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REVIEW PAPER OPEN ACCESS

A review on photocatalytic, antimicrobial, cytotoxic and other biological activities of phyto-fabricated copper nanoparticles

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Abstract

Since its advent, nanotechnology has become an indispensable area of research and innovation, introducing revolutionary changes in current research areas like engineering, medical sciences, drug discovery and formulations, optoelectronics and biosensors. Metallic nanoparticle synthesis has become a requisite of modern experimentation however, much of the research involves either silver or gold nanoparticles. Considering the fact, it is imperative to explore the potentials of other metallic nanoparticles as well. Current review focuses on exploration of potentials of Copper nanoparticles in various domains of research. The review highlights common synthesis methods of Copper nanoparticle synthesis and the superiority of green route over other approaches. Characterization techniques and multifarious biological potentials of Copper nanoparticles have also been reviewed. Researchers have recognized green synthesis route as the best alternative to traditional methods utilized for synthesizing copper nanoparticles. Green synthesized Copper nanoparticles have also been found to have superior antioxidant, antimicrobial, antifungal, cytotoxic and photocatalytic potentials. As of now, the exact mechanism behind synthesis and biological activities of Copper nanoparticles is not known. Identification of the exact mechanism can revolutionaries the discipline of nanotechnology.

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Introduction

The domain of nanotechnology has emerged from established areas of science like physics, chemistry, biology and engineering sciences. Nanotechnology involves intervention of novel strategies with the help of which atoms and small particles are manipulated. Nanoparticles (NPs), the key product of nanotechnology, are particles having dimensions ranging from 1–100 nm (Farias, Silva *et al.* 2014). The properties of NPs show immense variations to those of bulk materials due to their extremely small size (Petit, Lixon *et al.* 1993, Kaviya, Santhanalakshmi *et al.* 2011). With the advancement in nanotechnology, size controlled synthesis of nanoparticles can be carried out to furnish NPs that possess properties suiting a particular purpose. The properties that NPs possess are due to two core reasons, novel quantum impact and increased surface to volume ratio. As compared to their bulk counterparts, the pre-eminent surface to volume proportions in NPs imitates enhanced catalytic reactivity. Likewise such small dimensions of NPs signifies the influence of quantum impact on quality and properties of material (Hewakuruppu, Dombrovsky *et al.* 2013). Since its dawn, NPs have dominated different areas of science. The use of NPs have been reported in areas like catalysis; (Husen and Siddiqi 2014), Photonics; (Ren, Hu *et al.* 2009, Ahamed, Alhadlaq *et al.* 2014), gadgets; (Kamal, Khan *et al.* 2016), bio labeling; (Chen, Wang *et al.* 2012), detection; and surface upgraded Raman Scattering; (Cioffi, Torsi *et al.* 2005, Abboud, Saffaj *et al.* 2014, Ahamed, Alhadlaq *et al.* 2014, Sutradhar, Saha *et al.* 2014, Naika, Lingaraju *et al.* 2015), drug delivery (Longano, Ditaranto *et al.* 2012, Wali, Sajjad *et al.* 2017), etc. Copper Nanoparticles (Cu-NPs) have caught the eye of scientists lately owing to their biocidal properties and numerous applications in wound dressings (Giannousi, Avramidis *et al.* 2013, Kanhed, Birla *et al.* 2014, Shende, Ingle *et al.* 2015, Bramhanwade, Shende *et al.* 2016). Modern technologies like catalytic process, gas sensors, solar cells and high temperature super-conductors have also benefitted from Cu-NPs (Schilling, Bradford *et al.* 2010, Song, Vijver *et al.* 2015). This review climaxes green synthesis of Cu-NPs and describes how to characterize, and what are different activities of these used NPs.

Copper Nanoparticles (CuNPs)

Biosynthesis of Copper Nanoparticles (CuNPs)

Researchers in antecedent decades were hell bent on exploring greener and safer synthesis approaches for Nano metallic particles (Raveendran, Fu *et al.* 2003, Iravani and Zolfaghari 2013, Mittal, Chisti *et al.* 2013) with significant focus on methods that involved microorganisms (Mandal, Bolander *et al.* 2006) and other biological beings other than plants and plants extract (Thakkar, Mhatre *et al.* 2010). Plants and plant material based synthesis approaches were not properly explored. It wasn't until recent decade when researchers realized the potential of plants for metallic NP synthesis and the plethora of advantages that it has to offer, the foremost being circumvention of need to maintain cell cultures. An added advantage of utilizing plants as factories for NP synthesis is bypassing the chances of pathogenicity. This review describes the plant and plant extract methods so as to optimize the most appropriate method for the synthesis of Cu-NPs. The general scheme of synthesis route is shown in Figure 1.

