Chapter

Phyto-Metallic Nanoparticles: Biosynthesis, Mechanism, Therapeutics, and Cytotoxicity

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Abstract

Nanoparticles synthesized from noble metals have wide applications in therapeutics and medicine due to their excellent properties. Properties such as surface plasmon resonance, low toxicity, biocompatibility, and ease of surface modification account for the recent surge in nanoscience and technology. Noble metals such as gold, silver, copper, iron, and platinum with nano size are well-known metallic nanoparticles with increasing applications in nanomedicine. Biomedical applications of these particles especially for diagnosis and targeted drug delivery in living systems require considering the toxicity level. Because of their surface electrons, metal ions in solution affect cellular activities via cell division, apoptosis, DNA replication, homeostasis etc. They influence cell viability through metabolic outputs in both desired and undesired paths which may result in chemical and or biological toxicity to cells. Phyto-metallic nanoparticles biosynthesised from plant extracts are reported with improved functionalities for biomedical applications over those from chemical and physical methods. The synergies from the natural organic properties of the plant and the metallic properties elicit minimal cytotoxicity paving way for their different biomedical applications. This chapter is intended to provide an overview of recent advances and new perspectives in phyto-metallic nanoparticles, their biosynthesis and mechanism, therapeutics, and cytotoxicity to biomedical industries, research centres, and academia.

Keywords: biosynthesis, cytotoxicity, phytochemicals, nanoparticles, metal precursors, therapeutics

1. Introduction

Medicinal application of plants and the development of green nanotechnology stimulated the use of plant phytochemicals in the green synthesis of metallic nanoparticles (MNPs). Metals such as gold, silver, zinc, tin, platinum, lead, copper, palladium and so forth are easily bio-reduced to phyto-metallic nanoparticles (PMNPs) in the range 1 nm and 100 nm by phytochemicals from plants through biosynthesis and green nanotechnology methods [1]. These methods are reported to eliminate the use of toxic solvents and chemicals, minimize cost, and the loss of atom

economy associated with chemical and physical methods [1, 2]. In the biosynthesis of nanoparticles, bio-nanomaterials are synthesized using natural products of plant and plant-derived compounds (phytochemicals), microbes (bacterial, yeast, fungi, viruses, and algae), and animals. Plant phytochemicals are prevalently used due to their bioavailability and relatively low experimental costs. The phytochemicals possess functional groups such as hydroxyl (–OH), amide ($–NH_2C=O$), carbonyl (C=O), carboxylic (–COOH) etc. with reducing/stabilizing abilities through π-π dative bonding, hydrogen bonding, and electrostatic interactions [3]. This stabilization is reported to enhance the activities of a metal-based drug through size reduction, increase surface area, drug durability and biodistribution through tissue/cell binding [4]. During biosynthesis with phytochemicals, crude extract, or compounds isolated act as reducing/capping agents for single or bimetallic precursors to form their respective single PM-NPs or phyto-bimetallic nanoparticles (PBM-NPs) [1, 5]. These nanoparticles can interface with biological systems as drugs, diagnostic tools or as implants due to their physical, chemical, and biological properties.

For therapeutics and nanomedicine, metallic nanoparticles (MNPs) capped with plant extracts rich in phenolics, alkaloids, and terpenoids contents through biological methods have shown increased acceptance over chemical and physical methods [6]. The plant-based synthesis method of metallic nanoparticles as biomaterials is less expensive and eco-friendly. The method involves bio-reduction, nucleation and growth, capping and stabilization of metals and transition metals, notably gold (Au), silver (Ag), platinum (Pt), palladium (Pd), copper (Cu), iron (Fe), zinc (Zn) precursors using phytochemical constituents of plants. A unique property of noble metals is the surface plasmon resonance (SPR) phenomenon, due to the availability of free electrons oscillating at the metal surface near the visible frequency range (260–800 nm). Absorption of UV light in this region is responsible for the color changes observed from their aqueous solutions [7–9]. Interactions of surface electrons with reducing agents from phytochemicals cause the free electrons to collectively oscillate at a unique frequency specific to each metal. With the interaction between phytochemicals (capping agents) and metal precursors, the surface chemistry of the metals after synthesis is enhanced making PBM-NPs as good drug carrier for targeted drug delivery and improving biodistribution and clearance in the body [10, 11]. Biomedical applications of these materials in living systems require consideration of the toxicity level of the nanoparticles. The synergies provided by phytochemicals in the synthesized metallic nanoparticles are believed to reduce the inherent toxicity of metal nanoparticles with living cells and elicit selective cytotoxicity on bacterial and cancer cells [12]. Based on recent findings, schematic studies of PM-NPs in biomedical applications covers their activities as bactericidal, anticancer, antioxidants, antifungal, cytotoxicity, formation, and mechanism of action [13].

2. Biosynthesis of metallic nanoparticles

Synthesis of nanoparticles generally involves two approaches: the top-down and bottom-up approaches. The top-down approach requires physical methods to disintegrate bulk materials into smaller units in the nano range. Typical methods such as electron beam lithography, laser ablation, spray pyrolysis, arc discharge, milling and so forth are physical methods used in a top-down approach. On the other hand, the bottom-up is simply a build-up of nanomaterials from smaller atoms/molecules through chemical or biological methods. In the chemical method, chemical substances

with reducing properties are used to convert the metallic salt solution to a nanoscale [14]. Commonly used chemical reducing agents are sodium citrate, Cetyltrimethylammonium bromide (CTAB), sodium borohydride ($NaBH_4$), sodium tetrachloroaurate dihydrate salt ($NaAuCl_4.2H_2O$) etc. The physical and chemical methods are highly expensive and non-green methods resulting in increased environmental pollution and the release of toxic chemicals. Over the past few decades, there has been a surge in green chemistry through plant-based metallic nanoparticles research-based. The concept of green chemistry seeks to ensure the sustainable safety of humans, and the environment and process efficiency with the use of biodegradable and eco-friendly materials [15]. Thus, the biosynthetic route to PM-NPs helps to achieve this purpose with wide application in nanomedicine.

