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REVIEW

Biogenesis of metal nanoparticles and their pharmacological applications: present status and application prospects

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Abstract

Green chemistry approaches for the synthesis of metallic nanoparticles have become a new and promising field of research in recent years. Synthesis of metal nanoparticles [like gold (Au), silver (Ag), lead (Pb), platinum (Pt), copper (Cu), iron (Fe), cadmium (Cd), and other metal oxides such as titanium oxide (TiO), zinc oxide (ZnO), etc.] by various chemical and physical approaches as well as the biological approaches mediated by number of microorganisms have been actively found. Plant-mediated synthesis approaches are found to be more reliable and economic route to synthesize these metal nanoparticles. Owing to the biodiversity of plant biomasses, the actual mechanism by which the plant constituents have contributed to the synthetic process is yet to be fully known. Although the feasibility of controlling, the size and shape of nanoparticles by variation in reaction conditions have been demonstrated in many studies. Conventionally, nanoparticles are synthesized by chemicals and physicochemical methods using several chemicals which later on become accountable for various risk due to their general toxicity, so that solving the objective biological approaches is coming up to fill these gaps. The plant-mediated synthesis process undergoes highly controlled approaches for making them suitable for metal nanoparticle synthesis. In addition, biological synthesis of metallic nanoparticles is inexpensive, one-step, and eco-friendly method. In addition, the plant-mediated nanoparticles are used as potential pharmaceutical agents for various diseases such as malaria, HIV, cancer, hepatitis, and other diseases. Including this some other relevant information regarding nanopharmaceutical products, companies that are involve in the manufacturing and commercialization process and their clinical trial status are also discussed. This review article gives an overview of the plant-mediated synthesis of metal nanoparticles, possible compounds, and mechanisms that might be responsible for the reduction process as well as the potential pharmacological applications, currently available nanopharmaceutical products and their marketing status.

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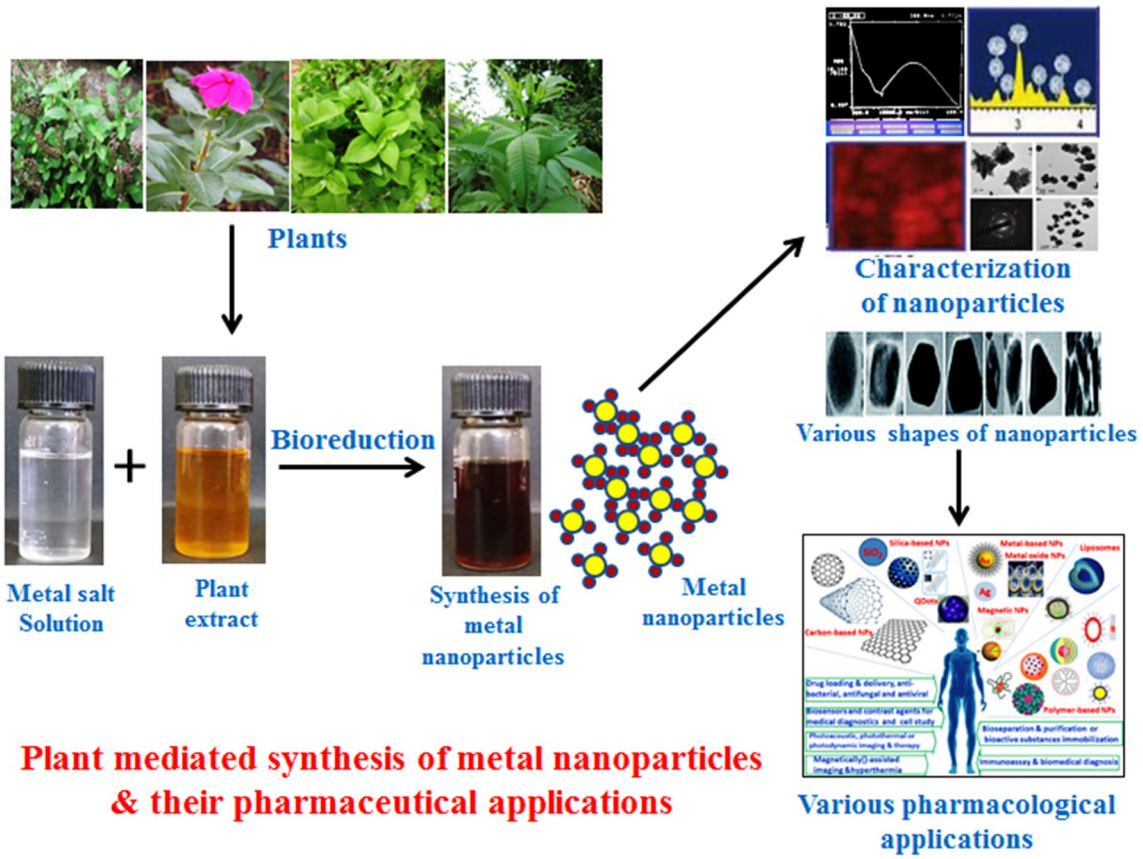
Graphical abstract



Keywords Biogenesis · Metal nanoparticles · Plant extracts · Pharmaceutical applications

Abbreviations

Nm	Nanometer
NIR	Near infra-red
kDa	Kilodalton
Au	Gold
Ag	Silver
Cu	Copper
Cd	Cadmium
CdS	Cadmium sulphide
Si	Silicon
Al	Aluminium
Zn	Zinc
Pb	Lead
Pd	Palladium
AsS	Arsenic sulphide
HIV	Human immunodeficiency virus

Introduction

Nanotechnology is one of the most effective and novel area of research in modern material science. This field of science is developing day by day and is making a valuable impact in the life science, specially biotechnology and biomedical science. Nanoparticle exhibits completely new properties, as they contain specific characteristics such as shape, size, and distribution. A number of processes are available for the biosynthesis of nanoparticles for, e.g., reduction in solution, radiation aspired, electrochemical, and microwave-assisted process and recently via green chemistry route [1]. The use of biological materials like plant extracts (leaves, flower, stem bark, fruit peels, seed, etc.), fungi, bacteria, and algae for the synthesis of nanoparticles offers a numbers of benefits of eco-friendlyness and compatibility for pharmaceuticals and other biomedical applications, as they do not require toxic chemical for the synthesis process [2]. Biosynthesis of nanoparticles is more unique and reliable not only because of its less toxicity as compared to some of physicochemical

production methods but also because it can be used to produce large quantities of nanoparticles that have well shape and size and are also free of combination [3]. The biological synthesis approaches may actually produce nanoparticles of a better defined size and morphology as compared to some of other physicochemical methods of production [4].

For the reduction of metal ions, use of plant extracts has been known since the early 1900s; however, the nature of the reducing agents involved in this method is still not well understood. Due to its simplicity, the use of plant or whole plant extract and plant tissue for reduction of metal ions has attracted significant attention within the last 30 years [5]. Use of plant extracts for making nanoparticles is quite simple and easy as compare to use of whole plant extracts and plant tissues. A diverse range of plant species has been reported for synthesis of metal nanoparticles. In plant extracts, some biomolecules are found which can be reducing metal ions to nanosized materials by a single-step mediated green synthesis approaches. In bioreduction process of metal ions, the plant-based biogenic reducing agents involve including the several water-soluble plant metabolites (like flavonoids, terpenoids, alkaloids, and phenolic compounds) and co-enzymes. This is due to the fact that various plant extracts contain different combinations and concentrations of organic reducing agents [6]. Plant extracts may be act as a reducing agent and stabilizing agent during synthesis of nanoparticles. Process for making plant extracts is readily extensible and may be cheaper process as compared to the other relatively expensive methods based on microbial processes [7] and whole plants [8]. Live plants can also be used for the synthesis of nanoparticles in addition to plant extracts [2]. Usually, a plant extract-mediated reduction involves the addition of aqueous extract with an aqueous solution of the corresponding metal salt. Reaction occurs at room temperature and it is completed within a very few minutes.

Due to the unique properties of metal nanoparticles like large fraction of surface atoms, large surface energy, spatial confinement, and reduced morphology make it significantly different from the corresponding bulk materials. These unique properties of nanoparticles make them applicable in the field of catalysis, agriculture, electronics, biomedical analysis [9], and even ground water purification [10]. Gold, silver, copper, iron, zinc, and other metal nanoparticles are used in food packaging, wound dressings, catheters for drug delivery, and so on due to the broad range of antimicrobial effects. Silver nanoparticles are known to be mostly used in the field of biomedical science due to their great antimicrobial effect; zinc and titanium nanoparticles are known to be used in cosmetics. The second application area of biological nanoparticles is the formulation of biosensors for various molecules related to environmental factors and agriculture. In addition, nanoparticles are also used in gene delivery and cell labelling in plants and in medicine [11]. Other applications of metal nanoparticles are still under research and in development, such as magnetically responsive drug delivery, photoimaging, and photothermal therapy. Nowadays, due to the physicochemical properties and the application of nanoparticles in many fields of sciences, scientific community decided to make extensive efforts to develop a novel route for producing nanoparticles. Although other physicochemical approaches cause environmental pollution by discharging heavy metals during synthesis process. Thus, the synthesis of nanoparticles using green approaches has the several advantages like non-toxicity, reproducibility in production, having easy scaleup, and well-defined morphology becomes new trends in nanoparticles synthesis [12]. In recent years, plants and microbes have found as new resources with considerable synthesis of organic metal nanoparticles [13]. In this review paper, we review the methods of making nanoparticles using different plant extracts, possible mechanism of nanoparticle synthesis, and their pharmaceutical applications, and products available in the market their clinical trial status are also reviewed.

Classical approaches for the synthesis of metal nanoparticles

Nanoparticles are frequently synthesized by either top–down or bottom–up approaches. Top–down approach is based on the mechanical methods of size reduction by breaking down the bulk materials gradually to nanosized structures. Bottom–up approaches are based on the assembly of atoms or molecules to molecular structure in nanoscale range [16]. Figure 1 shows the various methods for synthesis of metal nanoparticles. In top–down synthesis, nanoparticles are

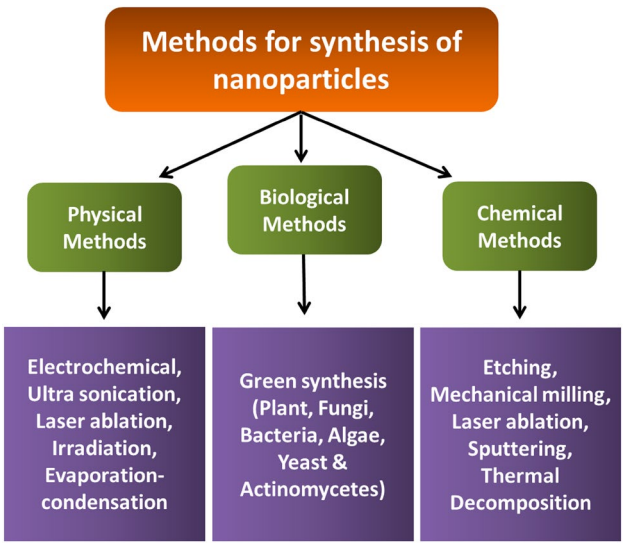


Fig. 1 Different methods for synthesis of metal nanoparticles

produced by their size reduction from a suitable starting material. This reduction in size may be achieved by various physical and chemical treatments. In top–down approaches, there will be imperfection in the surface structure of the product and is found which is a major limitation, because the surface chemistry and the other physical properties of nanoparticles mainly depend on the surface structure [14]. In bottom–up approach, nanoparticles are made up of smaller molecules for, e.g., by joining the atoms, molecules, and smaller structures [15]. In this the nanostructure, building blocks of the nanoparticles are formulated first and then assembled to produce the final particle [14]. Both chemical and biological approaches of metal nanoparticles depend on the bottom–up approaches [16]. In bottom-to-top approaches, synthesis of metal nanoparticles is achieved by chemical reduction method [15]. During this type of synthesis process, chemicals involved are toxic in nature and also led to non-ecofriendly by-products. Due to all these disadvantages of synthesis process, these are generally not employed for the synthesis of metal nanoparticles. Methods commonly used for the synthesis of nanoparticles are as follows:

Physical method of nanoparticle synthesis

Physical methods of synthesis of nanoparticles include UV irradiation, sonochemistry, laser ablation and radiolysis, and so on. It is found that during physical synthesis process, evaporization of metal atoms takes place, followed by condensate on various supports, in which the metallic atoms are rearranged and aggregated as small clusters of metallic nanoparticles [15]. Using physical approaches, we can get nanoparticles with high purity and definite shape. However, these processes are usually required highly sophisticated instruments, chemicals and radiative heating as well as high power consumption, which lead to high operating cost.

Chemical method of nanoparticle synthesis

Another method for the synthesis of nanoparticle is reduction of metal ions in solution using chemicals. On the basis of conditions of reaction mixture, metal ions may favour either the process of nucleation or aggregation to form small clusters of metals. The chemicals generally used as reducing agents are hydrazine, sodium borohydride, and hydrogen [17]. Some stabilizing agents like synthetic or natural polymers such as cellulose, natural rubber, chitosan, and co-polymers micelles are also used. These chemicals are hydrophobic in nature, so that they require the addition of some organic solvents such as ethane, dimethyl, formaldehyde, toluene, and chloroform. These chemicals are toxic in nature and are non-biodegradable, which limit the production scale. Along with this, some of the toxic chemicals may also contaminate the surface of nanoparticles and make them unsuitable for certain biomedical applications [18]. In this context to eliminate all these drawbacks of physical and chemical methods, scientists and researchers are focused on alternative process of metal nanoparticle synthesis.

Biological method of nanoparticle synthesis

In recent years, biogenic synthesis process of metallic nanoparticle has attracted considerable attention. In biogenic synthesis process, the synthesis of nanoparticles is achieved through microorganisms and plants [6]. The biosynthesis may actually provide nanoparticles of a better defined size and morphology as compared to some of other physicochemical methods of production [8]. It has been found that the microbial-based synthesis process is readily scalable, eco-friendly, and compatible with the use of product for pharmacological applications, but production through microorganisms is often more expensive than the production of plant-based materials. The main benefit of plant-based synthesis approaches over classical chemical and physical method is more eco-friendly, cheaper, and easily scale-up process for the large-scale synthesis of nanoparticles other than there is no need of to use high temperature, pressure, and toxic chemicals [19]. A large number of research papers have been reported on biological synthesis of metal nanoparticles using microbes like bacteria, fungi, algae, and plants (Table 1). This is due to their reducing or antioxidant properties that are responsible for the reduction of, respectively, metal nanoparticles. In addition, it is found that microbe-mediated synthesis is not applicable for large-scale production, because they require high aseptic condition and special maintenance, so that the use of plants for the synthesis of nanoparticles is more beneficial over microorganisms due to the easy scale-up process, no additional requirement of maintaining cell culture [20]. Use of plant extract for nanoparticle synthesis also reduces the additional requirement of microorganism isolation and culture medium preparation, which increases the cost-competitive practicability over nanoparticle synthesis by microorganisms. Plant-mediated synthesis is a one-step process towards synthesis, whereas microorganisms during the cause of time may lose their ability to synthesize nanoparticles due to mutation; thus, research on plant is expanding rapidly [9]. A number of synthesis process have been developed including chemical reduction of metal ions in aqueous solutions with or without stabilizing agents, thermal decomposing in organic solutions.