Extracts from a variety of plants have been used for preparing Cu-NPs with diverse range of sizes and shapes owing to the nature of extract and synthesis conditions. Cu-NPs are highly oxidant in nature that gives rise to unforeseen issues related to NP stability, aggregation and oxidation resistance. This hindered the focus on Cu- NPs synthesis as compared to other metals initially. Later on (Pedersen, Wang *et al.* 2008) it was concluded that Cu-NPs are oxidized only upon the surface at room temperature. NPs like gold and silver on the other hand (Rafique, Shaikh *et al.* 2017) are much better in withstanding oxidation as compared to Cu. Still, Cu-NPs synthesis can be an attractive contender for nano based research owing to its copiousness and inexpensiveness. With development in nanotechnology, aggregation and oxidation issues can also be addressed conveniently through capping agents like polymers (Balogh and

Tomalia 1998, Crooks, Zhao *et al.* 2001) and natural ligands.

The best solution in practice these days is synthesis of Cu-NPs by utilizing plants and plant based products that can serve as both capping and reducing agents. S. Renganathan *et al*, demonstrated the plant based synthesis approach for Cu-NPs by using *Capparis zeylanica* leaf extract. $CuSO_4$ solution was used as precursor salt while the leaf extract served as reducing agent for NP synthesis. The reaction was carried out for 12 h which resulted in Cu-NPs with cubical shape and size ranging from 50–100 nm. The antimicrobial potential of Cu-NPs was investigated against pathogenic bacterial strains including *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Subhankari and Nayak 2013). Shende *et al*, studied that *Citrus medica* Linn fruit extract can be used to reduce the $CuSO_4$ solution (Shende, Ingle *et al.* 2015). The synthesized nanoparticles were crystalline in nature with size range 20nm. The synthesized NPs showed good anti-microbial activites. (Shende, Ingle *et al.* 2015) Angrasan & Subbaiya carried out that *Vitis vinifera* leaves extract can be used to reduce the $CuSO_4$ solution. The synthesized NPs were characterized by UV-Vis and FTIR. The established nanoparticles showed potential anti-microbial activity against *Escherichia coli, Staphylococcus aureus, Pneumonia, Salmonella typhii and Bacillus subtilis* (Angrasan and Subbaiya 2014). G. Caroling *et al*, elaborated that *Guava* fruit extract has the potential to reduce the $CuSO_4$ solution. The prepared NPs were spherical in shape with size range 15-30nm. These prepared NPs showed anti-microbial activity against *Escherichia coli, Staphylococcus aureus* (Rafique, Shaikh *et al.* 2017). Kala, A *et al*, illustrated the production of Cu-NPs using *Datura innoxia*. The leaves extract of this plant were used which synthesized spherical NPs with the size of 5-15nm. These prepared NPs showed potential activity against rice pathogens (Kala, Soosairaj *et al.* 2016). Gopinath *et al*, synthesized Cu-NPs using leaf extract of *Nerium Oleander*. He and his fellows mentioned that these NPs have great potential to reduce $CuSO_4$ solution. The synthesized NPs were characterized by different techniques and hence showed that NPs are spherical in shape. The established NPs showed good bacterial activity against five different organism like *Salmonella typhii, Klebsiella Pneumonia, Escherichia coli, Staphylococcus aureus* and *Bacillus subtilis* (Gopinath, Subbaiya *et al.* 2014). Saranyaadevi *et al*, carried out that *Capparis zeylanica* leaf extract can be used to reduce the $CuSO_4$ solution. The prepared NPs were characterized by UV-visible spectroscopy, FTIR, XRD, SEM, EDX and TEM. The study showed that the synthesized NPs were cubical in shape and with the size range from 50-100nm. The synthesized NPs showed high bacterial activity against *Staphylococcus aureus, Pseudomonas aeruginosa* and *Escherichia coli* (Saranyaadevi, Subha *et al.* 2014). M Jayandran *et al*, produced CuNPs using leaf extract of *Curcumin*. The synthesized NPs showed potential to reduce copper oxide. The prepared NPs characterized through techniques of UV-visible spectroscopy, XRD, TEM. The synthesized nanoparticles showed that its average size is 60-100nm. The NPs were found both in cubic and rod shape. This study also showed potential bacterial activity against *Staphylococcus aureus, Bacillus subtillis, Escherichia coli, Staphylococcus Bacillus* (Jayandran, Haneefa *et al.* 2015).

Subbaiya and MasilamaniSelvam also reported plant based Cu NP synthesis using *Hibiscus rosa-sinensis* leaf extract as reducing agent. $CuNO_3$ was used as precursor salt and the mixture of salt solution and plant extract was kept for 48 h in dark. The resulting Cu-NPs were spherical in nature and showed great potential as antimicrobial agent against pathogenic *Bacillus subtilis* and *E. coli*. The study concluded that the Cu-NPs produced may serve as efficient drug for lung cancer therapy (Rafique, Shaikh *et al.* 2017).

Harne, S *et al*, carried out that latex of *Calotropis procera L.* can be used to reduce the Cu $(CH_3COO)_2$ solution. These NPs were synthesized and were characterized through the techniques of XRD, FTIR, TEM and EDX. This study showed that established NPs are polydispers spherical in shape and also presented that its average is 15±1.7nm. Cytotoxicity studies showed excellent viability at 120 µM concentration of copper nanoparticles (Harne, Sharma *et al.* 2012).