The biosynthesis of metal nanoparticles is a paradigm shift from the conventional physical and chemical methods due to their drawbacks. It is a biological method that applies green technology in the production of chemical substances using natural products of plants, microorganisms, and biomolecules from animals. The method has attracted huge attention as it displays efficient and effective utilization of the principle of green chemistry. Synthesis using plant extract and microorganisms is well documented with the advantage of being eco-friendly and does not involve the use of hazardous chemicals [2, 16]. However, the higher experimental cost and slow synthesis time due to microbial culture and growth, and the risk of infection with microorganisms are major concerns with the use of microorganisms. Biosynthesis through plant phytochemicals is relatively fast, safe, and suitable for large-scale synthesis [17]. Another biological method reported involves the use of natural products of animal origin. Although rarely used, this method involves biomolecules such as peptides or blood serum extracted from animals in nanoparticle synthesis [18, 19]. Animal blood serum consists of fibrinogen, globulin, albumin blood proteins and polypeptides that are biocompatible for use in the synthesis of NPs. These biomolecules are potentially reducing agents for metal ion reduction due to their involvement in oxidation/reduction reactions in animals. The redox properties, availability from slaughterhouses and their biocompatibility are reasons researchers used the blood serum as an alternative to the conventional synthesis of metallic nanoparticles [17].

In PM-NPs, extracts, and isolated bioactive compounds from plants serve as both reducing and stabilizing agents in place of chemical-reducing agents during biosynthesis. The effectiveness of biosynthesis with phytochemicals over non-biogenic synthesis was evidenced by Buono et al. [20] in the biogenic zinc oxide nanoparticles (ZnO-NPs) synthesis from the extract of *Lemna minor* (duckweed). The bioactive compounds of plants are mainly secondary metabolites (alkaloids, terpenoids, flavonoids, phenolics, steroids) that are not involved in the vegetative growth of plants but have an important function in the survival of plants as defense agents against herbivores, metal transporting agents, antibiotic agents, enzymes inhibitors etc. [3]. Activities of these secondary metabolites in green nanotechnology are reported to elicit bioreduction of metal ions to stable oxidation states through electron donations to metal ions to form stable atoms [14]. Because of this role of phytochemicals in green nanotechnology, much attention has been given to their extraction and isolation of the pure compounds.

2.1 Extraction and isolation of phytochemicals

Plant phytochemicals used for the synthesis of PM-NPs are mostly obtained from the leaves, stem, or tuber of the plant through decoction, infusion in water or aqueous

ethanol [21]. The plant materials collected are cleaned of dirt and dried under shade for a few days until completely dried before use. The shade-dried material is ground to particulate matter to achieve complete extraction and a high percentage yield. The extract obtained is then sieved and filtered using Whatman No.1 filter paper. Further purification by centrifugation (600–800 rpm for 20 minutes), washing and filtration with an appropriate syringe filter give a pure extract of the plant. The freshly prepared aqueous extract can be made to powder by heating at 70°C or through lyophilization [5]. The above method is considered simple and conventional but with the limitation of involving the use of excess solvent and longer extraction time. The non-conventional methods for extraction of plant phytochemicals involve the application of improved technology like microwave, ultrasound, pressurized liquid, and enzymes assisted extraction [21, 22]. Both methods yield crude extract which serves as a bio-reducing/capping agent for the synthesis of PM-NPs. To identify specific phytocompounds present in the crude extract and their roles in biosynthesis, the crude extract is subjected to further extractions/isolation and characterization procedures such as HPLC, LC-MS, Automated Flash chromatography, NMR etc. [3, 23]. The identification of the roles of pure compounds from a crude extract in nano synthesis is interesting to phytochemistry and plant enthusiasts. However, for cost consideration. a literature search of the chemical profile of the plant species and purchase of chemically synthesized compounds for use in synthesis is mostly employed.

2.2 Phytochemicals in metallic nanoparticles synthesis

The exploration of alternatives route to the synthesis of metallic nanoparticles used for nanomedicines lead to the discovery of plant species and phytochemicals having reducing potentials for metal ions. The phytochemicals for metallic nano synthesis could be derived from the whole plant material or specific parts such as the leaves, stem, flowers, seed, or root. Generally, plant species and their phytochemicals could be nano-active or inactive by showing potential for the bio-reduction of metal ions. As discussed in the introduction section, the ability of phytochemicals to reduce metal ions is usually first determined by the SPR of the bio-reduced metal measured by recording the UV-Vis scan ranging from 300 to 800 nm [15]. The frequency of SPR absorption depends on the metal ion involved, nanoparticle size, shapes, aggregation, and crystallinity of the nanoparticles. Generally, AuNPs exhibit SPR at 500–600 nm, AgNPs show absorption at 400–500 nm, PdNPs and PtNPs at 300–400 nm, and CuNPs (280–330 nm) [23, 24]. **Table 1** shows the SPR range, color changes and other properties of some reported PM-NPs. Measurement of SPR of the metal ion is followed by confirmatory analysis through physicochemical characterization by one or more of; energy-dispersive X-ray spectroscopy (EDX), X-ray diffraction (XRD), Fourier transformed infra-red spectroscopy (FTIR), high-resolution transmission electron microscope (HRTEM), dynamic light scattering (DLS), thermogravimetry analysis etc. Several scientific reports have shown that nano-active plants consist of secondary metabolites rich in flavonoids and polyphenols [32, 33]. PM-NPs synthesis begins with the selection of potential plant species. This is usually through phyto-chemical screening of the plant species to identify the presence of secondary metabolites known with capping/reducing potentials of metal ions. The screening may be done through spectrophotometric assay for polyphenol and flavonoid content of the total extract or by reacting the total extract with specific reagents that give a characteristic color change to secondary metabolites [20, 34]. Del Buono et al. [20] showed