Green synthesis of metal nanoparticles using plant extracts

Biosynthesis of nanoparticles is an approach that is compatible with green chemistry approaches in which the biomolecules secreted by the biomass can act as both reducing

Table 1 Nanoparticle biosynthesis using different sources and their possible mechanism

Biomass	Possible mechanism of nanoparticle biosynthesis	References
(A) Plants Leaves Stems Roots Shoots Flowers Barks Seeds	Secondary metabolites (alkaloids, flavonoids, saponins, steroids, tannins and other nutritional compounds) acts as reducing and stabilizing agents	[132]
(B) Algae Macro algae Micro algae	Polysaccharides have hydroxyl groups and other functionalities that can play important roles in both the reduction and the stabilization of nanoparticles	[8, 163]
(C) Fungi	Reducing enzyme intracellularly or extracellularly and the procedure of biomimetic mineralization	[54]
(D) Yeast	Membrane bound (as well as cytosolic) oxido reductases and quinones	[164]
(E) Bacteria	The microbial cell reduces metal ions by use of specific reducing enzymes like NADH-dependent reductase or nitrate dependent reductase	[56]

and stabilizing agents during the reaction. In recent years, plant-based synthesis of nanoparticles gained much attention due to its rapidity and its simplicity [21]. In nanoparticle synthesis using plant extracts, the extract of plant is simply mixed with the aqueous solution of the metal salt at room temperature, so that these processes can be considered as a green synthesis approach [22]. The actual mechanism for the synthesis of nanoparticle remains the same for microorganisms and plants both. Metal salts consisting of metal ions are first reduced by atoms by means of reducing agents. The obtained atoms then aggregated and form small clusters that grow into particles [23].

Several studies have been done on this area. In this aspect, Gardea and Torresdey reported possibility of using live plant *Alfa alfa* for the bioreduction of gold nanoparticles. They found that live plants successfully synthesize gold nanoparticles with size ranging from 6 to 10 nm [24, 25]. *Brassica juncea* and *Medicago sativa* were also used to produce gold nanoparticles at room temperature [26]. Similarly, Liu et al. [27] synthesized gold nanoparticles using extracts of *Chrysanthemum* and tea beverages. Apart from these, gold nanoparticles were also synthesized using buds of *Syzygium aromtaicum*. Synthesized gold nanoparticles were crystalline in nature and were 5–100 nm in size. Later, researchers found that flavonoids present in buds were responsible for the synthesis of gold nanoparticles [28]. A large number of plants are reported for biosynthesis of metal nanoparticles, which are mentioned in Table 2, and are discussed briefly in this review paper.

The agricultural wastes are usually throughout and their application is not investigated so much so far. Banana peels are examples of such a kind of abundantly available natural material. We usually discarded the banana peels, but recently, it is found that banana peel extracts can also be used for the synthesis of gold nanoparticles. Nowadays, researchers tried to utilize all these waste materials for the synthesis process. Gold nanoparticles synthesized by banana peel extract were found to be highly stable and have a size range of 300 nm, which is confirmed by the different molecular techniques [29]. Similarly, *Mentha piperita* extract was also used to synthesize round-shaped gold nanoparticles and showed antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli* [30]. *Coriandrum sativum* (family: Apiaceae) leaf extract when exposed to the aqueous solution of gold metal ions resulted in the extracellular formation of gold nanoparticles with spherical, triangle, truncated triangles, and decahedral morphologies [31].

Synthesis of gold and silver nanoparticles has been successfully achieved using leaf extract of *Aloe vera* [32] and *Camellia sinensis* [33]. Obtained results suggested that the optical properties of nanoparticles mainly depend on the initial concentration of the metal salts and the *C. sinensis* extract. *C. sinensis* extract contains caffeine and theophylline which may have contributed to reduction of the metal ions and formation of the nanoparticles. Production of spherical- and triangular-shaped silver and gold nanoparticles using the fruit extract of *Tanacetum vulgare* was achieved by Dubey et al. [34]. FTIR analysis of this revealed that the carbonyl groups were involved in the reduction of metal ions. It is also reported that the zeta potential of the silver nanoparticles has shown to variation when pH is varying, and a low zeta potential is recorded at strongly acidic pH [34]. Large size of nanoparticles can also be achieved by reducing the pH of the reaction.

In another study, Banerjee and Narendhirakannan [35] synthesize silver nanoparticles using *Syzygium cumini* seed extract as a reducing agent. They also studied their antioxidant activities. The synthesized nanoparticles have average size ranges of 93 nm. They also concluded that the green-synthesized nanoparticles have greater antioxidant activity

Table 2 List of plants reported for biosynthesis of nanoparticles

Plant name	Plant parts used	Type of nanoparticle synthesise	Size (nm)	Shape	Pharmacological applications	References
Abutilon indicum	Leaf	Ag, CuO	10–20	Spherical	Antimicrobial	[165]
Acalypha indica	Leaf	Ag	20–30	Spherical	Antibacterial	[166]
Acorus calamus	Rhizome	Ag	12.52–18.43	Triangular, Circular, Hexagonal	Antimicrobial	[167]
Aerva lanata	Leaf	Au	3–10	Spherical	Antimicrobial	[168]
Alfa Alfa	Leaf	Ni	12–20	Spherical	Antimicrobial	[54]
Allium cepa	Onion (bulb)	Ag	33.6	Spherical	Antifungal	[169]
Allium sativum	Leaf	Ag	4–22	Spherical	Antimicrobial	[170]
Aloe barbadensis	Latex	ZnO	5–50	Spherical	Antimicrobial	[171]
Aloe vera	Latex	Au, Ag	50–350	Spherical, Triangular	Optical properties	[172]
Alstonia scholaris	Bark	Ag	50	Spherical	Antibacterial	[173]
Alternanthera sessilis	Whole plant	Ag	40	Spherical	Antioxidant, antimicrobial	[174]
Anacardium occidentale	Fruit juice	Au/Ag bimetallic	~ 6 nm at 27 °C; 17 nm at 100 °C	Spherical, triangular	Antifungal	[175]
Andrographis paniculata	Leaf	Ag	67–88	Spherical	Hepatocuratie activity	[176]
Andropogon muricatus	Root	Ag	50–100	Triangular, Circular, Hexagonal	Antifungal	[177]
Annona muricata	Leaf	Ag, Au	3–10	Spherical	Antifungal	[178]
Anogeissus latifolia	Leaf	Pt		Spherical	Antibacterial	[179]
Argemone maxicana	Leaf	Ag	30	Spherical	Antimicrobial	[180]
Aristolochia indica	Leaf	Pb, Pd	> 200	Spherical	Antibacterial	[181]
Artemisia nilagirica	Leaf	Ag	70–90	Spherical	Antimicrobial	[182]
Artocarpus gomezianus	Fruit	ZnO	20–40	Spherical	Antilarvicidal	[183]
Artocarpus heterophyllus	Seed	CuO, Ag	3–8	Cubic Hexagonal Crystalline	Antilarvicidal	[184]
Avena sativa	Leaf	Ag	160–180	Spherical	Antifungal	[185]
Averrhoa carambola	Leaf	Ag	12–15	Spherical	Antifungal	[186]
Azadirachta indica	Leaf	Ag/Au bimetallic	50–100	Spherical	Antimicrobial	[187]
Balsamodendron mukul	Resin	Ag	5–10	Spherical	Antibacterial	[102]
Berberis aristata	Wood	ZnO	2–5	Spherical	Antiplasmodial	[70]
Boswellia ovalifoliolata	Leaf	Ag	30–40	Spherical	Antilarvicidal	[188]
Boswellia serrata	Gum	Ag	7–10	Spherical	Antibacterial	[189]
Brassica campertris	Seeds	Pd	> 120	Spherical	Antilarvicidal	[190]
Bryophyllum pinnatum	Leaf	Ag	10–22	Spherical	Antifungal	[191]
Butea monosperma	Bark	Ag	7–20	Face centred cubic	Antimicrobial	[192]
Cacumen platycladi	Leaf	Ag-Au alloy	< 30	Cubic Hexagonal Crystalline	Antifungal	[193]
Calotropis gigantea	Latex	Au, ZnO	30–60	Spherical	Antimicrobial	[194]
Calotropis procera	Flower	Ag	150–1000	Cubic Hexagonal Crystalline	Antifungal	[195]
Camelia sinensis	Leaf	NiO	30–40	Spherical	Antimicrobial	[196]
Carica papaya	Fruit	Ag	25–50	Spherical	Antimicrobial	[197]
Cassia fistula	Leaf	Ag	50–60	Face centred cubic	Antihypoglycemic	[198]
Catharanthus roseus	Leaf	Ag	48–67	Spherical	Antifungal	[199]
Cedrus deodara	Wood	Ag	8.62–9.12	Spherical	Antilarvicidal	[200]

Table 2 (continued)

Plant name	Plant parts used	Type of nanoparticle synthesise	Size (nm)	Shape	Pharmacological applications	References
Celastrus paniculatus	Seed	Ag	18–80	Cubic Hexagonal Crystalline	Antioxidant	[201]
Chenopodium album	Leaf	Ag, Au;	10–30	Quasi-Spherical	Antioxidant	[202]
Cinnamom zeylanicum	Leaf	Ag, Pd	45, 15–20	Spherical	Antibacterial	[201]
Cinnamomum camphora	Leaf	Pd	3.2–6.4	Spherical	Antioxidant	[203]
Cinnamomum zeylanicum	Leaf	Au	7–20	Spherical	Antimicrobial	[204]
Citrullus colocynthis	Calli	Ag	5–70	Triangle	Antioxidant, Anticancer	[205]
Citrus sinensis	Leaf, Peel	Au, Pd;	3.2–20	Cubic Hexagonal Crystalline	Antimicrobial	[206]
Clerodendrum inerme	Leaf	Ag	5–60	Spherical	Antibacterial	[207]
Clerodendrum serratum	Flower	CuO, Ni	25–50	Spherical	Antilarvicidal	[208]
Cocos nucifera	Coir	Pd, Si	2–10	Spherical	Antibacterial	[209]
Coleus amboinicus Lour	Leaf	Ag	35 ± 2 nm (at 25 °C), 10 ± 1 nm (at 60 °C)	Spherical	Antioxidant, Anticancer	[210]
Coriandrum sativum	Fruit	Ag	58.35 ± 17.88	Spherical	Antifungal	[211]
Cucurbita maxima	Petals	Ag, MgO	10–100	Cubic Hexagonal Crystalline	Antimicrobial	[212]
Cuminum cyminum	Seed	Au	1–10	Triangle	Antimicrobial	[213]
Curcuma longa	Leaf	Ag	44	Spherical	Antibacterial	[214]
Cymbopogon spp.	Leaf	Ag	15–25	Spherical	Antimicrobial	[109]
Datura metel	Rhizome	Ag, Au	200–500	Spherical, Triangular	Antimicrobial	[215]
Desmodium triflorum	Leaf	Ag	16–40	Quasilinear, Superstructure	Biological activities	[216]
Dillenia indica	Fruit	Ag	11–24	Spherical	Antibacterial	[217]
Diopyros kaki	Leaf	Ag	5–20	Spherical	Antibacterial	[218]
Dioscorea batatas	Root	Ag	20–35	Spherical	Cytotoxicity	[219]
Dioscorea bulbifera	Leaf	Pt	15–19	Spheres	Antibacterial	[220]
Eclipta prostrate	Leaf	CuO	11–30	Rod, triangular	Cytotoxicity	[221]
Embelia ribes	Fruit	Ag	120–160	Spherical	Antimicrobial, Antioxidant, Cytotoxic	[222]
Emblica officinalis	Leaf	Ag	35–60	Triangles, Pentagons, Hexagons	Antimicrobial	[223]
Enteromorpha flexuosa	Seaweed	CuO, MgO	5–27	Spherical	Antimicrobial	[224]
Eucalyptus camaldulensis	Leaf	Au, Ag	5.5–7.5	Spheres	Cytotoxicity	[225]
Eucalyptus chapmaniana	Leaf	MgO	3–21	Spherical	Cytotoxicity	[226]
Eucalyptus hybrid	Leaf	Ag, Au	10–20	Triangular, circular, hexagonal	Antiplasmodial	[142]
Eucommia ulmoides	Leaf	Au	2.78–5.76	Spheres	Biological activities	[227]
Euphorbia helioscopia	Root	FeO, SiO	30–90	Spherical	Biolarvicidal and pupicidal	[228]
Euphorbia hitra	Leaf	Au	19.5	Spherical	Antimicrobial	[229]
Euphorbia prostrata	Leaf	Ag, TiO	50–150	Rod, spherical	Antiplasmodial	[230]
Ficus benghalensis	Root	Au	29 ± 6	Spherical	Antimicrobial	[231]
Ficus carica	Leaf	Ag	2–15	Spherical	Antibacterial	[232]

Table 2 (continued)

Plant name	Plant parts used	Type of nanoparticle synthesise	Size (nm)	Shape	Pharmacological applications	References
G. max	Leaf	Pd	32–50	Spherical	Antibacterial	[233]
Galaxaura elongata	Flower	Au	Average of 24.5 nm	Triangular, circular, hexagonal	Biological activities	[234]
Garcinia mangostana	Flower	Cu/Ag Ag, Cu	18 nm, 10.5 nm	Spheres	Antiplasmodial	[235]
Gardenia jasminoides	Leaf	Fe, Pd	Average of 24.5	Rocklike appearance	Antibacterial	[236]
Gelidiella acerosa	Seed	Ag	35	Cubic hexagonal crystalline	Antilarvicidal	[237]
Gelsemium sempervirens	Whole plant	Ag	112	Spherical	Cytotoxicity	[236]
Geranium indicum	Leaf	Ag, Au	1–5	Spherical	Antioxidant	[110]
Gloriosa superba	Leaf	CuO	20–30	Spheres	Catalytic	[237]
Glycine max	Leaf	Pd	15	Cubic hexagonal crystalline	Antilarvicidal	[238]
Glycyrrhiza glabra	Root/rhizome	Ag	5–8	Spherical	Antibacterial	[239]
Grewia flaviscences	Leaf	ZnO	40–75	Cubic hexagonal crystalline	Biological activities	[240]
Gum powder	Leaf	Ag	5.5	Spherical	Antioxidant	[241]
Gymnocladus assamicus	Leaf	Au	4–22	Triangular, pentagonal, hexagonal	Catalytic	[242]
Helicteres isora	Root	SiO	12–15	Spherical	Antimicrobial	[243]
Hemidesmus indicus	Root	Ag	20–30	Cubic hexagonal crystalline	Antimicrobial	[244]
Hibiscus cannabinus	Leaf	Au	10–30	Spherical	Antimicrobial	[245]
Holarrhena antidysenterica	Seed	Ag	12–16	Spherical	Antibacterial	[246]
Hydrastis canadensis	Whole plant	CuO, ZnO	12–18	Face centred cubic	Antioxidant	[247]
Hypnea musciformis	Leaf	Ag	1–5	Spherical	Antimicrobial	[248]
Iresine herbstii	Leaf	Ag	44–64	Cubic	Biological activities	[249]
Jatropha curcas L.	Latex	TiO_2	16–40	Spheres	Antibacterial	[250]
Justicia adhatoda	Leaf	Ag-Au	35–50	Spherical	Antioxidant	[251]
Lansium domesticum	Fruit	Au	< 100	Spherical	Antimicrobial	[252]
Lawsonia inermis	Leaf	Au, Ag	7.5–65	Spherical, triangular, quasispherical	Antibacterial	[253]
Lippia citriodora	Leaf	Ag	15–30	Spherical	Antimicrobial	[254]
Lonicera japonica	Leaf	ZnO, CuO	20–50	Spherical	Antibacterial	[216]
Lycopersicon esculentum	Fruit	Ag	13–20	Triangular, hexagonal	Antioxidant	[255]
Magnolia kobus	Leaf	Au	20–60	Face centred cubic	Catalytic	[256]
Mangifera indica	Leaf	Ag	20	Spherical	Antioxidant	[257]
Medicago sativa	Whole Plant	Ag, Au, CuO	30–100	Triangular, Circular, Hexagonal	Antimicrobial	[258]
Melia azadirachta	Bark, Leaf	Ag	25–35	Spherical	Antimicrobial, Cytotoxicity	[259]
Memecylon edule	Leaf	Ag	10–12.5	Spheres	Antibacterial	[260]
Mentha piperita	Flower	Ag	2–10	Triangular, hexagonal	Antimicrobial	[261]
Mirabilis jalapa	Flowers	Au	100	Spherical	Antibacterial	[262]
Momordica cymbalaria	Fruit	Ag	30–35	Cubic hexagonal crystalline	Cytotoxicity	[263]
Morinda citrifolia	Root	Au	5–10	Spherical	Antimicrobial	[264]
Moringa oleifera	Leaf	Au	10–40	Spherical	Antimicrobial	[265]
Mucuna pruriens	Leaf	Ag	57	Triangular, circular, hexagonal	Antimicrobial	[185]