Correspondingly, many other plants and their extracts were used to synthesize the Cu-NPs. A comprehensive study is given in Table 1,2,3,4, which describes varied characterization techniques and also shows different activities of each Cu-NPs.

Table 1. Photocatalytic degradation of various harmful dyes through Biosynthesized Cu-NPs.

Plant	Part used	Size	Morphology	Characterization	Activity	Ref
Euphorbia esula L	Leaves	20–110nm	Spherical	UV-visible spectroscopy, XRD, FTIR and TEM	Catalytic activity in the reduction of 4-NP at room temperature in aqueous medium	(Nasrollahzadeh, Sajadi *et al.* 2014)
Thymus vulgaris L.	Leaves	56 nm	Spherical	UV spectrum, FTIR, XRD, FESEM, EDS, TEM, SEM	Excellent catalytic activity, convenient reusability and long-term stability	(Issaabadi, Nasrollahzadeh *et al.* 2017)
Azadirachta indica	-	-	-	UV-Vis spectroscopy, FTIR, TEM	Excellent catalytic activity in the presence of $NaBH_4$.	(Thirumurugan, Harshini *et al.* 2017)
Fortunella japonica	Fruit	5-10 nm	Spherical	UV–Vis spectroscopy, AFM, HR-TEM, XRD, Raman spectroscopy, FTIR	Act as a catalyst and showed good degradation percentage of 4-NP pollutant	(Singh, Kumar *et al.* 2017)
Banana	Peel	60 nm	Spherical	XRD, EDX, FE-SEM, FTIR, UV–Vis spectroscopy	Photo catalytic activity, degradation of Congo red (CR) under direct sunlight	(Aminuzzaman, Kei *et al.* 2017)
Abutilon indicum	Leaves	16.78 nm	Spherical	XRD, EDX, SEM, UV-Vis spectroscopy	Good photo-catalytic, antimicrobial and antioxidant activities.	(Ijaz, Shahid *et al.* 2017)
Rheum palmatum L.	Root	10–20 nm	Spherical	UV–Vis spectroscopy, FTIR, SEM, XRD, TEM	Catalytic activity for reduction of 4-NP, MB, and RhB	(Bordbar, Sharifi-Zarchi *et al.* 2017)
Centella asiatica (L.)	Leaves	2-5 µm	-	UV–Vis spectroscopy, SEM, IR spectroscopy and EDX	Used as catalyst for photocatalytic degradation of methyl orange (Organic pollutant)	(Devi and Singh 2014)
Broccoli	-	~4.8 nm	Spherical	UV-Vis, FTIR, TEM, DLS, XRD and cyclic voltammetry	High catalytic activity against 4-NP	(Prasad, Kanchi *et al.* 2016)
Cavendish banana	Peel	91.0 nm	Irregular and dumbbell	XRD, SEM, FT-IR, EDX and PSA	Photocatalytic activity/ degradation of red and green dye	(Leong 2016)
Euphorbia prolifera	Leaves	5–17 nm	Spherical	FESEM, EDS, elemental mapping, TEM and XRD	Excellent catalytic activity for the degradation of MB and CR in the presence of $NaBH_4$	(Momeni, Nasrollahzadeh *et al.* 2016)

Potential Applications of Copper Nanoparticles (Cu-NPs)

Cu-NPs have attracted several researchers owing to their catalytic and optical properties (Nasrollahzadeh, Sajadi *et al.* 2015) as well as their applications in engineering domains like electrical technology and mechanics (Kim, Lim *et al.* 2008, Salavati-Niasari, Davar *et al.* 2008). Cu NPs are imperative locum tenens for other NPs like silver, gold and platinum due to their applicability in thermal conducting materials and microelectronics (Eastman, Choi *et al.* 2001, Lu, Sui *et al.* 2001). When it comes to plant extract based NPs, the synthesized nanoparticles have added advantage of possessing medicinal properties acquired from capping agents present in plant extract. This enhances their potential applications in targeted drug delivery, medication, and cosmetics (Rafique, Shaikh *et al.* 2017). The antibiotic potential of Cu-NPs have paved the way for their applications in wound dressings, (Borkow and Gabbay 2009, Rubilar, Rai *et al.* 2013) while on industrial level, Cu NPs have been used in solar cells, gas sensors, (Atarod, Nasrollahzadeh *et al.* 2015, Nasrollahzadeh, Maham *et al.* 2015) superconductors with tolerance for high temperature and catalytic process (Carnes and Klabunde 2003, Li, Liang *et al.* 2008, Yuhas and Yang 2009). Cu-NPs because of their brilliant physical properties are used in antibiotics. The stability of Cu NPs upon matrix and their disincentive and bactericidal properties makes them suitable candidates for coating the equipment used in hospitals, (Li and Peterson 2006) antimicrobial materials, (Wang, Chen *et al.* 2002, Guduru, Murty *et al.* 2007) super strong materials, (Male, Hrapovic *et al.* 2004, Kang, Mai *et al.* 2007) sensors (Vukojević, Trapp *et al.* 2005, Xu, Zhao *et al.* 2006, Kantam, Jaya *et al.* 2007) and catalysts. (Athanassiou, Grass *et al.* 2006, Pecharromán, Esteban-Cubillo *et al.* 2006, Rodriguez, Liu *et al.* 2007).