Plant	Phytochemical	PM-NPS	SPR (nm)	Color change	Size (nm)	Morphology	Bioactivities	Reference
Leucosidea sericea	Procyanidin dimers and *Leucosidea sericea* total extract	Ag	424–432	Yellowish to brownish	2–7	c, s, t	Antioxidant, antibacterial, and enzyme inhibition (α-Amylase and α-Glucosidase)	Badeggi et al. [6]
Lemna minor (Duckweeed)	Total extract of duckweed	Zn	369	NA	11.7	c, s,	Maize Growth, Chlorophyll Content, Carotenoids, Anthocyanin and MDA	Buono et al. [20]
Terminalia mantaly	Total extract of *Terminalia mantaly*	Au	500–600	Pale yellow to ruby red	22.5–43	c, s,	Anticancer (Caco-2, MCF-7, and HepG2)	Majoumouo et al. [25]
Aspalathus linearis	Total extract, and two pure chalcone compounds (helichrysetin and helichrysin)	Au	536 (Total extract), 540 (Helichrysin), and 546 (Helichrysetin)	Pale yellow to ruby red	12.5 (Total extract), 6.7 (Helichrysin) and 2.02 (Helichrysetin)	c, s, h, t	Enzyme inhibition (α-glucosidase and α-amylase) glucose uptake (HEK293 kidney cells) and cytotoxicity (HaCaT cells)	Omolaja et al. [23]
Curcuma longa	Total extract C. longa extract	Cu	524	yellow to brick brown	5–20	a	Antibacterial (*B. subtilis* (+ve) and *E. coli* (−ve)	Jayarambabu et al. [26]
Eucalyptus robusta Sm	Leave extract	Fe	280	Appearance of black color	0.8	c, a, s	antioxidant and antimicrobial (*Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis*)	Vitta et al., [27]
Peganum harmala	Seed alkaloid fraction	Pt, Pd, and Pt-Pd respectively	269 (pt), 279 (Pd)	Yellow to dark brown	20.3 (Pt) 22.5(Pd), 33.5 (Pt-Pd)	c, s	Antioxidant and anticancer (A549 and MCF-7)	Fahmy et al. [28]
Averrhoa bilimbi	Fruit extract	Sn	280–290		3.08	c, s	Antioxidant and antimicrobial (*Klebsiella aerogenes, S. aureus*)	Nisha Elizabeth and Venkat Kumar [29]

Plant	Phytochemical	PM-NPS	SPR (nm)	Color change	Size (nm)	Morphology	Bioactivities	Reference
Citrus limon and *Citrus paradise* (grapefruits)	Fruit and peel extracts	Se	395	Pale yellow to brick red	4462	a, p	Antibacterial (*E. coli*, *M. luteus*, *B. subtilis* and *Klebsiella pneumoniae*)	Alvi et al. [30]
Viola betonicifolia	Leaves extract	Mn	NA	Yellowish green to brownish	10.5 ± 0.85 nm	c, s	Antibacterial (*K. pneumoniae* and *S. aureus*), antifungal (*Ammophilus fumigatus*), *Trichoderma harzianum*, and *A. flavus*, biofilm inhibition, anticancer (MCF-7) antioxidannt, and cytobiocompatibility (hMSC)	Lu et al. [31]

a, agglomerated; c, crystalline; h, hexagonal; s, spherical; t, triangular; p, polydisperse; NA, Not applicable.

Table 1.
Physicochemical properties of some plant-mediated metallic nanoparticles.

how the screening of *L. minor* (duckweed) plant for phenolic compound could be done through ultra-high-pressure liquid chromatography quadrupole-time-of-flight mass spectrometry (UHPLC-ESI/QTOF-MS). Once a plant is found to be nano-active, its optimum concentration for bio-reduction of the metal ion is determined using different concentrations on a pilot scale. The optimum concentration is then upscaled in the final synthesis. Two major synthesis procedures for PM-NPs have been reported. These procedures are the addition of phytochemicals to a stirring solution of a metal salt and the addition of a metal salt solution to a solution of phytochemicals on stirring. Akinfenwa et al. reported a procedure in which optimum concentration (10 mL of aqueous 5% each) of green rooibos extract, and aspalathin compound were added to a 90 mL of 1 mM heated solution of respective gold and silver precursors while stirring at 70°C. A similar procedure for zinc oxide nanoparticles where 25 mL of aqueous 1% mango seed extract was added to 75 mL of 10 mM zinc nitrate solution maintained at 30°C in an orbital shaker was described by Rajeshkumar et al. [35, 36]. Contrarily, different concentrations of the metal precursor are added to a predetermined concentration of phytochemicals. Thipe et al. explained this method in which 100 μL of 0.1 M $NaAuCl_4$ (in deionized water) was added to an aqueous solution of 2 mg resveratrol, a phytochemical from grapefruit in 6 mL of deionized water and the reaction mixture was stirred at room temperature and allowed to stir overnight to achieve optimal capping. Also, Elbagory et al. previously reported a method, for large-scale screening of plants with microtitre-plate. Through this method, the authors determined the optimum concentration for the biosynthesis of gold nanoparticles for further scale-up [36–38]. PM-NPs can also be synthesized by mixing plant extract clear solution with a predetermined concentration of the metal solution and boiling the above mixture at desired time and temperature while mixing. The choice of synthesis procedure depends on the hands-on experience of researchers and literature reports. In all cases, visual color change from the initial solution to the final is regarded as the first evidence for synthesis.

2.3 Mechanism and factors affecting the biogenic synthesis of metallic nanoparticles

Detailed literature report on the mechanism of biogenic synthesis using plant phytochemicals is still lacking although there exists extensive discussion on the roles of chemical functional groups present in plant phytochemicals. From a typical experience, proposed mechanism may proceed through a four-step reaction [16, 39, 40]. The first step which begins with the ionization of the metal in an aqueous solution and trapping of the metal ion on the surface of the phytochemical (dispersion medium) involves electrostatic interaction between the metal ions and the surface charge of phytochemicals. In the second step, attracted ions at the surface of the dispersion medium are reduced to form metal nuclei (nucleation) through electron transfer. In the case of an extract rich in polyphenol or other biomolecules, a metal-polyphenol framework is formed in the process. The continuous reduction and nucleation of ions result in the growth and accumulation of stabilized NPs. In the final stage, accumulated NPs are capped by plant phytochemicals which leads to the growth termination of NPs [24, 36, 41, 42]. Beyond the mechanism, researchers are also concerned about the size, shape, distribution of NPs, and time required in the synthesis. Hence, several factors that affect these properties have been identified and discussed. Factors such as the concentration and nature of plant extract, metal precursor concentration,

temperature, time, and pH play significant roles in the properties (shape, size, and crystallinity) of the synthesized PM-NPs [42–44].

The potential of any plant species for bio-reduction of metal ion for synthesis depends on the contents of its active biomolecules and their concentrations in the plant extract. Plant extracts with high concentrations of biomolecules like proteins, phenolics, and flavonoids are known to greatly enhanced PM-NPs formation. Literature report shows that polyphenols and flavonoids are one of the most frequently reported phytochemicals responsible for plant-mediated metallic nanoparticle synthesis [33]. *Hibiscus sabdariffa* is a tea plant rich in polyphenols, anthocyanine compounds, and flavonoids including hibiscic acid, ascorbic acid luteolin, gallic acid, chlorogenic acid, caffeic acid, protocatechuic acid, eugenol, quercetin, delphinidin-3-sambubioside, delphinidin-3-glucoside, cyanidin-3-sambubioside and cyanidin-3-glucoside [45]. Soto-Roblesa et al. studied the effect of the different concentrations (1%, 4%, and 8%) of *H. sabdariffa* extract on the biogenic synthesis of ZnO NPs and their application in the photocatalytic degradation of methylene blue dye. The result showed that the formation of smaller (5–12 nm) ZnO-NPs of uniform shapes and photocatalytic degradation of methylene blue was achieved with the highest (8%) concentration of *H. sabdariffa* extract compared to the 1%, and 4% concentration [41, 46].

