs. The specific interactions between anticancer drug DTIC and DNA or DNA bases were facilitated by AuNPs.

7.3. Environmental cleanup as defense against environmental challenge to medical biology

Although MNPs are increasingly being employed in different emergent areas, their use in environmental biotechnology is still limited. One of the key environmental challenges is the contamination of water bodies by different chemicals due to diverse anthropogenic and industrial activities. The most interesting application of MNPs is purification of drinking water contaminated with heavy metals and pesticides. Current limitations in removal of heavy metals have been tried to overcome through adsorption process on MNPs due to alloy formation. Au and mercury exist in several phases such as Au_3Hg , AuHg , and AuHg_3 .

The interaction of AgNPs with Hg^{2+} ions was investigated because enhanced ability of Ag to form alloy in different phases. It was found that the surface plasmon of AgNPs blue shifted along with a decrease in the intensity, immediately after the addition of Hg^{2+} ions ([Bootharaju and Pradeep, 2010](#)). Partial oxidation of AgNPs to silver ions is responsible for the decrease in intensity. The shift is attributed to the incorporation of mercury into the AgNPs. The mercury nanoparticle solutions exhibited plasmon absorption band below 300 nm. The Hg–Ag alloy nanoparticles, prepared by simultaneous reduction with sodium borohydride, exhibited a plasmon in the region of 300–400 nm. The potential of AgNPs to reduce a number of heavy metals can also be looked at as a method to prepare alloy nanoparticles; e.g., Ag–Hg bimetallic nanoparticles.

Recently colorimetric detections of heavy metals like arsenic, mercury, lead, etc., have also been tried by using MNPs. One of the important properties exhibited by functionalized MNPs surfaces is the detection of heavy metals. In one such method, heavy metal specific biomolecule functionalized AuNP can be utilized. An example of this approach is

the interaction of metal ions with nucleotides: Hg^{2+} promoted formation of thymine–thymine base pairs (Ono and Togashi, 2004). In a similar approach, ligands functionalized MNPs have been used for specific detection of metal ions. This ligand-metal ion complexation leads to observable optical changes at concentrations in the ppm level. Examples of such ligands are gallic acid (Pb^{2+}), cysteine (Hg^{2+} , Cu^{2+}), and mercaptoundecanoic acid (Pb^{2+} , Cd^{2+} , Hg^{2+}). Carboxylate group modified surface of AuNP can be induced to aggregate in the presence of Hg^{2+} and pyridinedicarboxylic acid, which is manifested in the form of colorimetric response, fluorescence quenching and enhancement of hyper-Rayleigh scattering intensity (Huang et al., 2007; Darbha et al., 2008).

The removal of pesticides by MNPs is a new addition to this field. Among other contaminants, presence of pesticide residue in potable water above permissible limit is of great concern to public health. This happens due to indiscriminate use of pesticide, specially belonging to organophosphorus groups, in agricultural practices. It is essential to reduce the concentration of pesticide in potable water but difficult to achieve by conventional chemical methods due to wide variation of their chemical structures. To meet these environmental challenges, very recently researchers are focusing on the development of methods based on nanotechnology. Very recently, Das et al. (2009) demonstrated adsorption of different organophosphorous pesticides on AuNPs surface. AuNPs was synthesized on the surface of the *R. oryzae* mycelia in a single set. The AuNPs adsorbed on mycelia were then used for adsorption of different organophosphorous pesticides. Following adsorption of these pesticides the surface morphology conspicuously changed compared the unadsorbed nanomaterial as depicted from atomic force microscopic images.

8. Conclusions

In this review, we provided an account of the biological methods for MNPs (green nano) synthesis, as well as their most promising applications in biomedical devices and in environmental processes. From the considerations as outlined in this review, it emerges that biosynthesis represents a promising route for MNPs production. In fact, biosynthesis results in low energy use and environmental impact, with respect to conventional chemical synthesis methods. Further, the high specificity of biomolecules involved in the biosynthesis process may enable an efficient control of MNPs size and shape, whose tight control is critical to optimize MNP-based devices and applications. Current nanotoxicological research aims to identify the physico-chemical characteristics of NPs responsible for the observed health effects. These results could be incorporated in the design of new engineered NPs. The challenge is to produce new nanomaterials that are without adverse characteristics and still fulfil the industrial requirements. This approach would have the advantage of initiating a sustainable and safe nanotechnology.

Biosynthetic MNPs have been observed in numerous fungal and bacterial species, and the molecular machinery needed for MNPs biosynthesis overlap significantly with the developed and optimized system for bioreduction and

detoxification of soluble metals. However, most published studies deal with MNP biosynthesis in viable microorganism, and the complexity of the system makes it difficult to identify the exact nature of the multiple biological agents responsible for the biosynthetic process. Further research with cell-free extract and biological fractions may lead to this identification and thorough understanding of the complex regulatory processes underlying the expression of metal reducing agents. Many green nanomaterials require new commercial production techniques, which increases the need for basic research, engineering research, and coordination of the two between the industrial and research communities. Toxicology and analysis protocols need to be developed and constantly updated to reflect advances in the science.

Little development in the field is being specifically targeted towards sustainability. This is a problem because the opportunity to develop green processes from the beginning is not being taken. The transformation to sustainable development is an enormous economic opportunity. Moreover, past achievement aimed at being able to watch the next generation prosper has come via terribly destructive methods. What is needed now is redevelopment – a paradigm shift in the approaches in providing aids to medical sciences. Clearly if nanotechnology is to be the key to the future, it should be developed with sustainability in mind from the outset.

Conflict of interest

There is no conflict of interest regarding the publication of this review in any journal between the authors, funding agencies or the host institute.

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