Table 2. Antibacterial activities of Biosynthesized Cu NPs.

Plant	Part used	Size	Morphology	Characterization	Activity	Ref
Vitis vinifera	Leaves	-	-	UV-Vis spectroscopy and FTIR	Anti-microbial activity against *E. coli, S. aureus, pneumonia, S. typhii* and *B. subtilis*	(Angrasan and Subbaiya 2014)
Nerium Oleander	Leaves	-	-	UV-Vis spectroscopy and FTIR	Good bacterial activity against *S. typhii, K. Pneumonia , E. coli, S. aureus* and *B. subtilis*	(Gopinath, Subbaiya *et al.* 2014)
Capparis zeylanica	Leaves	50–100 nm	Cubical Structure	UV-Vis spectroscopy, FTIR, XRD, SEM, EDX and TEM	Bacterial activity against *S. aureus, P. aeruginosa and E. coli*	(Saranyaadevi, Subha *et al.* 2014)
Curcumin	Leaves	60- 100 nm	Cubic and Rods	UV-Vis spectroscopy, XRD, TEM	Bacterial activity against *S. aureus, B. subtilis and E. coli*	(Jayandran, Haneefa *et al.* 2015)
Magnolia Kobus L.	Leaves	37–110nm	Spherical	UV-Vis spectroscopy, Inductively Coupled Plasma spectrometry (ICP), EDS, XPS, and HRTEM	Bacterial activity against *E. coli*	(Lee, Song *et al.* 2013)
Malva sylvestris	Leaves	14 nm	Crystalline	UV-Vis spectroscopy, FTIR, SEM, XRD	Antibacterial activity against Shigella and listeria bacteria	(Awwad, Albiss *et al.* 2015)
Aloe vera	Leaves	20–30 nm	Spherical	UV–Vis spectra, TEM, SEM, XRD, EDS	Antibacterial activity against fish bacterial pathogens	(Kumar, Shameem *et al.* 2015)
Garcinia mangostana	Leaves	20–25 nm	Spherical	TGA, SEM, XRD, TEM, DTA	Highly antibacterial against *E. coli* and *S. aureus.*	(Prabhu, Rao *et al.* 2015)
Ocimum sanctum	Leaves	79 nm.	Spherical	SEM, XRD, TEM, FTIR	Showed good antibacterial activity against *E-coli* bacteria	(Sadanand, Rajini *et al.* 2016)
Terminalia bellirica	Fruit	2–7 nm.	Spherical	UV–Vis spectrophotometry, FTIR, HRTEM, XRD, TGA	Antibacterial activity against *E.coli*	(Sadanand, Rajini *et al.* 2016)
Citrus medica	Fruit	20nm	Crystalline	UV–Vis spectrophotometry, NTA and XRD	Antibacterial activity against *E.coli* and *K. pneumonia*	(Shende, Ingle *et al.* 2015)

The small size of NPs adds to the bactericidal potential of NPs. The reactivity of Cu-NPs is also enhanced owing to its high surface to volume ratio allowing facile and close interaction with other membranes of microorganisms with highratio (Narayanan and El-Sayed 2004). The antimicrobial potency of NPs is enhanced due to the fact that metal ions are released in colloidal solution. The colloidal solution of Cu-NPs had been reported to possess considerable antimicrobial potential when compared with standard antibiotics like chloramphenicol. Their potency as replacement for standard antibiotics was evident against several bacterial and fungal strains studied by different researches (Ramyadevi, Jeyasubramanian *et al.* 2012, Rafique, Shaikh *et al.* 2017). Dispersed CuNPs with size ranging between 2–5 nm have been reported to possess good antibacterial potential with the capacity to retrench microbial concentration by as much as 99.9% (Wang, Chen *et al.* 2002). Implantation of Cu NPs having around 6 nm diameter in films of polyvinyl methyl ketone showed that development of microbial colonies was clearly inhibited (Guduru, Murty *et al.* 2007). The floor functionalization of these particles with cur cumin can also provide any other method for utilizing the curcuminoids toward practicable medicine transportation and therapeutics. (Jayandran, Haneefa *et al.* 2015) Various *in-vitro* techniques including the disk diffusion technique has been extensively used to elucidate the potential of Cu-NPs as antibacterial agents against plethora of bacterial strains and phyto pathogenic fungi. Several reports are present on inhibitory effects of Cu NPs against human pathogenic microbial strains like *E.coli*, *K. pneumoniae, P. aeruginosa, Propionibacterium acnes* and *Salmonella typhii*. Inhibition of fungal strains infecting plants like *Fusarium culmorum*, *F. oxysporum* and *F. graminearum* have also been reported (Shende, Ingle *et al.* 2015). Both copper and Silver NPs have been extensively studied for their bactericidal applications by implanting these NPs on suitable support like carbon, polymers, polyurethane foam and sepiolite (Li, Lee *et al.* 2006). Yoon reported efficient antibiotic potential of Cu-NPs in a comparative study with silver NPs against *E.coli* and *B. subtilis* (Yoon, Byeon *et al.* 2007).