The ratio of the concentration of the metal substrate to plant extract plays a key role in biogenic synthesis. Generally, a concentration range of 1–10 mM of the metal substrate is employed in the synthesis [47]. Within this range, a lower concentration of metal precursor takes longer reaction time but is beneficial for the formation of monodispersed spherical shape and non-aggregated nanoparticles during the nucleation and growth process. The use of a high concentration of the metal precursor has the advantage to speed up the reaction rate but often leads to polydisperse and amorphous NPs due to the aggregation of a large number of nuclei [10]. This is supported by a study conducted by Vitta et al. on the synthesis of iron nanoparticles from an aqueous extract of *Eucalyptus robusta* Sm using different concentrations of iron salt concentrations; 1 mM, 5 mM, and 0.1 M $(NH4)_2$ $FeSO_4.6H_2O$ (Mohr's Salt). The authors showed that the size distribution of FeNPs formed was dependent on the concentration of the metal substrate used, as the 1 mM concentration of Fe precursor gave average size distribution of 0.8 nm smaller than the size obtained with 5 mM and 0.1 M concentrations. Interestingly, this agrees with the report of the particle size distribution for Cu-NPs biosynthesized from *A. indica* leaf extract by Nagar and Devra [48]. Nagar and Devra, attributed an increase in particle size from 48.01 nm to 78.51 nm due to increased concentration of $CuCl_2$ substrate from 6×10^{-3} mol/L to 7.5×10^{-3} mol/L, respectively [27, 48].

The effect of temperature is noticeable mainly on the nucleation and NPs growth time, and the size distribution of PM-NPs. Most PM-NPs are formed between 30 and 90°C (working temperature) depending on the metal substrate used and their electrochemical potentials [49]. The working temperature is important for the excitation of electrons and interaction with phytochemicals for the bio-reduction of metals. In an experiment to study the effect of different temperatures (70, 75, 80, 85, and 90°C) on the size of the biosynthesized silver nanoparticle, Liu et al. [50] explained that high working temperatures have a positive effect on the nucleation kinetics constant k_1 and growth kinetics constant k_2. Nucleation rate constant k_1 was found to increases slightly when temperature was raised from 70 to 80°C, while it rises sharply when the temperature exceeds 80–90°C . To further the effect of temperature on the nucleation and growth of NPs, Jayachandran et al. [51] showed temperature dependence in the

biosynthesis of zinc oxide nanoparticles using *Cayratia pedata* leaf extract for the immobilization of glucose oxidase enzymes. From the selected working temperature of 55, 65, and 75°C. It was noted that ZnO NPs were formed with a working temperature of 65°C while no synthesis occurred at 55 and 75°C respectively.

The role of pH maintained for reaction synthesis is also a key factor to be considered for controlled synthesis. Different literature studies attributed the effect of pH on the stability, morphology, optical and bioactivity of the synthesized PM-NPs [39, 52, 53]. A comparative stability and biological activity (cytotoxicity and antimicrobial) study of AgNPs synthesized with citrate, and green tea by Bélteky et al. [52] reveals that both NPs are more stable in alkaline and neutral media than in acidic medium with higher stability for green tea AgNPs. Additionally, synthesis in alkaline and neutral pH tend to produce smaller size particles than in acidic pH [9]. Also, the effects of pH in synthesis reflects on the optical properties of the synthesized NPs and their therapeutic applications. The optical properties of ZnO NPs were shown to depend on the pH. This was demonstrated by the report of Thipe et al. [34] showing different colors of ZnO-NPs synthesized from orange fruit peel extract for antibacterial activities. In the study, pH values of 4.0, 6.0, and 9.0 had ivory color, pH values of 7.0 and 8.0 had burnt black color and white color was noticed at pH values of 10 and 11. With Pt NPs synthesis via orange peel extract, Karim et al. [54] illustrated different size distribution and crystallinity properties for pH 3, 5, 9, 11, and 13. The report shows a reduction in sizes (2 nm – 1.8 nm), agglomeration, and uniform spherical shapes of NPs as pH increase from pH 3 through pH 11. pH 11 was noted with the smallest particle size (1.8 nm) and uniformity (which could be standard for the biosynthesis of Pt-NPs) while at pH 13 particles became agglomerated.

3. Therapeutic applications of phyto-metallic nanoparticles

New innovative technologies to improve the development of novel therapeutics and treatment of disease conditions using combined synergies between synthetic and natural products have been of interest to many nanomedicine experts. Extracts from plant has a long history of usage as traditional herbal medicine, as prototype in the formulation of synthetic drugs and in the detoxification of heavy metal accumulation in the body [55, 56]. The pharmacological potentials of many plants are closely associated to the major phytochemicals they contain. For instance, plants rich in polyphenols are often indicated as therapeutic agents for complications resulting from oxidative stress. A systematic formulation of these therapeutic agents as nano drugs for use in biomedicine is gaining acceptance due to the rising preference for natural product-based therapies and their versatilities [32]. The bioinorganic network provided by PM-NPs and their biocompatibility make them suitable as a drug over conventional speciality drugs with many side effects. Hence, their roles in therapeutic applications such as in bactericidal, anticancer, antioxidants, antidiabetic, and photothermal treatment (PTT) are briefly discussed below.