Table 2 (continued)

Plant name	Plant parts used	Type of nanoparticle synthesise	Size (nm)	Shape	Pharmacological applications	References
Mukia maderaspatana	Leaf	Cu	3–7	Spherical	Antibacterial	[266]
Murraya koenigii	Leaf	Ag, Au	10–25	Cubic hexagonal crystalline	Biological activities	[267]
Musa balbisiana	Leaf	Ni	5–15	Spherical	Antimicrobial	[268]
Musa paradisiacal	Leaf	Au	6–17.7	Spherical	Antimicrobial	[269]
Myrmecodia pendan	Whole plant	SiO	1–10	Triangular, hexagonal	Antimicrobial	[270]
Negella sativa	Seed	Ag	12–15	Spherical	Antibacterial	[271]
Nelumbo nucifera	Whole plant	Ag	20	Triangular, circular, hexagonal	Antioxidant	[272]
Nerium oleander	Leaf	Au	12	Spheres	Antibacterial	[273]
Nyctanthes arbor-tristis	Flower	Au	19.8	Spherical	Catalytic	[274]
Ocimum sanctum	Leaf	Ag	20	Spherical	Antimicrobial	[275]
Ocimum tenuiflorum	Leaf	Ag	25–40	Cubic hexagonal crystalline	Antibacterial	[276]
Onosma dichroantha	Root	Au	12–25	Spheres	Antioxidant	[277]
Oryza sativa	Seeds	Pb, Ni	4–10	Face centred cubic	Antibacterial	[278]
Parthenium hysterophorus	Leaf	Au	15–25	Spherical	Antimicrobial, Cytotoxicity	[279]
Pelargonium	Leaf	Au	10–20	Spheres	Antimicrobial	[245]
Phyllanthus amarus	Leaf	Au	1–4	Cubic hexagonal crystalline	Antioxidant	[280]
Physalis alkekengi	Leaf	ZnO	12–15	Spheres	Antimicrobial	[128]
Phytolacca decandra	Whole plant	Ag, Au	> 50	Face centred cubic	Antimicrobial	[281]
Pinus resinosa	Bark	Pd	16–20	Triangular, circular, hexagonal	Antilarvicidal	[282]
Piper betle	Leaf	Ag	3–37	Spherical	Antimicrobial	[283]
Piper longum	Fruit	Au	14–32	Spherical	Antimicrobial	[284]
Platanus orientalis	Leaf	Fe	30–38	Spheres	Antioxidant	[285]
Plukenetia volubilis	Leaf	Ag	30–50	Spherical	Antimicrobial	[286]
Plumbago zeylanica	Root	Ag	< 100	Spherical	Antilarvicidal	[287]
Potentilla fulgens	Root	Ag	25–30	Spherical	Antimicrobial	[288]
Prosopis farcta	Leaf	CuO	2–4	Spherical	Antimicrobial	[289]
Prunus yedoensis	Leaf	MgO	20–60	Spheres	Antimicrobial	[290]
Psidium guajava	Leaf	TiO	50	Face centred cubic	Cytotoxicity	[258]
Psoralea corylifolia	Seed	Ag	2–10	Spherical	Antimicrobial	[258]
Pyrus sp.	Leaf	Au	25–30	Spherical	Antimicrobial	[91]
Quercus brantii	Leaf	AuO	10–50	Spherical	Antimicrobial	[291]
Rhododedendron dauricam	Flower	Au	200–500	Triangular, hexagonal	Antimicrobial	[292]
Rosa indica	Petals	Ag, Au	5–20	Spherical	Antilarvicidal	[293]
Rosa rugosa	Leaf	Ag	25–40	Spherical	Antimicrobial	[294, 295]
Rosmarinus officinalis	Leaf	Ag	10–20	Spheres	Antimicrobial	[296]
Ruta graveolens	Seed, Root	Ni, ZnO	40.3 ± 3.5	Face centered cubic	Antimicrobial	[297]
Salix alba	Leaf	Au	1–6	Spheres	Antimicrobial	[298]
Saraca indica	Flower	Ag	50–100	Spherical	Antimicrobial	[299]
Sesbania grandiflora	Seed	Au	12–32	Triangular, Hexagonal	Cytotoxicity	[300]
Sesuvium portulacastrum	Callus and Leaf	Ag, Au–Ag, Ag	30–60	Spherical	Antimicrobial	[301]
Sinapis arvensis	Seed	Ag	10–20	Spherical	Antioxidant	[302]

Table 2 (continued)

Plant name	Plant parts used	Type of nanoparticle synthesise	Size (nm)	Shape	Pharmacological applications	References
Skimmia laureola	Leaf	Ag	20–50	Spherical	Antimicrobial	[303]
Smilax china	Root	Ag	12–15	Spherical	Antimicrobial	[304]
Solanum nigrum	Leaf	ZnO	4 –10	Spherical	Catalytic	[305]
Swietenia mahogani	Leaf	Ag	5–20	Spherical	Antimicrobial	[306]
Syzygium cumini	Whole plant	Ag/Au bimetallic	50 nm Ag at pH 7	Spherical	Antimicrobial	[307]
Tridax procumbens	Leaf	CuO	12–18	Spherical	Antimicrobial	[308]
Tanacetum vulgare	Leaf	Ag	29–92	Spherical	Antioxidant	[309]
Tephrosia tinctoria	Stem	Ag	13–28	Spherical	Antioxidant	[170]
Terminalia catappa	Leaf	Ag, Au–Ag, Au	16 nm, 11 nm	Spherical	Antimicrobial	[305]
Thuja occidentalis	Whole plant	Ag	15–70	Spherical	Antimicrobial	[310]
Tinospora cordifolia	Leaf	Ag	34	Spherical	Antilarvicidal	[311]
Torreya nucifera	Leaf	Au	58.35 ± 17.88	Face centred cubic	Antifungal	[312]
Trachyspermum copticum	Leaf	Au	10–35	Spherical	Antimicrobial	[313]
Tridax procumbens	Leaf	Ag	40–60	Spherical	Antimicrobial	[314]
Trigonella-foenum graecum	Seed	Au	15–25	Spherical	Catalytic	[315]
Vigna radiate	Seeds	TiO	10–25	Spherical	Antioxidant	[299]
Vitex negundo	Leaf	Ag	6–50	Face centred cubic	Antibacterial	[290]
Withania somnifera	Leaf	Ag	5–40	Irregular, spherical	Antimicrobial	[108]
Ziziphus Jujuba	Root	Ag	18–80	Spherical	Antibacterial	[298]
Zizyphus mauritiana	Root	Au	5–10	Spherical	Antibacterial	[211]

as compared to seed extract of *S. cumini*. Similar work was carried out by Velusamy et al. [36] and they reported silver nanoparticle biosynthesis using leaf extract of *Azadiracta indica* and studied their antimicrobial activities. The synthesized nanoparticles have size ranges of < 30 nm and they were monodispersed and spherical in shapes. They also demonstrated that the synthesized nanoparticles have great antibacterial activity, which is confirmed by the degradation of test bacterial DNA. Results also suggested that the gum-mediated synthesized nanoparticles could be used as an antibacterial agent against a diverse range of clinical pathogens. It has been found that carbonyl compound of the plant extract plays a key role in the formation of gold nanotriangles by the slow reduction of gold ions ($HAuCl_4$) with the shape-controlling effect of [8].

Similarly, when aqueous solution of silver ions was incubated with *A. vera* extract, it produces only spherical silver nanoparticles. The colour change of brownish red colour and faint yellow colour in the reaction mixture indicates the formation of gold and silver nanoparticles, respectively. The leaf extract of *Cinnamomum camphora* has been recently known for the production of gold and silver nanoparticles [37]. Water-soluble heterocyclic compounds and polyol compounds are mainly found to be responsible for the reduction of silver ions or chloroaurate ions and the stability of nanoparticles, respectively.

Rhizome extract of *Discorea batatas* was also used for synthesis of silver nanoparticles [38]. These nanoparticles have antimicrobial properties against yeast *C. albicans* and *S. cerevisiae*. Silver nanoparticles of 10–20 nm were fabricated using the latex of *Jatropha curcus* which act as a reducing and capping agent [39]. Ankamar et al. [40] used fruit extract of *Emblica officinalis* for the synthesis of highly stable silver and gold nanoparticles.

Parida et al. [41] reported the synthesis of gold nanoparticles using the extracts of *Allium cepa*. They have an average size of 100 nm and have significant toxicity against several cancerous cell lines, specifically MCF7 breast cancer cell line. Further study revealed that they can be internalized by MCF7 breast cancer cells via endocytosis process [41]. Ravindra et al. [42] carried out a study to synthesize silver nanoparticles within cotton fibres loaded with silver ions. The leaf extract of *Eucalyptus citriodora* and *Ficus bengalensis* plants was used for the synthesis of the same. The synthesized nanoparticles have size ranges of 20 nm. They also show antibacterial activity against *E. coli*. Prasad and Elumalai [43] reported the silver nanoparticle synthesis through leaf extract of *Polyalthia longifolia*. Nanoparticles synthesize, where size ranges of 58 nm.

Njagi et al. [44] used aqueous extract of Sorghum bran to produce Fe (iron) and silver nanoparticles at room temperature.

Valodkar et al. [45] synthesized nanoparticles of 5–10 nm of silver and copper using latex of Euphorbiaceae. These nanoparticles have excellent antibacterial activity towards Gram +ve and Gram −ve bacteria [45]. Similarly, Velayutham et al. [36] used leaf extract of *Catharanthus roseus* to synthesize titanium dioxide nanoparticles. They have size ranges of 25–110 nm with irregular shape. Aqueous extract of these nanoparticles has been tested for larvicidal and adulticidal activities against the hematopathogens fly *Hippobosca maculate* and Sheep louse *Basicola ovis*. Obtained results confirm its significant larvicidal and adulticidal activities against test pathogens.

Huang et al. [46] also reported a one-step synthesis process of gold–palladium core shell nanoparticles using aqueous solution of Bayberry tannin at room temperature. The tannin preferentially reduced the Au^{3+}-to-gold nanoparticles when a mixture of Au^{3+} and Pd^{2+} was bringing into contact with the tannin [46].

Peel extract of *Punica granatum* was used for the synthesis of zinc oxide nanoparticles. Its antimicrobial activity was tested against *Aspergillus niger* and *Proteus vulgaris.* Results showed the highest antifungal activity against these two fungal strains. Synthesized nanoparticles were monodispersed and crystalline in nature with the size range of 25–30 nm [45].

Biosynthesis of cadmium oxide nanoparticles was achieved using flower extract of *Achillea wilhelmsii* which act as a reducing agent. The aqueous solution of cadmium ions when exposed to the flower extract was reduced and resulted in the formation of cadmium oxide nanoparticles [32].

Li et al. [47] synthesized Cu nanoparticles 40–100 nm using leaf extract of *Magnolia*. These Cu nanoparticles had antimicrobial activity against *E. coli* and these are also toxic-to-human adenocarcinomic alveolar basal epithelial cells (A549 cells). Similar work was carried out by Naik et al. [48], and they synthesize copper oxide nanoparticles using leaf extract of *Gloriosa superba*. SEM images indicate that they have particle size in the range of 5–10 nm. They also contain significant antibacterial activity against some Gram −ve bacterial species such as *Klebsiella aerogenosa*, *Pseudomonas desmolyticum*, and *E. coli*.

Amarnath et al. [49] reported the biosynthesis of palladium nanoparticles and their antibacterial activities and their stabilization by chitosan and grape polyphenols. Synthesized nanoparticles have size ranges of 20–60 nm. Similar results were also reported by Satishkumar et al. [50] and they produce palladium nanoparticles using the extract of *Cinnamon zeiflanicum* bark which act as a reducing agent. They also found that during synthesis process, the reaction pH, temperature, and the concentration of the extract did not affect the size and shape of the synthesized nanoparticles. Palladium nanoparticles are also synthesized by tea extracts [51]. Palladium nanoparticles of size range of 15 nm have also been synthesized using peel extract of *Annona squamosa*. The leaf extract of *Soybean* glycine max was also used for synthesis of palladium nanoparticles which have size range of 25 nm [52, 53].

The type of plant extract, its concentration, pH, the concentration of the metal salts, temperature, and contact time are also known to affect the rate of production of the nanoparticles, their quantity, and other characteristics. Nanoparticles of different shapes like spherical, decahedral, and hexagonal shapes can be obtained by varying the concentration of the plant extract [31]. Shankar et al. [54] found the presence of proteins and secondary metabolites in the water-soluble fractions of *Geranium* leaves and they demonstrated that terpenoids contribute to the reduction of silver ions and oxidized to carbonyl groups of metal ions. FTIR analysis suggested that ester C=O group of chlorophyll act as a reducing agent and also another protein involved in the surface capping of gold nanoparticles of *Geranium* leaf extract. Proteins and other ligands present in extract of various plant parts were found to be responsible for the synthesis and stabilization of nanoparticles [55]. Protein extract of *Capsicum annum* leaf was reported for the rapid precipitation of α-Se nanoparticles at room temperature. Later, it was found that the protein and vitamin C present in *C. annum* leaf extract were responsible for the synthesis of α-Se nanoparticles. Proteins found in the leaf of *C. annum* were also stabilized nanoparticles on their surfaces [47].

Kasthuri et al. [56] found the ability of apiin in the leaf extract of henna to reduce ions to gold and silver nanoparticles. Secondary hydroxyl and carbonyl group of apiin were responsible for the reduction. The size and shape of the nanoparticles could be controlled by changing the concentration of apiin. *Chenopodium album* leaf extract was used to produce silver and gold nanoparticles. These particles had quasi-spherical shapes and they also have size range of 10–30 nm [57]. Control over the shape along with the stability of nanoparticles produced by plants or plant parts is also possible, which is shown by the rapid biosynthesis of triangles of gold nanoparticles using leaf extract of tamarind. Similar results were shown when leaf extract of *A. vera* is used as a reducing agent for the biosynthesis of gold nanoparticles as well as silver nanoparticles which was in triangular crystalline form. For this aqueous solution of chloroaurate, ions were treated with *A. vera* leaf extracts. Percentage of gold triangles nanoparticles to that of spherical particles as well as their size can be modulated by varying the amount of extract in reaction medium [58].