Table 3. Cytotoxic and Anticancer Potency of Biosynthesized Cu NPs.

Plant	Part used	Size	Morphology	Characterization	Activity	Ref
Calotropis procera L.	Latex	15±1.7 nm	Polydisperse spherical	XRD, FTIR, TEM and EDAX	Cytotoxicity Studies showed excellent viability at 120 µM concentration of Cu NPs	(Harne, Sharma *et al.* 2012)
Eclipta prostrata	Leaves	31±1.2 nm	Spherical, hexagonal and cubical	UV-Vis spectra, FTIR, XRD, HRTEM, SEM	Have high antioxidant and cytotoxic activity	(Chung, Abdul Rahuman *et al.* 2017)
Ormocarpum cochinchinense	Leaves	2 µm and 1µmin	Cluster structure	UV–Vis Spectroscopy, FTIR, XRD, SEM,TEM, SAED	Significant cytotoxicity effect on human colon cancer	(Gnanavel, Palanichamy *et al.* 2017)
Prosopis cineraria	Leaves	18.9 to 32.09 nm	Spherical	UV-Vis absorbance, FTIR, XRD, FESEM, and EDX	Antimicrobial and anticancer activity	(Jinu, Gomathi *et al.* 2017)
Black bean	Seed	~26.6 nm	Spherical	XRD, FT-IR, XPS, Raman spectroscopy, DLS, TEM, SAED, SEM, and EDX	Significant activity to reduce cervical carcinoma colonies	(Nagajyothi, Muthuraman *et al.* 2017)
Acalypha indica	Leaves	26–30 nm	Spherical	UV–Vis spectroscopy, XRD, FT-IR, SEM TEM and EDX	Antimicrobial effect against *E. coli*, *P. fluorescence* and *C. albicans*. Potency against MCF-7 human breast cancer cell line	(Sivaraj, Rahman *et al.* 2014)
Solanum tuberosum	Starch	54 nm	Spherical	UV–Vis spectrophotometry, XRD, SEM	Antimicrobial activity, anticancer properties against standard strains and MCF-7 cell line	(Alishah, Pourseyedi *et al.* 2017)
Coleus aromaticus	Leaf	17-40nm and 21-48 nm	Spherical	HR-TEM, XRD, EDS, DLS, FTIR, FESEM	An efficient platform for intracellular mi-RNAs delivery and improving therapeutic outcomes for lung cancer.	(Wu, Wang *et al.* 2017)

The application of both of these NPs as disinfectants in clinical wastewater containing contagious microorganisms have also been reported (Lin, Vidic *et al.* 1996, Yu-sen, Vidic *et al.* 1998). Zain reported improved antibacterial efficacy in case of Ag-Cu bimetallic NPs as compared to Ag and Cu NPs alone (Zain, Stapley *et al.* 2014). The alloys of Copper NPs have been reported for their applications in catalysis process like gas detoxification water gas shift catalysts (Barrabés, Just *et al.* 2006, Bracey, Ellis *et al.* 2009). Changes in surface properties, conformation and size of NPs may aid in controlling catalytic properties of NPs (Niu and Crooks 2003, Hoover, Auten *et al.* 2006). High yield even in mild reaction conditions is main reason for popularity of Cu NPs in comparison to traditional catalysts (Phong, Khuong *et al.* 2011).

Characterization of Copper Nanoparticles

Several techniques can be used for the characterization of synthesized nanomaterial. Some of the most common characterization tools are UV–Visible Spectroscopy (UV-vis), Fourier transform infrared spectrum analysis (FTIR), X-ray diffraction (XRD), Scanning electron microscopy (SEM) and transmission electron microscopy (TEM).

UV–Visible Spectroscopy (UV-Vis): A variety of metallic salt precursors have been used for synthesis of numerous NPs through different methods. Literature shows that NP synthesis process usually takes 24 hours. Following the completion of reaction, different nanoparticles give SPR (Surface Plasmon Resonance) bands e.g. Cu NPs peaks can be observed between 200-800nm. These peaks can be efficiently measured using UV-Vis spectroscopy (Shobha, Moses *et al.* 2014).

Table 4. Miscellaneous biomedical applications of Biosynthesized Cu-NPs.