3.1 Bactericidal effects

The antibacterial potentials of various PM-NPs have been extensively discussed by different researchers given the resistance of bacterial to the first generation and conventional antibiotic drugs. Most reports show that the activities of the PM-NPs are

attributed to the binding and interaction of PM-NPs on surfaces of bacterial cell membranes. The interaction inhibits synthesis of new cell membrane thus preventing cell growth. Also, the binding of PM-NPs could disrupt the energy transduction process, and cause damage to the cell membrane through the generation of reactive oxygen species leading to the eventual death of bacterial cells [57–59]. The efficacies of the bactericidal effect of PM-NPs have been tested both as a singular drug and in combination treatment with conventional antibiotic drugs [9]. Among metals and metal compounds, Ag ions and Ag-based compounds are the most pernicious on microorganisms showing strong antibacterial properties [60]. Hence, PM- AgNPs are the most studied for the inhibition of a broad spectrum of both gram-negative (G-ve) and gram-positive (G + ve) bacteria species including *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus cereus, Salmonella enterica*, *Escherichia coli* and *Serratia marcescens* [60]. This was recently demonstrated by Balachandar et al., [61] for antibacterial activities of AgNPs mediated by *Glochidion candolleanum* (GC) leaf against *Bacillus subtilis, Listeria monocytogens* and *S. aureus* (G+ve)*; E. coli, P. aeruginosa, and S. enterica* (G−ve). The study shows a general inhibition for all bacteria based on the concentration of GC-AgNPs used. The highest maximum inhibition zone (12.2 mm diameter) due to GC-AgNPs was observed against S. enterica and for P. aeruginosa *(*11.8 mm diameter), *L. monocytogens* (11.0 mm), *S. aureus* (10.*9* mm) and 10.8 mm for both *B. subtilis and E. coli* in the descending order [61]. A similar result was presented by Nishanthi et al., [9], which showed a synergistic antibacterial activity of rind extract of *Garcinia mangostana* biosynthesized Au, Ag, and Pt NPs in combination with commercial antibiotics (penicillin G (2.0 μg), methicillin (5.0 μg), vancomycin (30 μg), gentamycin (50 μg), streptomycin (10 μg), ciprofloxacin (5.0 μg), azithromycin (30 μg) and clotrimoxazole (25 μg) and tested against *Staphylococcus* sp., and *Bacillus* sp. (G+ve) and *Pseudomonas* sp. and *Klebsiella* sp. (G+ve). The authors found that AgNPs, displayed relatively higher antibacterial activity when compared to AuNP and PtNPs against all the tested pathogens [9]. In addition to Ag, Au, and Pt NPs, biosynthesized ZnO-NPs, and FeNPs using extracts of orange fruit peel, and *E. robusta* Sm, respectively have been reported [27, 62]. ZnO/Zn $(OH)_2$ NPs are known to exhibit photocatalysis when illuminated with UV light producing reactive oxygen species (ROS), such as superoxide anion ($O_2^{\bullet-}$) or hydroxyl radical ($OH^{\bullet}$) which may cause disruption of the electron transport chain and or oxidative stress in the microbial cell membrane [59]. ZnO-NPs were shown to exhibit strong antibacterial activities towards *E. coli* and *S. aureus* at a concentration of 0.025 mg/mL without UV radiation after 8 h of incubation [62]. Vitta et al. [27] recorded no significant differences ($p > 0.05$) for *E. Coli* with Fe-NPs (positive control), while for *S. aureus, P. aeruginosa and B. subtilis*, statistically significant differences ($p < 0.05$) were found as there was an increase in the values of inhibition zone as the size of the nanoparticles diminished [62]. Also reported is, the biogenic synthesis and antimicrobial evaluation of Cu-NPs and Mg-NPs from leaf extracts of strawberry and *Viola betonicifolia (L.)* respectively. Bayat et al. [63] noted that the Cu-NPs like their Ag-NPs counterpart displayed a bactericidal effect on *P. aeruginosa* at an effective concentration (EC50) of 2.2 mg/mL. Interestingly, the authors indicated a higher antibacterial activity of Ag-NPs over Cu-NPs due to a greater minimum bactericidal concentration (MBC) of Cu-NPs (5 mg/mL) than for MBC of Ag-NPs (0.01 mg/mL). According to Lu et al. [31], synthesized *Viola betonicifolia*-MnO_2 NPs displayed higher antimicrobial and reductions in colony forming unit for *K. pneumoniae* (4.14 ± 0.03 $\log_{10}$ reduction),

and *S. aureus* ($4.65 \pm 0.07 \log_{10}$ reduction) respectively, than the value obtained from commercially available Mn-NPs [31].

Among other metals that have received considerable attention for the biosynthesis of PM-NPs as antimicrobial agents are titanium (TiO_2-NPs), palladium (Pd-NPs) nickel (NiO-NPs), selenium (Se-NPs), and tin (SnO_2-NPs) [30, 64–67]. Amanulla and Sundaram [64] reported that at dose concentrations from 6.75 to 50 mg/mL, TiO_2-NPs synthesized from orange peel extract showed bactericidal effects on *S. aureus, E. coli, and P. aeruginosa*. In a similar report, Pd–NPs (±3 nm) obtained via *Garcinia pedunculata roxb* leaf extract was observed to elicit antimicrobial activity against *Cronobacter sakazakii* AMD 04 at dose concentration from 0.39 mM and 0.52 mM [66]. From the report of Srihasam et al. [65], biogenic synthesis and antimicrobial activities of NiO-NPs from the leaf extract of stevia plant were implicated in significant bactericidal effects on *E. coli, Streptococcus pneumoniae*, *and B. subtilis* at a concentration of 200 μg/mL. Furthermore, Alvi et al. [30] demonstrated that Se-NP synthesized from *Citrus paradisi and Citrus limon* for antimicrobial activities against *E. coli, M. luteus, B. subtilis*, *and K. pneumoniae* show significant activities against all the bacterial pathogens when compared with the standard antibiotic Ciprofloxacin. SnO_2-NPs are also promising PM-NPs that have been found effective against microbes. SnO_2-NPs from fruit extract of *Averrhoa bilimbi* showed satisfying inhibitory activities against *S. aureus* and, *K. aerogenes* while from *Saraca indica* flowers were effective in inhibiting the growth of *E. coli* [67, 68].

3.2 Anticancer effects

The applications of metallic nanoparticles in the treatment of cancer cells from different organs such as breast, cervical, colon, ovarian, and lung cancers have attracted more interest in biomedicine. In this regard, MNPs act as nanocarriers due to the available large surface area for the attachment of a large number of vectors for targeted delivery at designated sites [69]. This method has been reported to improve the efficacy of anti-cancer drugs over traditional drugs which are sometimes identified and removed from the systemic circulation by the liver and the spleen [16, 36]. Usually, studies on anticancer potentials of nanoparticles require both in vitro and in vivo (animal and clinical) studies. In vitro, studies are mostly reported using conventional MTT and apoptosis assay to determine cell viability via cytoprotection, and extrinsic cell death respectively. In the experiment, a decrease in cell metabolic activities is implicated in the induced secretion of reactive oxygen species by cells due to biogenic NPs which gradually leads to the death of cellular components [70]. The values of half maximal inhibitory concentration IC50 are used to determine the cell behaviors when treated with PM-NPs. The in vivo experiment is a follow-up and confirmation of in vitro, although limited studies of in vivo antitumor studies are reported [71]. Because MNPs are functionalised and stabilized for selective delivery at specific sites, biodistribution and degradation of the MNPs may take much circulation time in systemic circulation resulting in metal accumulation and particle-induced toxicity of mammalian cells and tissues. Different biodegradable materials that help with bio-clearance such as plant phytochemicals, polysaccharides such as dextran and chitosan, polyvinyl alcohol (PVA), phosphorylcholine-based copolymers and so forth have been suggested for coating of MNPs [15, 72, 73].