Possible mechanism for synthesis of nanoparticles using plant extract

Until date, there are several studies and have been done on the screening and identification of plants for the controlled synthesis of metallic nanoparticles; however, a very little work has been done to understand the actual mechanism behind the synthesis of metal nanoparticles [47]. For the elucidation of actual mechanism and the biochemical pathway, involving in the biosynthesis of metal nanoparticles, it is necessary to find a novel approach in this field, so that the research on the underlying molecular mechanism is essential to control the shape, size, dispersity, and crystallinity of the metal nanoparticles. There are several hypothesis and have been proposed for the synthesis of metallic nanoparticles. The initial reports were published in the 1960 s and in the late 1990s; many other hypotheses have been proposed towards the biosynthesis of metal nanoparticles using plant extract [59].

Plant contains several types of secondary metabolites (Fig. 2) like terpenoid, sugars, polyphenols, alkaloids, proteins, and phenolic acids that play a crucial role during the biosynthesis of metal nanoparticles [60]. The FTIR study of *Cinnamon zeylanisum* extract suggested that they contain the terpenoids which associate with binding of metal ions. Terpenoids are the class of diverse organic polymer which contain five carbon isoprene chain and exhibit strong antioxidant activity. In case of *C. zeylanisum* extract, they contain the eugenol which is a terpenoid, and it plays a key role in the reduction of gold and silver nanoparticles. Further study carried out through FTIR revealed that the dissociation of proton of the eugenol is due to the presence of –OH group which leads to the formation of resonance structure that have capability of further oxidation, followed by nanoparticle formation [61].

Similarly, flavonoids come under the polyphenolic compounds that composed of various classes such as flavonoids, chalcones, flavones, isoflavonoids, anthocyanins, and flavanones. These compounds actively participated in the reduction and chilation of metal ions. The previous study reported that tautomeric transformation of flavonoids from enol form to keto form may release reactive hydrogen species which acts as a reducing agent for metal ions. Extract of *Ocimum basilicum* contains luteolin and rosmarinic acids which are flavonoid compounds that undergo through the tautomeric transformation process from enol form to keto form and ultimately lead to formation of silver nanoparticles from Ag ions [59].

Ketones and carboxylic acid groups of flavonoids are involved in the synthesis of gold nanoparticles. Carbonyl groups of flavonoids strongly depend on chelates the metal ions, as quercetin is a flavonoid and also a strong chelating agent. It can chelate at three positions involving the carbonyls and hydroxyls at C3 and C5 positions, while catechol at C3′ and C4′ sites. These groups are reported to chelate a number of metal ions like Fe^{2+}, Fe^{3+}, Co^{2+}, Cu^{2+}, Al^{3+}, Pb^{2+}, and Al^{3+} [62].

Kumar et al. [63] later found that the amount of polyphenols present in the plant extract can be an important parameter for the determination of size and distribution of synthesized metal nanoparticles. In case of synthesis of metallic and bimetallic nanoparticles using *Azadirecta indica* leaf extract, it was found that the *A. indica* leaf extract contains reducing sugars, which is responsible for the reduction of metal ions and the formation of corresponding nanoparticles. Flavonoids and the terpenoids found in the *A. indica* leave extract act as surface active molecules that also stabilizes the metal nanoparticles [19]. Figure 3 shows the possible mechanism behind the biosynthesis and stabilization of noble metal nanoparticles using different plant extracts.

Song et al. [64] also reported that some plant extract is used for the synthesis of noble metallic nanoparticles due to the presence of terpenoids and reducing sugars in them. They reported the synthesis of gold nanoparticles using *Magnolia kobus* leaves. Detailed study of these proposed that the leaf of *M. kobus* consists of terpenoids having functional group of amines, alcohols, ketones, aldehydes, and carboxylic acid which was found to be used for the stabilization of gold nanoparticles. Begum et al. [65] concluded that polyphenols or flavonoids present in the leaves were responsible for the synthesis of gold and silver nanoparticles which were later explained by the kinetic studies using FTIR and cyclic voltammetry. They also carried out a study and concluded that there is as such no gold or silver nanoparticles were synthesized in leaf extract lacking of flavonoids and polyphenols. Flavonoids present in the leaf extract of guava are also responsible for the bioreduction of gold nanoparticles [29]. In addition, Kasthuri et al. [56] also used the apiin, a flavonoid glycoside, which is isolated from the Henna leaf, for the synthesis of anisotropic gold and quasi-spherical silver nanoparticles. FTIR spectrum suggested that the carbonyl group present in the apiin contributes to the interaction the nanoparticles and apiin. Recently, numbers of reports have been published on the synthesis of nobel metal nanoparticles using plant extract with possible mechanism studies.

For the production of metallic nanoparticles, there are three important components which are as follows: reducing agent, stabilizing agent, and the solvent medium that can be used for the stabilization of metal of interest [66]. Nanoparticle biosynthesis is regarded as a green process, because the biomass itself can act as both the reducing agent and the stabilizing agent. In addition, most of the plant-mediated biosynthesis approaches could be performed in aqueous medium in place of organic solvents which is

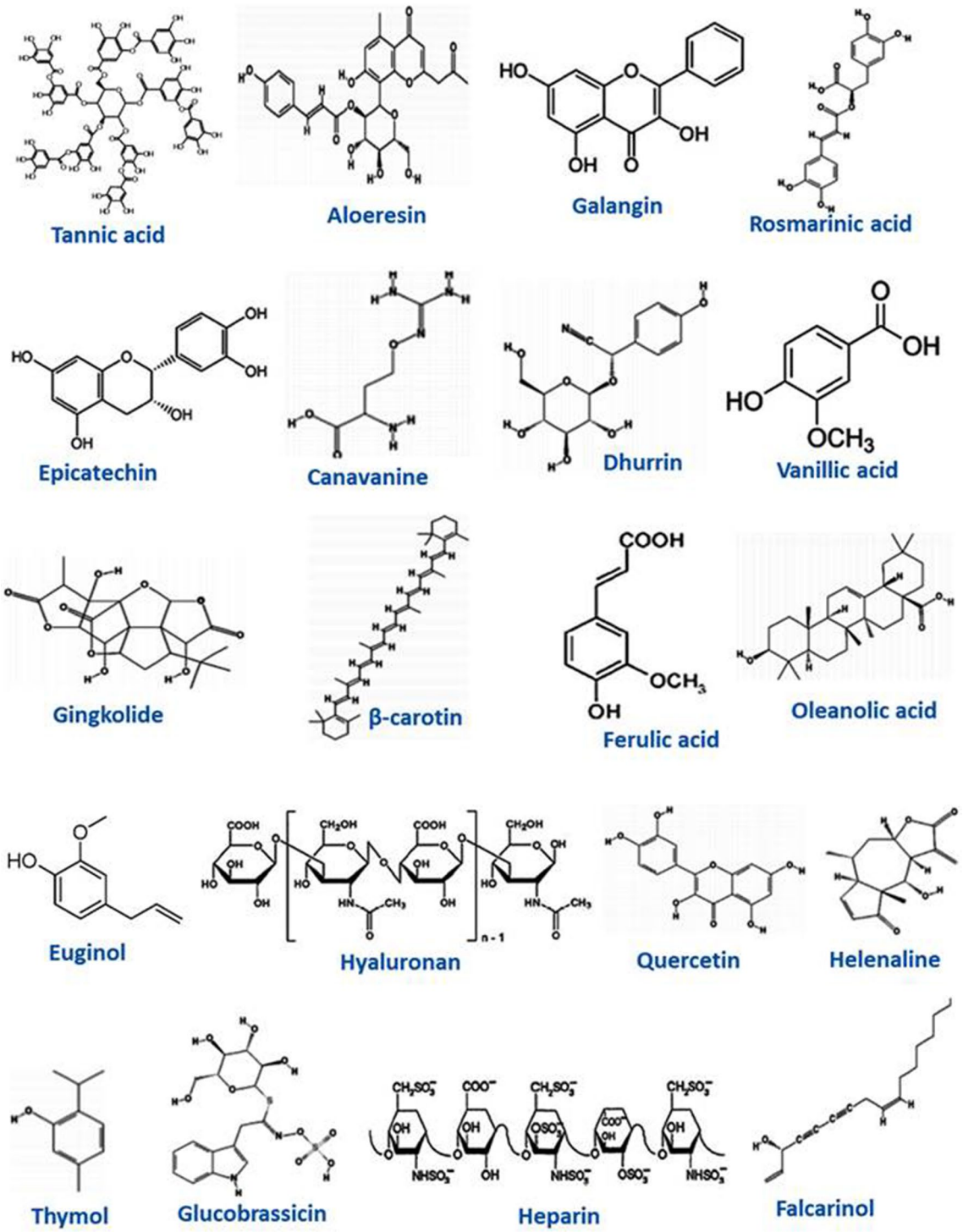


Fig. 2 Different types of secondary metabolites involved in biosynthesis of metallic nanoparticles

another advantages and apparently more eco-friendly and cost effective. Lukman et al. [67] proposed that there are three different reaction regimes occurred during the biosynthesis process: a short incubation period, a growth phase, and a termination period. It was found that the growth rate of particle is usually slower than the reduction process and also the nucleation of metal ions, which leads to the higher concentration of small size particles. Metal ions could interact with the biomass through the ionic bond with the bioorganic reducing agents such as flavonoids and terpenoids in

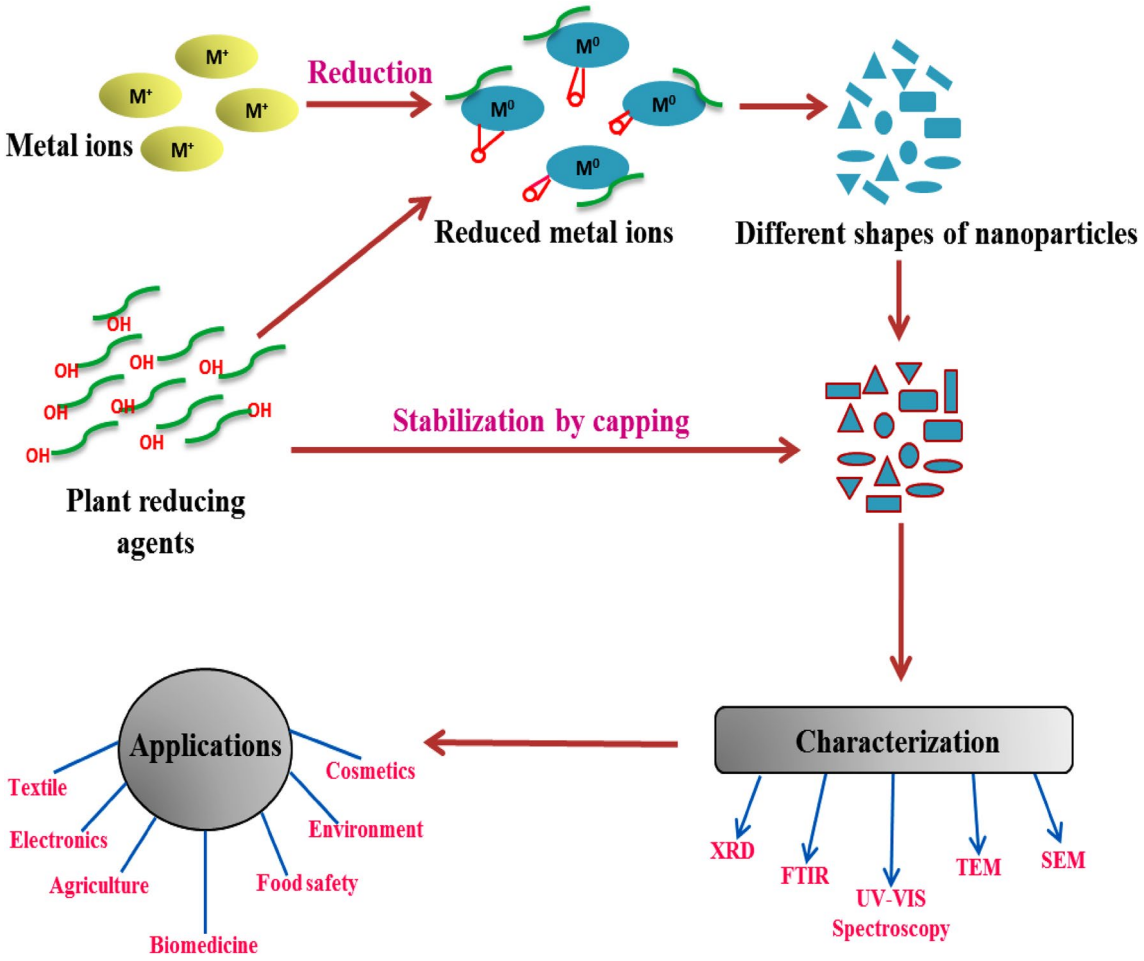


Fig. 3 Schematic diagram showing the possible mechanism behind the biosynthesis of metallic nanoparticles

the absence of other strong ligands. It was also reported that the adsorption of reducing agents on the surface of metallic nanoparticles is due to the presence of π-electrons and the carbonyl groups present in their molecular structures.

Recently, the research group at NCL (National Chemistry Laboratory), Pune, India has reported the rational and the mechanism while synthesizing gold and silver nanoparticles from different plants such as neem, geranium, lemon grass, tamarind, and chick pea. Further reports suggested that the geranium leaves consist of some special kinds of proteins and secondary metabolites which were contributed to the reduction of silver ions and oxidization of carbonyl groups. Furthermore, in FTIR analysis, they found a band of 1748 cm^{-1} to easter C=O group of chlorophyll, which were also supported their proposed hypothesis [68]. They also found that proteins found in geranium leaves were responsible for surface capping of gold nanoparticles synthesized by aqueous leaf extract. While in case of *Cymbopogan flexuous*, aldoses found in the extract which act as a reducing agent for the formation of gold nanotriangles due to the reduction of $AuCl_4^-$. After reduction aldehydes and ketones bind with new synthesized nanoparticles which rendering them "liquid like" and also provides stability at room temperature [69]. These aldehydes and ketones present in the leaf extract play an important role in directing the shape and size of gold nanoparticles. Similar study was carried out by a group of researchers in which they uses tamarind leaf broth for synthesis of gold nanoparticles. Further study suggested that the leaf broth of tamarind consists of an acid group and may be tartaric acid which act as capping agents. It was also found that this tartaric acid was also responsible for the stability of bioreduced gold nanoparticles [47]. In another study, *Cicer arietinum* was used for the synthesis of $CaCO_3$ crystals, and the study concluded that CO_2 released during the root growth stage which may react with the Ca^+ ions to produce $CaCO_3$ crystals (Shankar et al. 2004). Further FTIR analysis suggested that the presence of amide I and II peaks and also the gel electrophoresis analysis was also confirmed the presence of two protein bands of 33 and 39 kDa that may be responsible for the stabilization of $CaCO_3$ crystals [70].

During the gold nanoparticle synthesis through the *Chilopsis lineasis*, the inductive coupled plasmon and X-ray diffraction studies of synthesized nanoparticles suggested that the ionic form of salt was transported across the root membrane and translocated inside the plant which is followed by the reduction of metal salt [71]. Dwivedi and Gopal [57] found that the carbonyl groups and carboxylate ions present in the *C. album* leaf extract influence the reduction process and the stability of metal nanoparticles, respectively.