Plant	Part used	Size	Morphology	Characterization	Activity	Ref
Commelina nudiflora	Whole plant	45-100 nm	Spherical	UV–Vis spectrophotometer, FESEM, EDX, XRD	Strong antioxidant, antifungal and antibacterial activity	(Kuppusamy, Ilavenil *et al.* 2017)
Cassia auriculata	Leaf	23 nm	Spherical, polydispers	UV-Vis, EDS, SEM, TEM and DLS	Drug delivery vehicle for anti-rheumatic agents.	(Shi, Tang *et al.* 2017)
Rubus glaucus	Fruit/ Leaf	43.3 nm	Spherical	UV–Vis spectrophotometry, DLS, TEM, SAED, XRD	Antioxidant potency evaluated against DPPH	(Kumar, Smita *et al.* 2015)
Carica papaya	Leaf	~150 nm	Star-like structure	UV–Vis, SEM, TEM, HR-TEM, EDX, XRD	Water purification, degrade chlorpyrifos in water	(Rosbero and Camacho 2017)
Cissus quadrangularis	Leaf	30 ± 2 nm	Spherical	UV–Vis spectroscopy, XRD, FTIR, SEM, TEM, EDAX	Anti-fungal activity against *A. niger* and *A. flavus*	(Devipriya and Roopan 2017)
Saraca indica	Leaf	40–70 nm	Spherical	UV-Vis, FTIR, XRD, EDX, XPS, SEM, TEM and HRTEM	Applications in fluorescence emitting materials.	(Prasad, Patra *et al.* 2017)
Eichhornia crassipes	Leaf	28 ± 4 nm	Spherical	UV–Vis spectroscopy, FTIR, FESEM, EDX	Highest inhibitory effect against plant fungal pathogens	(Vanathi, Rajiv *et al.* 2016)
Punica granatum	Peel	40 nm	Spherical	UV–Vis spectroscopy, FTIR, SEM, XRD	Mortality efficacy against green peach Aphid	(Ghidan, Al-Antary *et al.* 2016)

The formation of NPs can be monitored by observing the changes in peak formation with increasing time or increasing concentration of reactants (Precursor salt or Biological extract), each effecting the UV-vis absorption spectrum as the reaction proceeds and concentration of NPs increase (Yin, Wu *et al.* 2005, Swarnkar, Singh *et al.* 2011, Abboud, Saffaj *et al.* 2014).

The X-ray diffraction (XRD) Analysis: XRD is the most widely used technique for studying the metallic nature of NPs. This is done by analyzing the unit cell for its translational symmetry, shape and size.

The electron density within the unit cell can also be studied using XRD. All this information can be gathered from peak locations generated through XRD. The peak intensities are also used for specifically identifying the location of atoms (Shobha, Moses *et al.* 2014).

Fourier Transform Infrared
(FTIR) Spectroscopy: FTIR spectroscopic analysis is carried out to record the infrared intensity against the wavelength of emitted light. When it comes to nanoparticles, FTIR is a useful tool for identifying the nature of functional groups present in biological extracts that took part in capping and reduction of synthesized NPs.

The spectra obtained through FTIR provides the details of optical properties of NPs that may include the extinction cross-section, resonance wavelength and the scattering to absorption ratio (Shobha, Moses *et al.* 2014).

Microscopic techniques: Microscopic techniques are used to identify the morphological features of NPs. The micrographic image obtained using these techniques unfolds details about the shape and size of metallic nano particles in the series (Subhankari and

Nayak 2013).SEM image also reveals the details about uniformity of NP size and shape and aggregation state of NPs (Shobha, Moses *et al.* 2014).

Energy dispersive X-ray: EDX, also known as energy dispersive X-ray analysis (EDXA) is used for elemental analysis or composition of different elements in a sample. During EDX, a beam of electrons are focused upon the sample resulting in emission of X-rays. The X-rays emitted are then analyzed qualitatively and quantitatively. Quantitative analysis involves identification of elemental concentration in a sample be analyzing the peak intensities while qualitative analysis, involves identification of different X-ray peaks and their positions specified within the spectrum.

Elements with atomic numbers ranging from 4-92 can be easily detected through EDX. Since the number of emitted X-rays is in direct proportion with elemental concentration of each element in sample (Shobha, Moses *et al.* 2014).