Addressing the drawback of drug residence time and biodistribution MNPs as a potential anticancer agent in mammalian cells, Akinfenwa et al. [36] showed that phytochemicals from *Aspalathus linearis* plant from PM-NPs could serve to reduce,

capped, and increase bio-clearance of biosynthesized AgNPs and AuNPs. From the results of the study, the authors highlighted that AgNPs are more efficacious showing antiproliferation effects on human hepatocellular carcinoma (HepG2), and neuroblastoma (SH-SY5Y) cells in vitro than AuNPs. In a complementary report by Alharbi and Alsubhi [74], in vitro anticancer activity of AgNPs prepared using fruit extract of *Azadirachta indica* on pneumocyte lung tumor (A549) cells show that all treatments involving biosynthesized AgNPs only, and AgNPs in combination with cisplatin were more toxic to A549 cells than with the extracts and cisplatin only. A remarkable combination of both in vitro and in vivo anticancer experiments of biogenic AgNPs was demonstrated by Kabir et al. [70]. The authors concluded that Ag/AgCl-NPs synthesized from *Geodorum densiflorum* rhizome extracts inhibit human cancer cell proliferation in vitro and also for Ehrlich ascites carcinoma (EAC) cell growth in vivo. From the in vitro experiment, the authors found that samples treated with *G. densiflorum*-Ag/AgCl-NPs induced apoptosis in glioblastoma stem cells (GSCs), pancreatic cancer (BxPC-3) and breast cancer (MCF-7) cells. While in vivo, there was inhibition of up to 60 and 95% of EAC-mice cell growth at the doses of 2 and 4 mg/kg/day after intraperitoneal treatment respectively. Noteworthy is the overall increase in mice life span by 75% compared to EAC-bearing control mice which gives credence to the efficacy of PM-NPs. A prototype drug for chemotherapeutic treatment of cancer is Cisplatin, a platinum coordination complex found with most antitumor properties although with some side effects such as neurotoxicity, ototoxicity and renal impairment. Formulation of the complex analogue for cancer therapy through biosynthesis is a welcome idea to overcome its side effects. In the study of the anticancer effects of PtNPs synthesized from black cumin seed extract, Aygun et al. [75] found that PtNPs were efficient against the proliferation of MDA-MB-231 breast and HeLa cervical cancer lines (IC50: 36.86 μg/mL and 19.83 μg/mL, respectively). The result agrees with a previous result by Chuang et al. [76] of biogenic PtNPs from peppermint leave extract which showed a decrease in the viability of HTC 116 colon cancer cells at an IC50 value of 20 μg/mL. Similarly, dose-dependent anticancer activities of biogenic Au NPs (inhibition of MCF-7 cells by 70.2%), CuO NPs (decrease breast cancer MDA-MB-231 viability and increase ROS at IC50: 20 μg/mL), MnONPs (cytotoxic against MCF-7 cells at 120 μg/mL concentration), ZnO NPs (toxicity on both A549 and MOLT4 cells and a size reduction in A549 tumor), NiO NPs (toxicity against HepG2 cancer cells, IC_{50}: 37.84 μg/mL) and Se NPs (decrease in cell viability at a concentration of 2–6 μg Se/mL) have been described as promising anticancer agents through different studies [31, 77–82].

It is believed that combining two metals in biosynthesized as bimetallic NPs (BMNPs) often synergize their effects with more biological potentials than their monometallic counterpart. As anticancer agents, biogenic BMNPs have been reported with improved activities over their respective single metals [5]. Several reports supported this hypothesis. Tamimi et al. [83] report showed that chemically synthesized bimetallic Ag-Cu NPs showed significant toxicity on MCF-7 cells at 10 μg/mL concentration than the separate AgNPs (20 μg/mL), and Cu-NP (showed no toxic effects). Hence, the hypothesis should be true for biogenic BM-NPs. Fahmy et al. [28] in their report on green synthesis of Pt-Pd NPs using *Peganum harmala* L. seed alkaloids revealed that bimetallic Pt–Pd NPs exhibited significant cytotoxic activities against A549 (IC50; 8.8 μg/mL) and, MCF-7 (IC_{50}; 3.6 μg/mL) cells when compared to the individual metals, and carboplatin standard (IC_{50}; 23 and 9.5 μg/mL,). In the study, relatively lower anticancer activities of each mono MNPs of Pt NPs and PdNPs for A549 and MCF-7 were noted at IC_{50}; 10.9 μg/mL and 6.7 μg/mL, and IC_{50}; 31 μg/

mL and 10.8 μg/mL, respectively [28]. A similar study by Athinarayanan et al. [84] revealed that bimetallic Pt-Cu NPs synthesized with catechin extract of green tea induced cell death in human cervical cancer dells (SiHa) cells with increasing the dose and time with IC_{50} value of the Pt-Cu NPs ranged from 32 to 35 g/mL for 24 and 48 h. All these reports of BMNPs from plants portend higher efficacy in therapeutics within the limit of acceptable toxicity.