Soft metals like Au(III) exist in the form of $[AuCl_4^-]$, so that it prefers to the binds through only soft ligands such as amino and sulfhydryl groups of biomass, especially when the soft ligands are positively charged at acidic pH [19]. Obtained results of the previous researches also suggested that the formation of nanoparticles could be the results of the heterogeneous nucleation and growth followed by Ostwald ripening. For the growth of crystals during the biosynthesis process, the extraneous catalytic substances which were released from the plant biomass can be scaffold. Ostwald ripening also takes place along with crystal growth which causes broadening of size distribution. Several reports have been found that the Ostwald ripening might be involve during the biosynthesis of metal nanoparticles in which the smaller particle could migrate towards the closest neighbouring particles of large size, which induces the growth of larger particles and depletion of smaller particles [72, 73]. These nanoparticles consist of excessive Gibbs free energy which could be then minimized by the transformation into more energetically favourable changes which are directed by the bioorganic capping molecules [73].

Sugars present in plant extract can also induce the synthesis of metal nanoparticles. It is reported that glucose which is a monosaccharide can act as reducing agent. Other monosaccharides such as fructose, which contain a keto group, may act as antioxidants by undergoing a series of tautomeric transformations from a ketone to an aldehyde. Reducing capability of disaccharides and polysaccharides depends upon their individual monosaccharide components, to form an open chain from within an oligomer and hence to provide access to an aldehyde group. Sucrose in contrast has no ability to reduce metal ions due to glucose and fructose monomers are linked in the form of open chain which is not available. Glucose is known as a strong reducing agent as compared to fructose, because the antioxidant activity of fructose is limited by the kinetics of tautomeric shift [74].

Gardea-Torresdey et al. [25] published their first attempt in the formation of gold nanoparticles inside living plants. After that, one research group found that *Alfa alfa* plant roots are capable for absorbing the silver in the form of Ag[0] from the agar medium and make then also capable of transfer it to the shoot portion in the same oxidation state. The SEM/TEM analysis of this study revealed that the roots of *Alfa alfa* were capable of absorbing the silver ions and they accumulated inside the *Alfa alfa* plant tissue and then undergone nucleation and finally form nanoparticles. However when the dead tissue of *Avena sativa* is when used for the synthesis of gold nanoparticles, results proposed that the functional groups such as carbonyl group and amino and sulfhydryl groups present in the cell wall also get incorporated in the bioreduction of Au[III]-to-gold nanoparticles [75].

Similarly, Li et al. [76], proposed a model of "recognition–reduction-limited nucleation and growth" to explain silver nanoparticles formation from Chilli extract. According to this model, protein present in the chilli extract first trapped the silver ions on their surface via electrostatic interaction force, so that the silver ions are reduced by these proteins leading to the changes in the secondary structures of proteins and finally leads subsequently to the formation of silver nuclei. During the study of the biosynthesis of gold and silver nanoparticles using *C. camphora* leaf extract, Huang et al. [37] reported that the polyols found in the leaf extract of *C. camphora* were responsible for the reduction of silver and gold ions. Later on, while working on palladium nanoparticles using *C. camphora* plant, it was reported that there will be heterocyclic compounds found that might be responsible for the reduction of palladium ions to palladium nanoparticles as well as the stabilization [77].

Gruen [78] carried out an investigation, in which they reported that amino acids such as lysine, cysteine, arginine, and methionine have the ability to reduce silver ions. Similarly, Tan et al. [79] studied the effect of all 20 amino acids to determine their potential for reduction and stabilization of metal ions. The study revealed that the tryptophan amino acid acts as the strongest reducing agent for the gold metal ions, while the histidine acts as a stabilization agent for gold ions. Later, it was found that amino acid binds with metal ions through carbonyl groups of side chains for, e.g., nitrogen atom of the imidazole ring of histidine and the carbonyl group of glutamic acid and aspartic acid. Other amino acid like cysteine, methionine, serine, threonine, thymine, asparagine, and glutamate also binds with their side chains and frequently to the metal ions [80]. Panigrahi et al. [74] reported that the sucrose is unable to reduce to silver ions and palladium chloride into corresponding nanoparticles. Cysteine contains the thiol group in their side chains that also act as a reducing agent for the metal ions. Study carried out by Tan et al. [79] describes the actual process to how the amino acid sequence affects to protein stability to reduce the metal ions. They also explained that the strong sequestration of metal ions to the peptide was inhibited the subsequent reduction of metal ions.

In another study, it was reported that the palladium nanoparticles were synthesized using the leaf extract of *Diopyros kaki*. Obtained results indicate that this is not an enzyme-mediated synthesis, because extract is prepared at high

temperature of 90 °C. At this high temperature, the rate of nanoparticles is very high and there is no peak obtained when study was carried out in FTIR [81]. Similar results were obtained by Satishkumar et al. [47], and they synthesize palladium nanoparticles using *Curcuma longa* tuber extract. Synthesis of gold and palladium nanoparticles was also reported by Nadagouda and Verma [56], and they use coffee and tea leave extract. They found the caffeine and polyphenols present in the coffee and tea extracts, where first form complex with silver and palladium nanoparticles simultaneously. However, Kamp and Marshell found that the plants have limited capacity for the reduction of any metal ions and it depends on the reduction potential of metal species. They were working on the uptake of various silver salt solutions by hydroponically grown *B. juncea*, and they found that metal nanoparticle formation by plant extract is limited to noble metals. Bar et al. [39] reported that the silver nanoparticles also synthesize using the latex of *J. curcus*, in which the cyclic octa peptides (Curcacyclins A and B) act as a reducing agent for the reduction of Ag^{+}-to-Ag nanoparticles. In addition, there is an enzyme found in the latex of *J. curcus* which introduced stabilization of nanoparticles.

Verma et al. [82] reported that in plants, several physiological and biochemical pathways take place simultaneously for the reduction of metal ions into metal nanoparticles. Prarthna et al. [83] carried out the biomimetic synthesis of silver nanoparticles using *Citrus lemon* extracts, and they were found that the citric acid present in the *C. lemon* acts as both reducing and stabilizing agents for the synthesized nanoparticles. When callus extract of *Citrullus colocynthis* is used for the synthesis of silver nanoparticles, it was found that there could be polyphenols with aromatic ring and is found which bound at amide region [84].

Narayanan and Sakthivel [85] reported that plant-mediated synthesis is not an enzymatic process, because normally, the extract is heated at 90 °C, so that at this high temperature, the enzyme can denatured. According to them, phytochemicals found in the plant metabolites such as flavonoids, terpenoids, sesquiterpenes, and the functional groups present in these phytochemicals are actually involved in the reduction and capping of nanoparticles. Similarly, saponins present in the leaf extract of *Memecylon edule* helps in the reduction and stabilization of silver and gold nanoparticles, respectively [86]. It was also found that the hydroxyl groups found in the polysaccharides and the carboxyl group play an important role in the reduction of metal salt into metal nanoparticles. In addition, the amino groups of polysaccharides can act as a stabilizing agent for the nanoparticles [5]. In a similar way when the *Coleus aromaticus* leaf was used for the synthesis of gold and silver nanoparticles, it have been found that the presence of aromatic amine, amide I, phenolic groups, and the secondary alcohols may act as a reducing agent for the nanoparticle synthesis [87]. Recently, it was also reported that the fenugreek seed extract has the potential to synthesis and the stabilization of gold nanoparticles. This is due to the presence of flavonoids in seed extract which act as a powerful reducing agent for the reduction of chloroauric acid, whereas the carboxylase group present in the protein can act as a surfactant to attach onto the surface of nanoparticles. This is stabilized through electrostatic force.

For the stabilization of nanoparticles in a dispersing medium, there must be a repulsive force to overcome the Vander wall force which causes the coagulation [88]. The repulsive force can be mediated through either steric or electrostatic stabilization. Kumar et al. [63] found that the *M. sativa* seed extract is used for the synthesis of silver nanoparticles. They found that synthesized nanoparticles have well-defined shape without aggregation. This is due to the strong interaction between the chemically bound capping agents which is interacted with the tendency of the nanoparticle aggregate. Capping of gold nanoparticles could also be achieved by secondary metabolites from the marine sponge *A. elongata*. This forms a coat on the nanoparticles to prevent it from the agglutination and also stabilizes the nanoparticles [89]. All these observations suggested that the formation of nanoparticles with different morphologies is a result of aggregation of smaller particles. The smaller nanoparticles then rearranged to get a stable structure, although other factors like the plant biomass and the reaction condition used during the biosynthesis process might be responsible in the formation of nanoparticles with particular shape and size that could also provide a higher state of stability [1].

Characterization of nanoparticles

After synthesis of nanoparticles, their characterization is also important. Nanoparticles are generally characterized by their size, shape, dispersity, and surface area [90]. Homogenizations of all these properties are important in many applications. The common techniques for the characterization of nanoparticles are as follows: UV–visible spectrophotometry, powder X-ray diffraction (XRD), dynamic light scattering (DLS), Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), transmission electron microscopy (TEM), and energy-dispersive spectroscopy (EDS), [61].

The UV–Visible spectroscopy is a commonly used technique among them [82] in which the light wavelength in the range 300–800 nm is generally used for the characterization of metal nanoparticles in the size range of 2–100 nm [91]. For the characterization of gold and silver nanoparticles, spectrophotometric absorption measurements in the size range of 500–550 and 400–450, respectively, used. UV–Visible spectrum of ZnO nanoparticles synthesized from *A. vera* shows absorption peak

ranging from 358 to 375 nm and this is due to their surface plasmon resonance [92].

Similarly, the dynamic light scattering (DLS) is used for the characterization of surface charge and the size distribution of nanoparticles which is suspended in liquid medium [93].

X-ray diffraction (XRD) pattern is also important for the phase identification and characterization of the crystallinity of nanoparticles and phase distribution of the biosynthesized nanoparticles [94]. For the structural information of the nanoparticles, X-rays are penetrated into the nanomaterials and the resulting diffraction pattern is compared with the standard pattern to get the final information. Arumugama et al. [95] found that XRD peaks located at angles (2ɵ) of 28.51, 33.06, and 47.42 correspond to 111, 200, and 220 planes, in comparison with the standard diffraction pattern; it shows the face centre cubic phase of CeO_2 nanoparticles.

Elemental composition of nanoparticles is commonly determined using energy-dispersive spectroscopy [96].

For the morphological characterization of nanoparticles at the nanometre and nanoscale ranges, scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are normally refers [97]. TEM analysis TiO_2 nanoparticles explored that they are mostly spherical in shape in the range of 10–30 nm. Further study carried out using SAED revealed that they have crystalline structure [98]. It has been found that TEM has 1000-fold higher resolution as compared to SEM.

FTIR is also used for the characterization and identification of surface chemistry. Organic functional groups (like carbonyls and hydroxyls) are found to attach to the surface of nanoparticles and other surface chemical residues are generally determined using FTIR. Sankar et al. [99] reported that FTIR spectroscopy is also used to determine the nature of functional groups that are present on the surface of nanoparticles and might be responsible for the synthesis and stabilization of metal nanoparticles. The FTIR spectrum of ZnO nanoparticles synthesized using *A. vera* extract shows peaks between 600 and 400 cm^{-1}. In general, functional group bands observed at 3450, 3266, and 2932 cm^{-1} are allotted to stretching of alcohols and C–H stretching of alkanes, respectively, for the nanoparticle synthesized using plant extract *of A. vera*. Silver nanoparticles synthesized using leaf extract of *Solanum turvum* leaf extract show peaks at 1648, 1535, 1450, and 1019 cm^{-1} and further study on this found that peak at 1450 cm^{-1} of carboxylate ions was found to be responsible for the stabilization of silver nanoparticles [100].

Effects of various factors to the formation of nanoparticles mediated by plants

This has been widely accepted that microorganism and plant extracts can be used to synthesize metal nanoparticles. However, different controlling parameters, such as metal salt concentration, mixing ratio of biological extract and metal salt, pH value, temperature, incubation period and aeration, still require optimization for producing homogenous nanoparticles of a similar size and shape. Biological synthesis approaches can also provide an additional capping layer on synthesized metal nanoparticles with the attachment of several functional groups which are found to be biologically active, which can enhance the effectiveness of metal nanoparticles [101]. Influence of various factors to the formation of monodispersed, stable, and high-yield biological nanoparticles using plant extracts is as discussed below:

Temperature plays an important role to control the aspect ratio, relative amounts, size, and shapes of nanoparticles. Variation in temperature in reaction conditions results in changes in fine tuning of the size, shape, and optical properties of nanoparticles [75]. It has been found that leaf extract of two plants *M. kobus* and *D. kaki* shows more than 90% conversion of gold nanoparticles at a reaction temperature 95 °C with in a very short period of time suggesting reaction ratio of higher or comparable to those of nanoparticles synthesis by chemical methods [65]. Synthesized gold nanoparticles were shown to increase their size at higher reaction temperature which is due to an increase in fusion efficiency of metal ions which dematerialize super saturation [93]. pH of the medium also affects the size of nanoparticles at great concern. Researchers found that by altering the pH of the medium, gold nanoparticles synthesized by the plant extract of *A. sativa* were majorly controlled. It is also found that when co-precipitation method was used to synthesize magnetite nanoparticles, their formation has also been found to be influenced by pH.

However, other than pH and temperature, there are other factors also play an important role in nanoparticle synthesis [102]. Similarly, the bond group energy was found to be increased when dopant concentration is increased in ZnS samples which were further determined by optical absorption spectroscopic techniques. When aqueous solution of auric chloride is treated with high concentration of NaCl, the size of gold nanoparticle decreases with increase in NaCl concentration, nanoparticles synthesized have size range of 5–16 nm, and those which were synthesized without the addition of NaCl solution have size ranges of 11–32 nm [103]. Chloride, bromide, and iodide have to be known to affect nanoparticle formation in plants. Chloride promotes the growth of triangle nanoparticles, while the iodide causes alteration in nanoparticle morphology and induces finally of aggregated spherical nanoparticles. In case of copper nanoparticles, chloride ions cause formation of diamond-shaped nanoparticles. When sundried biomass of plant *Cinnamonum camphora* leaf was when treated with aqueous solution of silver or gold metal ions at ambient temperature, it produces both gold and silver nanoparticles of size ranges (55–80 nm) which are spherical or triangular in shapes that

could be attributed to the comparative protectable of secondary metabolites from leaf extracts. The polyol water-soluble heterocyclic compounds are mainly known to be responsible for the reduction of silver ions or chloroaurate ions [104].

Pharmacological applications of nanoparticles

Nanoparticles synthesized by various methods have been widely used in diverse in vitro diagnostic applications [105]. It has been found that gold and silver nanoparticles have widely used as an antimicrobial agent for a wide variety of human and animal pathogens [106]. Silver nanoparticles are already reported to widely applicable as an antimicrobial agent in a commonly available medicines and consumer products [98]. Nanoparticles can also be used as a biosensor. Gold nanoparticles can be used for the treatments of illness and also the staining of glasses and enamels [107]. Metal nanoparticles have emerged as a new drug delivery strategy for transporting drugs and gene through the nanosized delivery systems, because they have high surface area, low toxicity, and tunable stability. Citrate-stabilized gold nanoparticles were widely used to target HSC3 cancer cells (human oral squamous cell carcinoma). These gold nanoparticles were coated with anti-EGFR (Epidermal growth factor receptor) to target the cancer cells [108]. The efficiency of gold nanoparticles was enhanced by photo thermal effect which is increased 20 times more due to the local heating effect induced by the irradiation of light. Other pharmaceutical applications are discussed below.