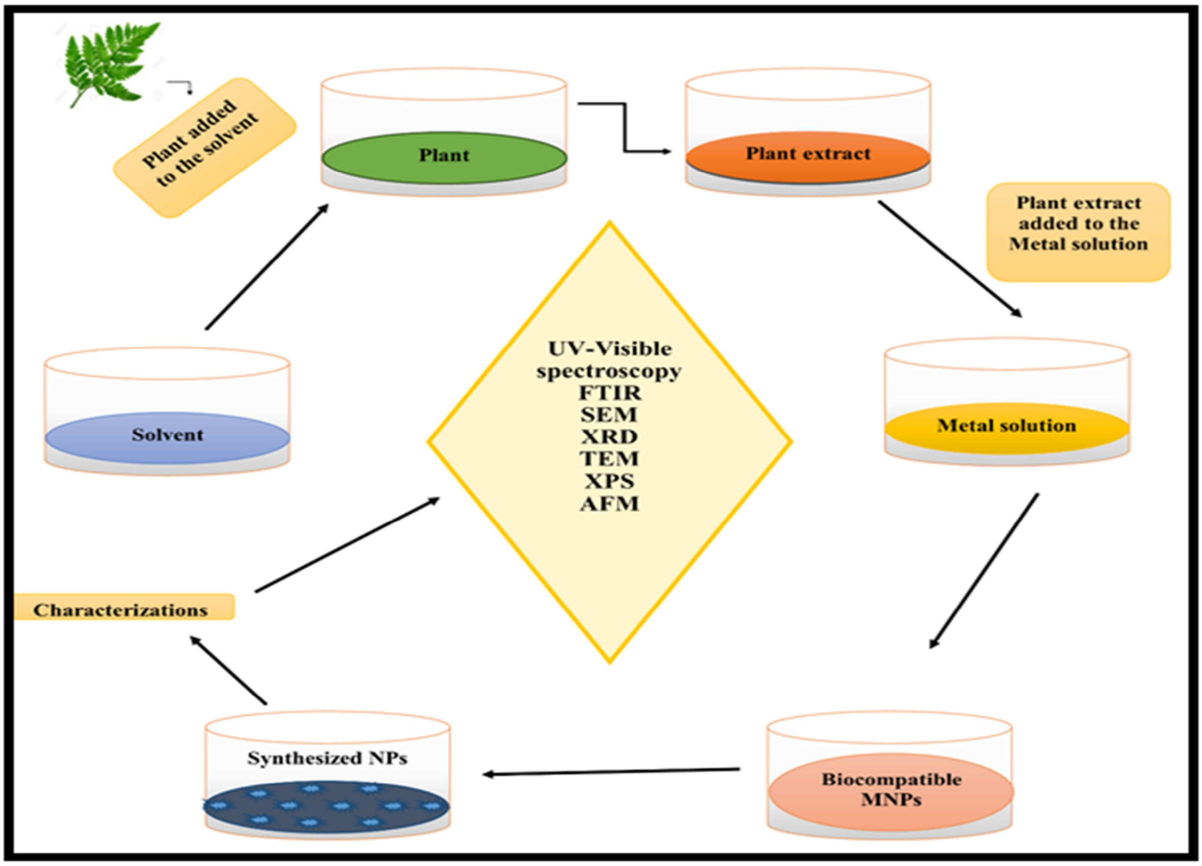

Fig. 1. Biosynthesis of Nanoparticles (NPs).

Antimicrobial activity of copper nanoparticles

This section deals with antimicrobial activity studies conducted using different concentrations of copper nanoparticles against human pathogenic bacteria belonging to various genera and species. Using 100 ml of copper oxide nanoparticles of 46 nm synthesized by Tabernaemontana divaricate at concentration of 50 ug/ml in well plate method showed 17 mm zone of inhibition against urinary tract pathogen *E.coli*(Sivaraj, Rahman *et al.* 2014). Twenty microliter of copper nanoparticles of 5–45 nm synthesized using brown alga *Bifurcaria bifurcata* showed inhibition zone of 14 and 16 mm, respectively, against *Enterobacter aerogenes* and *Staphylococcus aureus* (Abboud, Saffaj *et al.* 2014). Copper oxide nanoparticles synthesized by tea leaf or coffee powder extract exhibited inhibition zone of 5–16 mm against *Shigella dysenteriae, Vibrio cholerae, Streptococcus pneumoniae, Staphylococcus aureus* and *E.coli* at concentration from 1 to 200 lg/ disc (Sutradhar, Saha *et al.* 2014). Using 40 ml of *Vitis vinifera* synthesized copper nanoparticles showed inhibition zone from 8 to 18 mm against *Bacillus subtilis, Escherichia coli, Klebsiella pneumoniae, Salmonella typhii* and *Staphylococcus aureus* (Angrasan and Subbaiya 2014). Minimum inhibitory concentration of copper nanoparticles ranged from 31.25 to 250 lg/ml against *E.coli, Enterococcus faecalis, Pseudomonas aeruginosa, Shigella flexneri, Salmonella typhimurium, Proteus vulgaris, Staphylococcus aureus* and *Klebsiella Pneumoniae* (Ahamed, Alhadlaq *et al.* 2014). *Gloriosa superba* synthesized copper nanoparticles of 5–10 nm exhibited antibacterial activity against *Klebsiella aerogenes, Pseudomonas desmolyticum, E.coli* and *Staphylococcus aureus* (Naika, Lingaraju *et al.* 2015).