3.3 Antioxidants potentials

Over-expression of free radicals is regarded as a lead factor to a variety of diseases including cancer, hyperglycemia, hyperlipidemia, inflammation, and so forth via apoptosis signaling pathways and oxidative stress on cellular components. Free radicals such as reactive nitrogen species (RNS; nitrogen dioxide, NO_2), reactive sulfur species (RSS; hydrogen sulphide, H_2S), reactive chlorine species (RCS; hypochlorous acid, HOCl), and most especially reactive oxygen species (ROS; superoxide, ($O_2^{\bullet-}$), are pro-oxidants which induce cellular oxidative stress [85]. Natural antioxidants produced by cells help to check on the excess production of ROS by scavenging activity. However, when the ROS level becomes higher than the natural antioxidant activities of cells, the use of natural antioxidants from plants or food rich in antioxidants to mitigate oxidative stress becomes necessary. Interestingly, compounds of the phenolic and flavonoid classes especially vitamins A, C, and E, quercetin, and rutin have been shown to attenuate ROS-induced oxidative stress with different radical-based and metal-related assays [86, 87]. Methods used to evaluate free radical scavenging includes 1,1-diphenyl-2-picryl-hydrzyl (DPPH) radical, 2,2-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS) radical, ferric reducing antioxidant power (FRAP), nitric oxide (NO), superoxide ($O_2^{\bullet-}$), hydroxyl ($OH^{\bullet}$) cupric reducing antioxidant capacity (CUPRAC), Trolox equivalent antioxidant capacity (TEAC) assays etc. [88]. It is proposed that during the interaction, the metal ions in PM-NPs scavenge free radicals by electron transfer and proton loss thus inhibiting oxidative DNA damage. Hence, the therapeutic potentials of PM-NPs are largely associated with the phenolics, and antioxidant properties of the phyto-reducing agent and the metal ions used during synthesis. According to Vera et al. [89], the antioxidant activities of plant phytochemicals are a strong indication of the synthesis efficiency of MNPs and their biomedical applications. Antioxidant-functionalized NPs are reported to show comparative advantages over antioxidants due to their high permeability and stability during membrane trafficking. Different PM-NPs have demonstrated nano-antioxidant activities which serve as an alternative route to the use of conventional synthetic antioxidant therapy. For example, *Rhazya stricta* plant (Apocynaceae), used in folk medicine in the Middle East and Indian subcontinent is reported with antioxidant activities. When functionalized as AgNPs, exhibited superior two-folds antioxidant activity measured at 75.16% ± 0.04 over the plant extract (43.12% ± 2.1) [90]. It is also documented that the antioxidant activity of biosynthesized MnO_2 NPs using leaves extract of *Viola betonicifolia* on linoleic acid peroxidation was higher (84.94 ± 0.77%) than for the leaves extract and a little less than that of ascorbic acid (90.57 ± 1.21%) standard [31]. When the inhibition of DPPH radicals of FeNPs from an aqueous extract of *E. robusta* leaves was compared to the extract alone, Vitta et al. [27] showed that FeNPs were significantly more potent ($p < 0.01$) than the extract alone, showing IC50 values of 81.63 ± 11.75 μg/mL and 423.14 ± 73.27 μg/mL respectively [27]. Overall, the improved antioxidant activities of PM-NPs have opened

research interest in phyto-nano therapy for the repair of damaged cellular macromolecules (like proteins, lipids, DNA) and regulation of cellular functions from degenerative and pathological ailments such as aging, cancer, diabetes, and neurodegenerative diseases.

3.4 Antidiabetic application

Type 2 diabetes is a result of hepatic dysfunction and insufficient insulin secretion from pancreatic β-cells for glucose uptake accounts for over 90% the worldwide diabetic patients [91]. Being a global disease, a lot of efforts on developing therapeutic agents and advocacies to reduce the increasing number of undiagnosed and diabetes are being explored. Synthetic drugs such as sulfonylureas, metformin, acarbose are among current antidiabetic drugs. In addition to these synthetic drugs, natural products from plants general and plant-derived phytochemicals such as chalconaringenin 2′-*O*-β-*D*-glucopyranoside and aureusidin 6-*O*-β-*D*-glucopyranoside, obtained from flower extract of *H. arenarium* have been reported [55]. Despite the several *in vivo, in vitro,* and clinical studies, till date, a complete cure for treatment of diabetes is yet to be achieved. Recently, several nanomedicine research are focusing on nanoscale drugs by combining the synergies between potential antidiabetic phytochemicals and metallic nanoparticles. In this regard, Ul Haq et al. [92] showed that plant mediated silver nanoparticles from *Taverniera couneifolia* (*TC*-AgNPs) significantly improved Alloxan-induced diabetic Wistar rats. The effects of *TC*-AgNPs on the lipid, liver, and kidney profiles of treated rats (10 mg/kg body weight) were observed with lowered blood glucose levels, and improvements in the lipid, liver, and renal profiles after treatment with *TC*-AgNPs. A similar therapeutic application of ZnO NPs synthesized from *Amygdalus scoparia* stem bark extract showed significant antidiabetic potentials on treated rat (30 mg/kg). As reported, a higher level of insulin and lower AST, ALT, lower blood glucose, higher levels of IR, GluT2, and GCK expression and lower TNFα expression were recorded when compared with the STZ induced diabetic rats [93]. These reports together give insight into the biomedical and therapeutic application of phyto-metallic nanoparticles.

3.5 Photothermal and photocatalytic effects

The most important property of zerovalent metallic NPs is their electronic excitation and light scattering characters under incident laser beam. The absorption and scattering of light give rise to intense colors and interesting optical properties. These properties are used in theranostic nano probe and therapy in biomedicals such as in biosensing, tissue imaging, molecular imaging, cancer therapy etc. Photothermal therapy is less invasive using therapeutic agents like noble metals and near infrared radiation (NIR). Specifically, AuNPs are known to exhibit excellent photothermal transduction in the interconversion of heat-to-light by absorbing light in the near infrared region (NIR; 700–1400 nm). For example, NIR laser radiations delivery by AuNPs could induce stimulations in cells for necrosis, healing of open wound, in pain relief therapy etc. This property of gold and the paramagnetic property of iron metals and irradiation by NIR have been used for active targeting cancer cells, drug carrier and delivery, and removal of cancer cells [94]. The synergy between the NIR and PM-NPs (as therapeutic agents) has been explored by different researchers. Ali et al. [95] and Wang et al. [96] studies showed an enhanced cytotoxicity on lung (A549), and breast cancer (MCF-7) cell lines when treated with NIR irradiated synthesized *Cordia*

myxa L. leaf extract-PtNPs and *Memecylon edule* leaf extract-graphene oxide nanoparticles (GO-NPs) respectively. The effects were induced apoptosis in MCF-7/A549 cells due to photothermal transduction (conversion of low energy into heat) by the respective PtNPs and GO-NPs.