Antimicrobial activity

Silver nanoparticles are well known for their antimicrobial activities, especially for their antifungal, anti-inflammatory, and antiviral activities. It has been found that silver nanoparticles inactivate the microbes by interacting with microbial enzymes, proteins or DNA to inhibit their multiplication [109]. Product forms by the interaction of silver and thio containing compounds where found to be highly active against several bacterial activities [110]. Antibacterial activities of silver nanoparticles were found to be shape dependent. For this, Elechiguerra et al. [111] carried out a study in which they used different shaped silver nanoparticles against some Gram −ve bacteria such as *E. coli*. They found that truncated triangular nanoparticles show the strongest activity as compared to spherical-shaped nanoparticles and nanorods. Silver nanoparticles were also found to be highly active against human immunodeficiency virus (HIV) infections [111]. Valodkar et al. [47] found that during in vitro study of silver and gold nanoparticles of size range of 1–10 nm, and they could interact with the glycoprotein of HIV-1 and inhibited the binding of virus to the host cells.

Sondi and Salopek-Sondi [112] found that silver nanoparticles are highly active against pathogenic bacteria. They disrupt the polymer subunits of cell membrane of pathogens. These nanoparticles subsequently stop the cell membrane and inhibit protein synthesis mechanism of bacterial system. It has been found that high concentrations of silver nanoparticles have higher permeability than those of lower concentration of silver nanoparticles and consequently rapture the cell wall of bacteria [56]. Antony et al. [113] reported that silver nanoparticles synthesized by *Rhizophora apiculata* show low number of bacterial colony in the text plate as compared to the silver nanoparticle-treated cell which is due to the smaller size of the particles and large surface area that induce increase in the membrane permeability and cell distraction. Metal nanoparticles bind with active sites of bacteria to inhibit the cell cycle function [114]. Antibacterial properties of silver nanoparticles can be used as disinfectant to clean the materials and devices used in hospitals. Extracellularly synthesized gold and silver nanoparticles were effectively used in cleaning the materials such as clothes and some medical devices used in hospitals to prevent infections with pathogenic bacteria [115]. Silver nanoparticles also used in topical ointments and creams for the prevention of infection during burns and wounds [115]. Another study was carried out to study the effect of chemically and biologically synthesized silver nanoparticles on Gram +ve and Gram −ve bacteria, and obtained results were indicate that biogenic silver nanoparticles have higher toxicity then that of chemically synthesized silver nanoparticles. Suresh et al. [116] have found that different chemical and biological coatings on the nanoparticles have highly significant effect on their toxicity which could be the result of interaction between capping agent with the bacteria. This study shows that the biologically synthesized silver nanoparticles have the highest antibacterial activity due to their stronger surface interactions with the bacteria which is achieved by their biological capping agents.

Fungicidal effects of biosynthesized metal nanoparticles have more potential then the commercially available antibiotics such as amphotericin and fluconazole. Plant extract-based synthesized silver nanoparticles have been used against *Candida* sp. They showed membrane damage and damage in fungal intracellular components and then finally lead to the death of fungal cell [117]. Commercially available antifungal agents have limited applications and they cause more adverse effect and less recovery from the microbial diseases. Like that, a commercial drug induces side effects such as liver damage, nausea, renal failure, increased body temperature, and diarrhoea after administration of drugs. Nanoparticles are found to be novel and more effective drug against microbes. Silver nanoparticles

are active against spore-producing fungus and they effectively inhibit the fungal growth. Fungal cell is mainly made up of fatty acids and proteins. When fungal spore is bound with metal nanoparticles, it showed significant changes in their membrane structure [25].

Mechanism of antimicrobial activity of nanoparticles

The actual mechanism of antimicrobial activity of metal nanoparticles is still not clearly known. However, there are several reports available describing the possible mechanism behind its antimicrobial activity. It has been found that antimicrobial property of metal nanoparticles largely depends upon on several parameters including size, shape, and the surface charge of the particle [118]. Nanoparticles bind with the bacterial cell wall and can easily penetrated into it especially in Gram −ve bacteria, and then, they stop the protein synthesis, inactivate the DNA and the enzymes, and finally lead to death of the bacterial cell. In addition, nanoparticles also have large surface area for powerful microbial interaction [91]. Figure 4 shows possible mechanism of antimicrobial action of metal nanoparticles [331]. Activity of nanoparticles also depends on the morphology of nanoparticles. Pal et al. [91] reported that silver

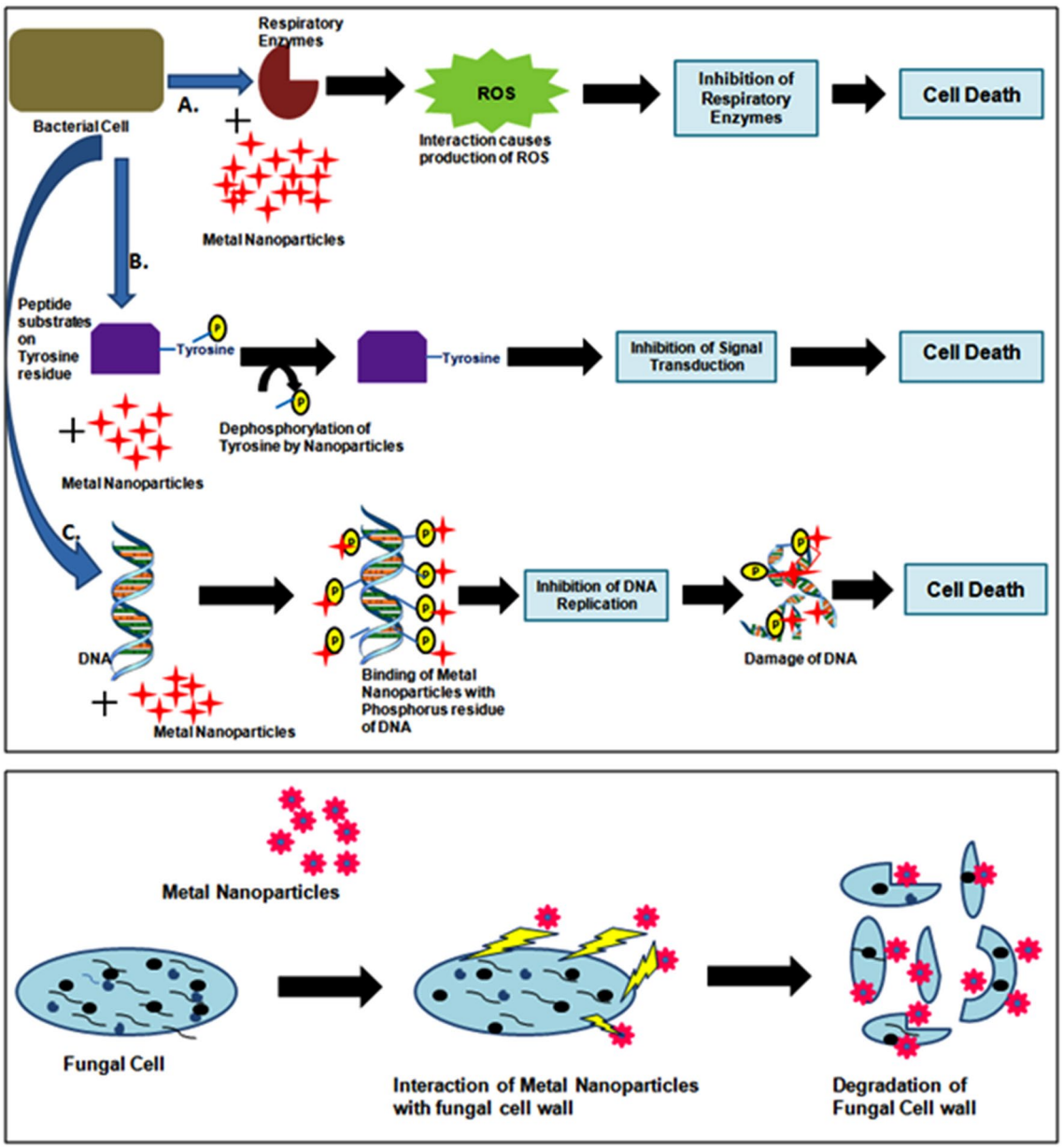


Fig. 4 Diagram showing possible mechanism of antimicrobial activity of metal nanoparticles

nanoparticles with the same surface area but having different shapes can show diverse antimicrobial activity which may be due to difference in their effective surface area and active facets. Nanoparticles with triangular shapes show the highest antimicrobial activity, and this is due to that they have larger surface area-to-volume ratios and also their crystallographic structures. Due to their large surface area, nanoparticles accumulate on the surface of bacterial cell wall and enter by endocytosis. Sometimes, silver nanoparticle produces free radicals which may also cause the cell death of microbes. Because the free radicals have the capacity to damage the cell wall and the respiratory tract and make them more porous which ultimately terminate the microbes [119]. Another report leads to the fact that nanoparticles can regulate the signal transduction process in bacteria. In bacteria, signal transduction process is induced due to phosphorylation of protein substrates. It has been found that the nanoparticles alter the phosphorylation of peptides in bacteria. They dephosphorylate the peptides of tyrosine residue which causes the hindrance of signal transduction and thus leads to death of microbes [120]. The electrostatic force between the negatively charged bacterial cell and the positively charged nanoparticles is also another important factor for the antimicrobial activity. We all know that the Gram +ve and Gram −ve bacteria have different cellular membrane structures; most of them, they contain a -ve charge on their cell surface, so that the silver nanoparticles show greater antimicrobial activity as compared to Gram +ve bacteria [121]. In addition, it was also reported that the silver nanoparticles interact with sulfur and phosphorus residues of the DNA and inhibit the replication of DNA and thus lead to death of microbes. Silver is soft acid and there are natural trends that soft acid reacts with soft base [122] and the sulfur and phosphorus are soft bases. Microbes contain sulfur and phosphorus to their cellular constituents and also the DNA is mainly build up of sulfur and phosphorus residues. The nanoparticles react with these sulfur and phosphorus of DNA and cell surfaces and finally lead to death of microbes. However, further research is needed to find out the actual mechanism of this.

Anticancer activity

Toxicity of plant latex capped silver nanoparticles was tested against human lung carcinoma cells, and through this study, researchers found that these silver nanoparticles are toxic-to-AS49 cells in a dose-dependent manner. Later, detailed study of this suggested that plant latex can act as stabilizing agents for the silver nanoparticles in water and can also be responsible for the transportation of nanoparticles to the target cells [64]. Gibson et al. [123] successfully synthesized gold nanoparticles of 2 nm size which is incorporated within a chemotherapeutic drug, Paclitaxel. TGA analysis of this reveals that about 70 molecules of paclitaxel could be attached with one gold nanoparticle. This kind of biomolecules can be used as scaffold for the delivery of large biomolecules such as nucleic acid like DNA/RNA [124] also the peptides and proteins [82]. Similarly, Mukherjee et al. [125] found that gold nanoparticles attached with VEGF antibodies can be effectively used in treatment of B-chronic lymphocytic leukemia. However, there are many applications of gold and silver nanoparticles in biomedicines, but the toxicity issue of these nanoparticles is also a major issue to consider. Pan et al. [126] suggested that instead of biologically synthesized gold and silver nanoparticles, chemically synthesized nanoparticles cause more toxicity. While gold and silver nanoparticles synthesized by natural bioreduction method may offer an alternative way which cause low toxicity and are highly biocompatible. In addition to the compositional of nanoparticles, it is their ligand chemistry, which is also an important parameter that affects the biocompatibility of nanoparticles [92]; Rajkumar and Abdul Rehuman [127] found that silver nanoparticles also exhibit larvicidal activity against filariasis and malaria vectors and are also active against some plasmodial pathogens and cancer cells [42].

Anti-inflammatory activity

Anti-inflammatory effect is important for wound healing mechanism. Anti-inflammation is biological channel process which produces some compound such as cytokines and interleukins, which is produced by specific T lymphocytes, B lymphocytes, and macrophages [128]. Endocrine systems secreted various inflammatory mediators like enzymes, antibodies etc. Anti-inflammatory agents such as cytokines, IL-1 and IL-2 are secreted from the primary immune organs [84]. These inflammatory mediators are found to be involved in the biochemical pathways and also control the expansion of diseases. It is reported that gold and platinum nanoparticles synthesized from plant extracts have significant positive wound healing mechanism and tissue regeneration through inflammatory functions [129], so that it can be concluded that gold and platinum nanoparticles are used for the preventing inflammation naturally.

Antiviral activity

Obtained results suggested that plant-derived nanoparticles can be used as alternative drugs for the treatment and control of growth of viral pathogens. Viruses enter to the host very rapidly and multiply their colonies very frequently. Silver nanoparticles synthesized by plant extract can be act as potent antiviral agent for a wide range of viral infections. Suriakalaa et al. [130] studied the efficiency of biosynthesized silver nanoparticles against HIV pathogens. They found that these nanoparticles have effective anti-HIV action at an early stage of reverse transcription mechanism. It is reported

that metallic nanoparticles can be used as strong antiviral agent, because they inhibit the entry of viruses into the host system. Mechanism for anti-HIV activity is found that metallic nanoparticles have multiple binding sites to bind with gp120 proteins of viral membrane to control the function of viruses. These bio-based nanoparticles are found to be active against cell free viruses and also the cell associated viruses [131]. Recently, it has been found that gold and silver nanoparticles are successfully used for the inhibition of post-entry stage of the HIV-1 life cycle, so that metal nanoparticles can be used as effective antiviral drug against retro viruses.

Antioxidant activity

Metal nanoparticles also contain antioxidant activities. Antioxidant agents mainly include enzymatic and non-enzymatic substances that can be regulate the formation of free radicals. These free radicals are found to be responsible for the causing cellular damage including brain damage, cancer, and atherosclerosis [132]. These free radicals are generated by reactive oxygen species (ROS) such as hydrogen peroxide, superoxide dismutase, and hydrogen radicals. It is reported that the biomolecules such as proteins, lipids, fatty acids, glycoproteins, phenolics, flavonoids, terpenoids, and sugars strongly controlled the growth formation of free radicals [133]. Antioxidant efficiency of silver nanoparticles was found much higher than that of other synthetic commercially available materials such as ascorbic acid and so on. Scavenging effect of antioxidants is found to be useful for the management of several chronic diseases such as diabetes, cancer, AIDS, nephritis, and metabolic disorders. Biosynthesized metal nanoparticles contain high phenolics and flavonoids content in the extract [134].

Anti-plasmodial activity

Nanoparticles are found to be used as anti-plasmodial agents. In recent years, most common diseases are spreading everywhere by vectors. Control of these vectors is more required in endemic disease situation. Advanced specific anti-plasmodial agents are found to be ineffective against some of the vectors. Use of metal nanoparticles as anti-plasmodial agent is found to be more economic but less effective to control the target organism in the health care centres [135], so that effective and affordable anti-malarial drugs are required to control the plasmodial activity. Last few decades, plants have been used as traditional sources for the development of drug for anti-malarial diseases. Jayaseelan et al. [135] found that plant-derived chemicals such as quinine, artemisinin, and aromatic compounds are efficiently used against malarial parasites. Due to their high resistance, alternative drug is required to immediate control of pathogens. It is found that plant-derived nanoparticles such as gold, platinum, palladium, and silver are used for the effective control of malarial population in the environment. In addition, the silver nanoparticles synthesized by plant extracts are found to be useful for the suppression of malarial parasites and their proliferation.