Using 20 ml of copper nanoparticles of 33 nm synthesized by *Citrus medica* showed inhibitory activity against *E.coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Propionibacterium acnes* and *Salmonella typhii*(Shende, Ingle *et al.* 2015), while 100 ml of copper nanoparticles of 26.51 nm synthesized using *Garcinia mangostana* at 0.2–1.0 lg/ml concentrations showed antibacterial activity against *E.coli* and *Staphylococcus aureus*(Prabhu, Rao *et al.* 2015). Monodisperse copper nanoparticles of 50 nm have minimum inhibitory concentration ranging between 1.875 and 3.75 lg/ml against standard and clinical strains of *Staphylococcus*, including methicillin resistant *Staphylococcus aureus* and *Candida* species (Kruk, Szczepanowicz *et al.* 2015). Copper oxide nanoparticles of 54 nm synthesized using *Solanum tuberosum* showed minimum inhibitory concentration and minimum bactericidal concentration ranging between 200 and 1000 lg/ml against *Bacillus cereus, Enterococcus, E.coli, Pseudomonas aeruginosa, Shigella sonnei* and *Staphylococcus epidermidis* (Alishah, Pourseyedi *et al.* 2017). Good antimicrobial activity shown by copper nanoparticles against the pathogenic bacteria belonging to various genera and species suggests their use as antimicrobial agent. Copper nanoparticles with antimicrobial activity can be employed for the production of a broad range of polymer/ copper Nano composites to be used in the preparation of antibacterial paints/coatings for application in household, biomedical and aerospace industries. Moreover, copper nanoparticles immobilized into polymer matrix can be employed in the food packaging for retarded deterioration, enhanced shelf life, ensuring good quality and safety of packaged food.

Disease organization by means of copper nanoparticles

Many fungal and bacterial pathogens cause diseases in cultivated crops and thus resulting in yield losses. The antimicrobial activity exhibited by copper nanoparticles against plethora of pathogenic micro-organisms (both bacteria and fungi) has piqued the interest in utilization of Cu NPs as agents for disease control in agriculture. Studies carried on *in-vitro* antifungal activity of copper nanoparticles reported the maximal antifungal activity against *Curvularia lunata* MTCC 2030 followed by *Alternaria alternata* MTCC6572, *Fusarium oxysporum* MTCC1755 and Phoma destructive DBT66(Kanhed, Birla *et al.* 2014). Copper nanoparticles manufactured using *Citrus medica* also manifested inhibitory activity against plant pathogenic fungi, *Fusarium culmorum, F. oxysporum* and *F. graminearum* (Shende, Ingle *et al.* 2015). In another study, copper nanoparticles displayed maximum antifungal activity against *Fusarium equiseti* with 25 mm zone of inhibition followed by *F. oxysporum* and *F. culmorum* (Bramhanwade, Shende *et al.* 2016). Copper nanoparticles of 20–50 nm at a concentration of 450 ppm could inhibit 93.98% growth of the *Fusarium* specie after 9 days of incubation(Viet, Nguyen *et al.* 2016). Copper-based fungicide has been used in disease inhibition and treatment in many plant species (Borkow and Gabbay 2005). Field studies under protected cultivation using three different copper-based nanoparticles of indistinguishable sizes, i.e. 11–14 nm and shapes, Cu_2O, CuO and Cu/Cu_2O, respectively, against *Phytophthora infestans* on *Lycopersicon esculentum* revealed that copper-based NPs were more efficient than the four registered copper-based agrochemicals. Along with the propitious potency, it was also found that copper-based nanoparticles did not instigate any irreparable damage/deleterious effect to the plants(Giannousi, Avramidis *et al.* 2013). In exploring copper nanoparticles for disease management, it is just the dawn of an era which has to go long way for safeguarding the plants from disparate diseases in imperishable manner.

Conclusions

Green synthesis of nanoparticles, once considered as an emerging field is a well-established domain of research in nanotechnology with surplus applications. Copper nanoparticles offers a range of applications in medicine, drug delivery, wound dressing, bio labelling, water purification optics, catalysis, structural engineering and several other domains of science and technology. Copper nanoparticles have also been found to have potent antibacterial and antifungal activities and can hence prove to be an effective alternative source to destroy drug resistant microbial species. Due to such diversified range of applications, Copper nanoparticles can prove as suitable and inexpensive alternatives to costly nanoparticles like gold. However, the exact mechanism with which the phytochemicals reduces and stabilizes these nanoparticles is yet to be understood. Complete understanding of this mysterious process will help enable the scientists to use targeted phytochemicals to reduce and cap nanoparticles followed by usage of intentionally designed nanoparticles for specific purposes. This will also help in designing nanoparticles with desired shape and size.

Abbreviations

Cu: Copper, Cu-NPs: Copper Nanoparticles, DLS: Dynamic light scattering, EDAX: Energy dispersive X-ray analysis, EDS: Energy-dispersive spectroscopy, FTIR: Fourier transform infrared spectroscopy, HRTEM: High resolution transmission electron microscopy, NPs: Nanoparticles, UV–VIS: Ultra-violet visible spectroscopy, SEM: Scanning electron microscopy, XRD: X-ray Diffraction, TEM: Transmission electron microscopy.

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