In photocatalysis experiment, the decolorization of dyes; methyl orange, methylene blue, Eosin Y, etc. by UV light in the presence of metal catalyst which result in degradation products are usually reported. During UV irradiation of samples, the photocatalysts cause electron excitation from the Valence to the Conduction band where the material becomes chemically responsive indicated by absorption peak at λ wavelength. The difference between the valence and the conduction band is calculated as Bandgap (Eq. 1). Phytochemical-inspired metallic nanoparticles could improve the photocatalytic degradation of dyes for treatment of wastewater through reduction of conduction electrons for UV absorption spectral determination. This effect was implied by Gupta and Chundawat [97] for the photocatalytic deterioration of methyl orange by fungus mediated PtNPs for potential application in wastewater remediation.

$$E_g = h\ c_e V/\lambda \text{ or } E_g = 1240_e V/\lambda \quad (1)$$

H = 6.626×10^{-34} JS, c = 3×10^{8} ms^{-1}, λ = absorption wavelength.

4. Cellular uptake and toxicity of PM-NPs

Cellular uptake of PM-NPs accounts for the dose of internalized NPs and their interactions in physiological media. The uptake of NPs has been investigated by different methods; quantitatively using inductively coupled plasma-mass spectrometry (ICP-MS), inductively coupled plasma-optical emission spectroscopy (ICP-OES), and inductively coupled plasma-atomic emission spectroscopy (ICP-AES). The qualitative method uses transmission electron microscopic (TEM), energy dispersive X-ray (EDX) analysis, colourimetry, and fluorescence imaging. Cellular uptake experiment is important to understand the stability of NPs and their toxicities on both normal and cancer cells. Most uptake studies discussed uptake efficiency and toxicity. Still, the exact mechanisms of cellular uptake for PM-NPs in different cells have not been well characterized [98]. It is however clear that in the process of uptake NPs used as drug carriers permeate biological barriers of the bilayer cell membrane (consisting of hydrophobic and hydrophilic layers) through a passive diffusion pathway to distribute the NPs within cells. Most studies show that permeation and assimilation of NPs depend on several factors such as surface modification/interactions between the NPs and the cells, size, shape and concentrations of NPs [99]. NPs have surface charges (positive, negative, or neutral) that attract ions of opposite charges in the cytosol for cellular uptake. Different reports have shown that positively charged NPs show better cellular uptake than neutral and negatively charged NPs [2]. This is supported by a report of high cellular uptake of AuNP synthesized from *A. linearis* by SH-SY5Y and HepG2 cells. The authors attributed the uptake of AuNPs at a concentration of 5.368 μg/mL and 3.625 μg/mL by SH-SY5Y and HepG2 cells respectively to high acidity and positive surface charges from *A. linearis* [36, 100]. Also, the nano (small) size factor of PM-NPs plays an important role in the cellular internalization of NPs. Because microorganisms and cell organelles such as DNA have nano-size ranges, they can cross the plasma membrane faster and with uniform distribution for intracellular

particle trafficking. Different reports revealed that smaller-size PM-NPs (≤ 40 nm) easily permeate cells than sizes greater than 50 nm. Amaliyah et al. demonstrated that the antibacterial activity of biogenic AgNP from *Piper retrofractum* Vahl fruit extract was facilitated by the entry of the small sizes (1–5 nm) AgNPs through *E. Coli* and *S. Aureus* [98, 101].

Nanotoxicological assessment of NPs has become essential before application in therapy to determine their toxicity safe level. Toxicological studies are mostly conducted in vitro using standard toxicological assays, such as the MTT assay, colony forming efficiency (CFE), lactose dehydrogenase (LDH) assays and so forth in immortalized cell lines. MTT assay measures cell viability via mitochondrial enzymatic activities, CFE checks the ability of a single cell to form a colony by survival from toxic media, and LDH assay measures the damage to the cell membrane. Every organism is made up of natural defense mechanisms which protect it from toxic exogeneous particles. Despite this, exposure to MNPs beyond a threshold could overcome the body's defense to cause hazards [102]. Toxicity by MNPs may occur during preparation or on therapeutic administration leading to cytotoxicity and oxidative DNA damage. Like cellular uptake, the toxicological behavior of NPs is dependent on their surface activities and morphological properties (size, shape, and agglomeration). It is well-known that spherical, smaller sizes and non-agglomerated NPs are more compatible and less toxic to cell membranes. Again, the toxicity of NPs is dependent on exposure concentration and the amount of the NPs that reached the targeted cells [15]. PM-NPs are considered non toxic due to the synergy that exist between metals and bioorganic networks of the reducing phytochemicals. However, PM-NPs have safe level if delivered to specific cancer cells to elicit DNA damage and cell multiplication [103]. Cellular toxicity of PM-NPs is beneficial when it displays specificity on targeted cells. The therapeutic potential of PM-NPs is lost where it is toxic against normal cells. Toxicity on cells is generally established through in vivo and in vitro experiments. Few published reports have also shown the toxic effects of PM-NPs on normal cells and these reports are briefly discussed. For example, Majoumouo et al. [25] reported in vitro cytotoxic effects of biosynthesized *Terminalia mantaly* extracts gold NPs (TM-AuNPs) investigated on cancer (Caco-2, MCF-7 and HepG2) and non-cancer (KMST-6) cell lines. According to the study, *T. mantaly* extracts showed some cytotoxicity towards the cancer cells while the TM-AuNPs exhibited more cytotoxicity on all the cells. The effects of PM-NPs concentrations on toxicity were studied in vivo on EAC cells using *G. densiflorum* -AgNP. At a higher concentration of 4 mg/kg/day, the biosynthesized inhibited growth of mice tumor cells up to 95% greater than 60% recorded on a dose of 2 mg/kg/day [70].

5. Conclusions

In summary, the synthesis of phyto-metallic nanoparticles is a paradigm shift and preferred approach to conventional environmentally unfriendly and unsustainable nanodrugs. Tremendous efforts are being made to combine the principle of green chemistry and nanotechnology for application in nanomedicine. Phytochemistry and drug development from phytochemicals functionalized on metal nanoparticles have been revisited. Factors like morphology of nanoparticles, time, temperature and pH are identified as critical in the synthesis and therapeutic applications of phyto-metallic nanoparticles. Reviews of several scientific results that compared the effectiveness of phytomediated nanoparticles with their separate phytochemicals, and separate

metallic nanoparticles as potential therapeutic agents favored phytomediated nanoparticles. A more definitive conclusion on the subject will unfold with further investigations. This chapter gives current insights into the green biogenic synthesis of nanoparticles, mechanisms, therapeutic applications, uptake, and cellular toxicity.

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Conflict of interest

The authors declare no conflict of interest.

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