Anti-diabetic activity

Metallic nanoparticles are also used for the management of diabetes mellitus (DM). DM is a group of metabolic dysfunction in which person has high level of sugars in their blood. To control this certain food, and balanced diet or synthetic insulin drugs can be used at certain level, but their control treatment is a big challenge. Nowadays, metal nanoparticles can be used as alternative drug to control the DM. One study was carried out by Daisy and Saipriya [136], and they found that gold nanoparticles have good therapeutic activity against diabetic models. They used animal model such as mice for their study. They found that gold nanoparticles significantly reduce the alkaline phosphatase, uric acid, and serum creatinine in treated mice. They also found that the gold nanoparticles treated diabetic mice showed a decrease in the HbA (glycosylated haemoglobulin) level in a normal range. Similarly, Swarnalata et al. [137] found that silver nanoparticles synthesized by *Sphaeranthus amaranthoides* effectively inhibited α-amylase and acarbose sugars in diabetes-induced animal models. Later, they found that it is mainly α-amylase inhibiting compound that is present in the ethanol extract of *S. amaranthoides* [138]. Pickup et al. [139] reported that metal nanoparticles are used to control diabetes with certain level of side effects. Clinical studies in mice successfully controlled the sugar level of 140 mg/dl in silver nanoparticle-treated groups [132].

Clinically approved nanopharmaceutical products

The evolution of nanoscience and nanotechnology, which uses formation and utilization of materials at nanometre scale range, has been attracted a number of industries and particularly the pharmaceutical industry [140]. Nanotechnology is considered as a novel technology to solve the problems and can be applied as a group of ideas and approaches that can be applicable in pharmaceutical industry. In nanotechnology-based pharmaceutical products, several terminologies have been introduced including nanomedicines, nanoparticles, nanobiotechnology, and nanopharmacological are the general terminologies used to define nanotechnology for pharmaceutical applications. Nanoparticle-based pharmaceutical drugs, their marketing, and current clinical trial status are listed in Table 3. Nanotechnology has a wide range

Table 3 Overview of nanoparticle based pharmaceutical drugs and their clinical trial status

Nanoparticle based drugs	Company	Trade name/generic name/brand name	Therapeutic use	Clinical trial status/approval/ indication	References
Liposomal as nanocarriers					
Annamycin	Callisto	L-Annamycin	Acute lymphocytic leukemia, acute myeloid leukemia	Phase I	[142]
Cisplatin	Transave	SLIT Cisplatin	Progressive osteogenic sarcoma metastatic to the lung	Phase II	[142]
Vincristine	Inex, Enzon	nco TCS	Non-Hodgkin's lymphoma	Phase II/II	[142]
Doxorubicin	GP-Pharm	Sarcodoxome	Soft tissue sarcoma	Phase II	[142]
Fentanyl	Delux Therapeutics	aeroLEF	Postperative analgesic	Phase II	[142]
AmBisome®	Gilead Sciences, Inc.	Amphotericin B	Treatment of Cryptococcal Meningitis in HIV-infected patients, Treatment of visceral leishmaniasis	FDA 1997	[141]
DaunoXome®	Galen Limited, Seagoe Industrial Estate.	–	Treatment of advanced HIV-related Kaposi's Sarcoma	FDA 1996	[141]
DepoCyt®	SkyePharma Inc.	Daunorubicin citrate	Leukemias, lymphomas, and other hematologic cancers	FDA 1999/2007	[141]
DepoDur®	Flynn Pharma	Morphine sulfate extended-release liposome injection	For treatment of chronic pain in patients requiring a long-term daily around-the-clock opioid analgesic	FDA 2004	[141]
Doxil®	GlaxoSmithKline Manufacturing S.p.A. Parma, Italy	Doxorubicin HCl	AIDS-related KS, multiple myeloma, ovarian cancer (IV)	FDA 1995	[141]
Marqibo®	Talon Therapeutics, Inc.	VinCRIStine sulfate	Treatment of adult patients with Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies	FDA 2012	[141]
Mepact™	Takeda Austria GmbH	Mifamurtide	It boosts the immune system to kill cancer cells by making it produce certain types of white blood cells called monocytes and macrophages	Europe 2009	[141]
Myocet®	TEVA B.V. Swensweg 5 2031 GA Haarlem Netherlands	Doxorubicin	Metastatic breast cancer (IV)	Europe 2000	[141]

Table 3 (continued)

Nanoparticle based drugs	Company	Trade name/generic name/brand name	Therapeutic use	Clinical trial status/approval/ indication	References
Visudyne®	Valeant Pharmaceuticals, Inc	Nvartis AG	Photodynamic therapy of wet age-related macular degeneration, pathological myopia, ocular histoplasmosis syndrome (IV)	FDA 2000	[141]
Abelcet®	Sigma-Tau PharmaSource, Inc.	Amphotericin B	Systemic fungal infections (IV)	FDA 1995 and 1996	[141]
Amphotec®	Alkopharma USA, Inc.	Amphotericin b	Prescribed for life-threatening fungal infections. It is also effective in treating leishmaniasis	–	[141]
Pegylated proteins and polypeptides as nanopharmaceuticals					
Adagen®	Sigma-Tau Pharmaceuticals, Inc.	Pegademase bovine	Adenosine deaminase deficiency—severe combined immunodeficiency disease	FDA 1990	[169]
Cimzia	–	Certolizumab pegol	Crohn's disease, rheumatoid arthritis	FDA 2008	[141]
Neulasta	Amgen	Pegfilgrastim	Febrile neutropenia, In patients with nonmyeloid malignancies; prophylaxis (SC)	FDA 2002	[169]
Oncaspar	Sigma-Tau Pharmaceuticals, Inc.	Pegaspargase	Acute lymphoblastic leukemia	FDA 1994	[141]
Pegasys	Roche Ltd	PEGINTERFERON ALFA-2A	Hepatitis B and C	FDA 2002	[141]
Peglntron	Roche Ltd	PEGINTERFERON ALFA-2B	Hepatitis C	FDA 2001	[169]
Somavert	Pharmacia & Upjohn	Pegvisomant	Acromegaly, second-line therapy	FDA 2003	[169]
Macugen	Valeant Pharms LIc	Pegaptanib sodium	Intravitreal Neovascular age-related macular degeneration	FDA 2004	[169]
Micera	Roche Ltd	Epoetin beta and Methoxy polyethylene glycol	Anemia associated with chronic renal failure in adults	FDA 2007	[141]
Polymer-based nanoformulations as pharmaceuticals					
L-Leucine, L-glutamate copolymer and Insulin	Flamel Technologies	Basulin	Type I Diabetes	Phase II	[142]
Polyglutamate camptothecin	Cell Therapeutics	CT-2106	Colorectal and Ovarian cancers	Phase I/II	[142]
PEG anti TNF-α antibody fragment	Nektar	Cimzia	Rheumatoid arthritis and Crohn's disease	Phase III	[142]
HPMA copolymer-DACH platinate	Access Pharmaceuticals	ProLindac	Ovarian cancers	Phase II	[142]
Polycyclodextrin camptothecin	Insert Therpeutics	IT-101	Metastatic solid tumors	Phase I	[142]
Calcium phosphate nanoparticles vaccine adjuvant	BioSante	BioVant	Vaccine adjuvant	Phase I	[142]
Poly-L-lysine denrimer	Starpharma	VivaGel	Antimicrobial protection from genital herpes and HIV infection	Phase I	[142]

Table 3 (continued)

Nanoparticle based drugs	Company	Trade name/generic name/brand name	Therapeutic use	Clinical trial status/approval/ indication	References
Nanocrystalline 2 methoxyestradiol	Elan, EntreMed	Panzem NCD	Schizophrenia	Phase II	[142]
Paclitaxel nanoparticles in porous, hydrophilic matrix	Acusphere	AI-850	Solid tumors	Phase I	[142]
Copaxone	Teva Pharmaceuticals USA, Inc.	Glatiramer acetate injection	Multiple sclerosis (SC)	FDA 1996/2014	[141]
Eligard	Tolamr Pharmaceuticals Inc.	Leuprolide	Advanced prostate cancer (SC)	FDA 2002	[141]
Opaxio	Cell Therapeutics, Inc.	Paclitaxel poliglumex	Glioblastoma	FDA 2012	[141]
Renagel	Genzyme corporation	Sevelamer	Hyperphosphatemia (oral)	FDA 2000	[141]
Zinostatin stimalamer	–	Neocarzinostatin	Primary unresectable hepatocellular carcinoma	Japan 1994	[141]
Genexol	Samyang Biopharm	–	Metastatic breast cancer, pancreatic cancer (IV)	South Korea 2001	[141]
Nanocrystals					
Emend	Merck & Co., Inc.	Aprepitant	Emesis, antiemetic	FDA 2003	[141]
Megace ES	ENDO PHARMS INC	Megasterol	Anorexia, cachexia	FDA 2005	[169]
Rapamune	PF PRISM CV	Sirolimus	Immunosuppressant	FDA 2002	[169]
Tricor	AbbVie	Fenofibrate	Hypercholesterolemia, hypertriglyceridemia	FDA 2004	[141]
Triglide	Shionogi, Inc.	Fenofibrate	Hyperlipoproteinemias	–	[141]
Protein–drug nanoconjugates					
Abraxane	Celgene	–	Metastatic breast cancer, non-small-cell lung cancer (IV)	FDA 2012	[169]
Kadcyla	Roche and ImmunoGen	Ado-trastuzumab emtansine	Metastatic breast cancer	FDA 2013	[169]
Ontak	EA Pharma Co., Ltd.	Denileukin diftitox	Primary cutaneous T cell lymphoma, CD25-positive, persistent or recurrent disease	FDA 1994/2006	[141]
Surfactant-based nanoproducts					
Fungizone	Abbott Healthcare Pvt. Ltd.	–	Systemic fungal infections (IV)	FDA 1966	[141]
Diprivan	Fresenius Kabi USA	Propofol	Sedative–hypnotic agent for induction and maintenance of anesthesia (IV)	FDA 1989	[141]
Metal-based nanoformulations					
Feridex	AMAG Pharmaceuticals, Inc.	Ferumoxide	Liver/spleen lesion MRI (IV)	FDA 1996 Manufacturing discontinued in 2008	[141]

Table 3 (continued)

Nanoparticle based drugs	Company	Trade name/generic name/brand name	Therapeutic use	Clinical trial status/approval/indication	References
Feraheme	AMAG Pharmaceuticals, Inc.	Ferumoxytol	Treatment of iron deficiency anemia in adults with chronic kidney disease	FDA 2009	[141]
NanoTherm	Magforce the nanomedicine company	–	Local ablation in glioblastoma, prostate, and pancreatic cancer (intratumoral)	Europe 2013	[141]
Virosomes					
Gendicine	Benda Pharmaceutical, Inc.	Gendicine	Head and neck squamous cell carcinoma	People's Republic of China 2003	[141]
Rexin-G	Epeius Biotechnologies Corp.	Rexin-G	For all solid tumors	Philippines 2007	[141]

of scope in bio-pharmaceutical industry including diverse areas such as nanomedicine, diagnostic tools, biosensor, biomarker, implant technology, nanorobots, and as vector or carrier molecules of diagnostic and therapeutic approaches. Various nanotechnology-based pharmaceutical products are as follows:

Liposomal nanocarriers Liposomes are composed from phospholipids and cholesterols in liquid medium; they are identified by their internal spaces; and most of them are surrounded by single or multilayered phospholipid bilayers. The size distribution of liposome can range from 25 to 1000 nm. Most commonly used liposomes typically display a size range of between 50 and 200 nm. Liposomes are mainly used as drug carrier or drug-loading system for delivery of drugs. The hydrophilic molecules can be encapsulated within the aqueous internal space and the hydrophobic molecules are entrapped within the phospholipid bilayer membranes. To prepare the liposome suitable for therapeutic applications, their size distribution has to be controlled that can be achieved by passing them continuously under elevated pressure through membranes with definite pore size. Doxil is the first approved liposomal drug; in this, the PEG (polyethylene glycol) chains are present on the liposomal surface. PEG is encapsulated to phospholipids in the liposomal membrane through one-step chemical conjugation reaction [141].

Lipid-based nanoparticulate products Also known as non-liposomal nanoformulations. The uses of liposomes as nanocarriers have significant applications in drug delivery. Ambelcet and Amphotec are lipid-based nanoformulations. However, the electron microscopic images and other relevant data to support their unique ribbon and disk-like structure of these formulations occur to be unavailable [141].

PEGylated proteins and polypeptides as nanopharmaceuticals The physiological macromolecules like proteins, enzymes, and other molecules would already accept as nanopharmaceuticals due to their size alone. Nanoengineering techniques added some additional features and properties to the native macromolecules. PEGylation of biologically active macromolecules increases their hydrodynamic radius, prolong circulation, and retention time and decreases the proteolysis and renal excretion. PEGylation mainly includes attachment of PEG chain to biologically active molecules like proteins, amino acids, enzymes, etc. for extending their blood life reducing their immunogenicity. Enzon Pharmaceuticals (Piscataway, NJ, USA) established in 1981 a biotech company, which brought a large variety of PEGylated protein pharmaceutical products to the market.

Polymer-based nanoformulations as pharmaceuticals It contains a very heterogenous group of nanosize therapeutics. Eligard, Genexol, Opaxio, and Zinostatin Stimalamer are some common examples of them.

Surfactant-based nanoproducts Recently, surfactant-based nanoformulation has been evaluated. Fungizone is

a product that comprises dry powdered mixture of water-insoluble AMB and sodium deoxycholate. When buffer is added to this, deoxycholate solubilizes the drug-forming polydisperse micelles. The critical micelle concentration of deoxycholate (CMC) having size range of 2–6 nm. Estrasorb is considered as "micro-encapsulated estradiol" and described as estradiol "encapsulated using a micellar nanoparticle technology" in the package insert provided by Novavax, Inc (Gaithersburg, MD, USA) [141].

Metal-based nanoproducts Feridex is considered as an aqueous colloidal solution of superparamagnetic iron oxide particles (SPION). SPION has diameter of around 5 nm that has been surface modified with dextran which causes an increase of the particle size by increasing the hydrodynamic diameter of up to 150 nm. While ultra-SPION particles are below than 50 nm size. In 1996, Feridex was approved by FDA to administrate as a contrast media of magnetic resonance imagine (MRI). Particles of iron oxide are directly internalized by the cells of the MPS system. However, malignant transform cells contain limited ability to internalize the iron oxide. After the use of MRI liver and spleen lesions can be recognized easily than surrounding tissues, because they were not transformed. Production of Feridox was ended in 2008. Ferumoxytol which is formerly known as feraheme is an FDA-approved drug used for the treatment of iron deficiency anemia of adult people. They release the iron molecules inside the macrophages of MPS system. Ferumoxytol has been adopted as a novel superparamagnetic iron oxide colloidal blood pool contrast agent, and recently, it is under investigation as a new imaging agent for MRI-based diagnosis of cancer and other cardiovascular diseases [141].

Protein–drug nanoconjugates A large number of albumin-based therapeutic products are currently in clinical trials. Recently, albumin has received significant attention as a potential carrier for several therapeutic drugs relevant for improving the pharmacokinetic profile of the drugs. Abraxane is an albumin-based pharmaceutical product which contains 130 nm size nanoparticles from albumin conjugated with paclitaxel. Kadcyla and Ontak are referred as targeted therapeutic drugs and are immunoconjugates and a recombinant fusion protein, respectively [142].

Nanocrystals Nanocrystals comprise unique group of pharmaceuticals and they contain 100% water-insoluble drug without any additional nanocarrier system. The solid particles dissolved in aqueous medium by the Noyes–Whitney equation. According to this equation, surface area is directly proportional to the dissolution velocity. Due to this, micronization is commonly known for the formulation method of sparingly soluble compounds. Nanocrystals have unique properties as an increased dissolution pressure, which can directly attribute to their nanometre size [141].

Clinical trials of nanopharmaceutical products

In recent years, there has been a quite increase in the development of nanoparticle-based drugs and their commercialization. There are more than 150 companies and developed nanoparticle-based therapeutic products. Still, 24 nanoparticle-based therapeutic drugs have been approved for clinical uses. In this liposome, encapsulated drugs and the polymer–drug nanoconjugates are the two major classes which accounts for more than 80% of the total commercially available nanoparticle-based drugs. The biomedical applications of nanoparticle-based products are gaining more attention recently as a continuous increasing demand of nanoparticle-based pharmaceutical products. Although the recent advancements needed more attention and study to understand that nanoparticle-based drugs delivery system require additional regulatory process for final therapeutic approvals [142]. This process is highly expensive, versatile and essential regardless of the type of nanoparticle and its application. The conventional method of clinical approval of therapeutic compounds as well as nanoparticle-based products is a complex development. These are broadly categorized into following three phases: first is preclinical phase; second is clinical phase and third one is the post-marketing phase. Preclinical phase includes drug discovery, development of formulation and animal studies, clinical phase are further categorized into clinical phase I, II and III trial, post-marketing phase is considered as phase IV [143]. The guidelines for these phases are specific for a particular country. The preliminary requirement to initiate a clinical trial is to study the effect, safety, toxicity and the detailed data generation. Clinical trial phase I is conducted to explain the safety and approve the pharmacokinetic parameters like dose and forms of doses. Phase II trials are conducted to demonstrate safety, efficacy, toxicity and tolerability and the validation of this efficiency are typically performed in phase III clinical trials [144, 145]. For the demonstration of claimed clinical effect of a formulation a large number of patient populations are required. Clinical trials are the most expensive part of the drug development process [146, 147].

Case studies

There are several examples are available that highlights the growing occupancy of nanoparticle-based products in drug delivery and also in the treatment of several diseases like cancer, HIV, HSV-2 etc. Nanoparticles are actively used in the treatment of cancers as there are no pharmaceutical drugs or dosages available that able to cure this disease completely [148]. Chemotherapy and radiotherapy are approaches used in recent years to cure this but it has been found that it only extend the life span of cancer patients, including this while undergoing these this kind of therapy they also damages

the nearby healthy tissues, that has been always a matter of social debate. In recent years the nanoparticle-based drug carriers have provided an alternative approach with accessible therapeutic potential and applications that has been evaluated for their activity against these diseases. Some examples are discussed below.

Sarcodoxome

Sarcodoxome is a liposomal formulation made up of doxorubicin developed and produced by GP Pharma for the treatment of sarcoma generally soft tissue sarcoma. Soft tissue sarcoma are tumors which developed in soft tissues and joints and several other organs of the body like muscles, tendons, blood vessels, fats, nerves and synovial tissues. These are collectively referred as soft tissue sarcomas instead of their site of origin, because they exhibit similar symptoms and similar microscopic features and also share the similar treatment approaches and processes. Due to the heterogeneity of treatment of soft tissue sarcoma, the diagnosis and treatment of this cancer is challenging. Sarcodoxome is a non-pegylated liposomal product which contains Lipochromane 6. Lipochromane 6 provides stability to the formulation. Doxorubicin is entrapped on the wall of liposome which differentiates it from other conventional liposomal anti-cancerous drugs. It is also effective to treat the patient having advanced stage of sarcoma. It has been found that doxorubicin along with palliative treatments is the only therapeutic approach that is successful to treat the advanced stage of sarcoma patients. As compare to ifosfamide or dacarbazine that are conventional drugs, doxorubicin has been found to be superior to both of it. Early researches also proven that doxorubicin is highly active as compare to other therapeutic drugs or combination of therapeutic agents. GP Pharma conducted phase I and II clinical trials in Spain. Sarcodoxame initially introduced as orphan drug by EMEA in 2006. In 2007 company also successfully received similar status by USFDA. Phase III clinical trials have been done in 2011, 30% patients infected with soft tissue sarcoma shows successfully efficacy to this drug.

VivaGel

It is a dendrimer (nanoparticulate product) based product which is used for the treatment and prevention of bacterial vaginosis. The product is manufacture and commercialized by Starpharma Ltd., Australia. VivaGel is used for the prevention of genital herpes (HSV-2), HIV and other sexually transmitted diseases. The product is composed of water based vaginal gel (3% wt/wt) of SPL7013 which is an active ingredient of this formulation and produced by using Carbopol. Product is mainly composed dendrimer system with 32 amino groups and had been constructed by addition of 4 layers of L-lysine to the divalent core of SPL7013. Carbopol971PNF was used as gel thicker due to their FDA -GRAS status [149, 150]. The formulation was also tested in patient with HIV, HSV and BV. VivaGel was used for the bacterial vaginosis, which is a most common vaginal infection. In some cases the bacterial vaginal also causes HIV and other severe sexually transmitted infections. The infection also causes vaginal infections, abnormal vaginal discharge and reduced quality of life. Clinical trials have done with VivaGel have shown their affectivity and tolerance in sexually active young women and men. Due to its high activity in the prevention of HIV, this has also received a fast track status from FDA.

Opaxio

Opaxio is formerly known as Xyotax. It is polymer–drug nanoconjugate which consist paclitaxel and a biodegradable polyglutamate polymer. It is used for the treatment of cancers. Currently it is in clinical trials of ovarian and non-small cell lung cancer patients. It is also being tested for other cancers [151]. Opexio is a drug came into focus when PG-TXL company L.P. filled a patent entitled 'water-soluble paclitaxel prodrugs' in the year 1998 [152]. Further development of this product was done by Cell Therapeutic Inc. in 1998. Previously it is known as CT-2103, XYOTAX, paclitaxel polyglumex and presently known as Opaxio. Opexio enters into the tumor tissue and by the endocytosis process it is taken up by the tumor cells. Because of it is made up of biodegradable amino acid, it is metabolized by lysosomal enzymes dominantly cathepsin B. After metabolism drug is releases in the cells and results in suppression of tumor cells. Opaxio is inactivates during circulation and hence this polymer–drug nanoconjugate is considered to be safer than the other conventional paclitaxel therapeutics [152]. Currently it is undergoing Phase III clinical trials however clinical approval data for this product is not announced yet. Preclinical data published from year 1999 to 2003 shown that this product has superior properties due to its polymer contents, other properties may also include its biodegradability, lack of immunogenicity, solubilizes the hydrophobic drugs and also stable in blood circulations. It has been found that it has significantly lower toxicity than the other conventional paclitaxel containing drugs, when administered as an infusion; this is due to the presence of polymer–drug conjugate having good tolerability and lower toxicity. This was in addition to the post-administered tumor suppression exhibited by this product [152, 153]. Results of clinical trials published in American Journal of Clinical Oncology depicted with promising outcomes in phase I trials conducted on 12 patients with esophageal or gastric cancer. Phase II and III clinical trials were initiated from 2001 to evaluate the safety,

toxicity and efficacy of a Opaxio and the phase III trials are still in progress [154].

Rexin G

Rexin G is known as the "first targeted injectable molecular genetic medicine" [155]. It was clinically approved in the Philippines in the year 2007. Rexin G represents a nanopharmaceutical in which the nanomaterial, virus was prefabricated by nature. Phase I and II clinical trials have been done in united states between the years 2007 and 2012. Total six clinical trials have been made to evaluate the safety and efficacy of the Rexin G, in which 4 trials have been completed and 2 have been eliminated. Results of these 6 trials have not been available [155]. Rexin G is a virosome, which are formulated in nanocrystal form. Rexin G comprises a non Willebrand factor derived collagen binding motif was introduced via genetic engineering tools into the murine leukemia virus ectotrophic envelop protein, without changing its wild type infectivity [156].

Market outlook of nanopharmaceutical products

Last few decades new technologies and approaches have been evolved for the treatment of several diseases. Application of nanotechnology-based approaches for the development of drug delivery systems based on nanocarriers brings lots of hope and enthusiasm in modern drug delivery researches. Modern nanoscale based drug delivery devices shows several advantages including higher intracellular uptake of drug molecules than the other conventional approaches of drug delivery. In targeted therapeutic approaches nanocarriers can be conjugated with a ligand as antibody to support this [157]. The empty virus capsid can also be used for delivering drugs as a new delivery strategy. Although, toxicity concern of the nano size formulations should not be ignored. So that in this area more attention and research is needed to evaluate both the short term and long term toxicity analysis of the nano size drug delivery systems. In recent year's nanoscience and nanotechnology has been attracted considerable attention from the media as well as government funding agencies. Pharmaceutical companies now involved in the development of nanoparticle-based pharmaceutical products widely vary from big pharmaceutical industries to small start ups. Currently the market size for nanomedicine and nano pharmacological products is very small. Several Indian companies have known for the developments of nanomedicines that are in clinical trial stages, some of them have been reached phase III clinical trials [157]. Mostly the large pharmaceutical industries usually focuses on nanomedicines as their core portfolio product, at the same time the medium or small companies exclusively focus on marketing of nanomedicines [158]. Currently a large number of companies focus on application of nanotechnology in life sciences, they receive funding for this through equity capital, with preferential funding being received at a later stage, a trend similar to the biotechnology industry. In the US there is a user lead by venture capitalists (VCs) and IPOs with regards to nanotechnology-based therapeutic products related financing. According to the Ernst and Young (2008), around 308 worldwide companies who are working with nanomedicinal products and about one-third of them are commercially traded. They reported that about 52% of these companies operated from the US, followed by 21% from the Germany. These organizations are majorly categorized into following 2 groups:

(a) Industries mainly focus on life sciences applications of nanotechnology platforms.
(b) Well established pharmaceutical and other life sciences companies working on nanoparticles based therapeutic products for new development and innovations.

Some nanotechnology-based pharmaceutical companies are as follows [159–162]:

Purocom, Delhi, India is come into existence in the year 1992. Product is highly effective against the disease causing pathogenic strains of bacteria. It is mainly based on the silver nanoparticles. Silver nanoparticles are known for their great antimicrobial potential. It is recommended that it kills over 650 different bacterial species.

Aquanova, situated in Germany. It develops the micelle like encapsulation technology based on metal nanoparticles for applications in food, cosmetics and several pharmaceutical products.

Ablynx, situated in Belgium. It produces nanobodies, antibody derived therapeutic proteins which comprises unique physicochemical characteristics of naturally occurring heavy chain antibodies.

Nanobio Chemicals is a nanotechnology-based company, situated in Bilgaum, Karnataka, India. It is working on production of nanotechnology-based biofertilizers and pesticides.

Prakruthik Health Care Pvt. Ltd is situated in Hyderabad, India. It has launched nanoparticle-based cosmetic creams and herbal drugs.

Kenstar placed in Aurangabad, Maharashtra. It has launched water purifiers, which kills the harmful bacteria and viruses and make water pure. They generally use silver nanoparticle ceramic balls for water purification.

Azaya therapeutics is a pharmaceutical company situated in USA. It works on novel drug delivery system. Significant problem associated with delivery of water-insoluble drugs has been successfully achieved by nanotechnology platform addresses its proprietary protein which stabilized liposome.

Dabur pharma, situated in New Delhi, India. It is the one of the leading company of India. It is working on development of novel root for drug delivery system for Paclitaxel. Nanoparticle-based delivery system has accepted as potential super generic also the better safety and pharmacokinetic properties.

NanoViricides, situated in USA, are nanobio-phramaceutical company which utilizes nanoscale range products to produce drugs against a wide range of human and animal pathogenic viruses.

Aposense, placed in Israel. It is a well known nanopharmaceutical industry working on introduction of novel agent based on the identification and targeting of cells undergoing apoptosis.

Research needs and future prospects

Metal nanoparticles are considered as one of the most attractive research areas with various applications like electronics, textiles, antimicrobial, bioremediation, catalytic and several biomedical applications. The present review summarizes literature for understanding of biosynthesis of metal nanoparticles using plant extracts and their pharmacological applications. Synthesis of metal nanoparticles using plant extract is useful not only because its reduced environment but also because it can be used to produce large quantities of nanoparticles. In biosynthesis process of nanoparticles plant extract act as a reducing agents as well as stabilizing agents also. There are mainly two reasons to be explored in the biosynthesis of metallic nanoparticles, they are as follows: Firstly to identify the active metabolites of plants which is involved partially/fully in the metal reduction reaction and the second is laboratory scale production of metallic nanoparticles to extent their large-scale production and increase their functional mechanism against a wide range of pathogenic organisms.

A detailed study is required to give actual mechanism of biosynthesis of metal nanoparticles using biomolecules present in different plant extracts that would be valuable to improve the properties of metallic nanoparticles. The most of biosynthesis approaches reported earlier are committed to only silver and gold nanoparticles which may be due to their usefulness in biomedical sciences particularly in disinfection science. This reports concerned to the various other metals and their oxide nanoparticles like Pb, Pd, Ru, CeO_2, CuO, MgO, FeO, TiO_2 and ZnO nanoparticles synthesized by biological methods which also have essential roles in human benefits. Other considerable efforts is also require to obtain secondary metabolites from the natural resources so that it can be used as reducing, stabilizing and capping agents in the biosynthesis process of nanoparticles. The most of these researches have been carried out in research laboratories at small scale level but exploration and uses of nanoparticles at large-scale level in agricultural field, environment, medical sciences, catalysis and other field of sciences to achieve the future demands of growing population of world is necessary.

Concluding remarks

This review paper summarizes the recent research advances in the field of metal nanoparticle synthesis through plant extract and critically discusses the various mechanism proposed behind it. Plants or their extracts can be effectively used in the biosynthesis of metallic nanoparticles, as a greener approach. By using the plants control over the size and shape of nanoparticles thought to be very simple and easy. Nanoparticles synthesized through plants have been used in various applications. However the actual mechanism of synthesis of such metallic nanoparticles using plant extracts is not fully known. Only a few clues are available like involvement of phenolics, steroids, proteins and reducing agents in the synthesis of nanoparticles. Nowadays elucidation of the mechanism of plant extract-mediated synthesis of nanoparticles is a very new area of current research. Hence the information available in this article may be useful in understanding in the mechanism of synthesis of nanoparticles using plants as well as it also opens the way for exploring other plants for this purpose. There is a critical need in the field of nanotechnology is to develop a reliable, eco-friendly and cost effective approaches for the synthesis of metallic nanoparticles. To accomplish this it is necessary to use natural bioresources like plants and microbes. Plants can be used as an efficient source to produce metal nanoparticles.

The major advantages of green synthesis of nanoparticles are their application in protecting the environment, which is also one of the most important aspects in protecting the environment. We can also control the shape and size of the nanoparticles by varying in the reaction conditions. However the biosynthesis of nanoparticles by using plant system is still at its initial stage and currently still under exploited. The plant biomolecules such as flavonoids, reducing sugars, terpenoids, proteins and alkaloids are known to play important role during the bioreduction of metallic nanoparticles. However due to the complex nature of plant systems, more experiments are required to elucidate the synthesis mechanism so that a better process design can be implemented. Including this nanoparticles are providing a new direction to therapeutic strategies and providing a new hope for the treatment of several diseases. The success of nanoparticles based pharmaceutical

products in clinical trials will thus not only boost future research but also provide a new therapeutic regime for some of the untreatable diseases, in addition to improved patient compliance.

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Compliance with ethical standards

Conflict of interest It is hereby stated that the authors have no competing interests.

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