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ARTICLE

Utilization of Mother Nature's Gift for the Biofabrication of Copper/ Copper Oxide Nanoparticles for Therapeutic Applications

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Abstract: This review enumerates the green *cum* biosynthesis of copper/copper oxide nanoparticles (Cu/CuO NPs) using plant and biogenic extracts. Moreover, it explores the biogenic synthesis of Cu/CuO NPs using different methods and elaborates on biological and eco-friendly modes of synthesis using different plant species. The survey revealed that biological methods involve the use of plant extracts, bacteria, protozoa and fungi. However, plant mediated nanomaterials synthesis is the best technique. Some of the microscopic characterization techniques, like XRD, SEM, TEM, FTIR, XPS, BET and UV–Vis, have been discussed to explore the size, shape, structure, composition and porosity of Cu NPs. The current review highlights the phytosynthesis, characterization and therapeutic applications of Cu/CuO NPs. The therapeutic applications of Cu/CuO NPs, like antimicrobial, anti-parasitic and anticancer activities against a variety of gram-negative and positive bacteria, fungi and human cancer cells, respectively, have been discussed.

Keywords: Biosynthesis, Phytosynthesis, Cu/CuO NPs, Microscopic techniques; Therapeutic applications.

Introduction

Research all over the world on green nanotechnology enhanced the scientific revolution of the twenty-first century. Metal nanoparticles have varieties of applications, like catalytic, energy storage, environmental remediation, biological, and so forth [1]. There are various chemical and synthetic routes that have been employed to synthesize nanoparticles due to their various applications in scientific, technological, pharmacological and biomedical sectors [2]. One of the interesting and human beneficial biogenic synthesized metallic nanoparticles is copper nanoparticles (Cu NPs). In the synthesis of Cu NPs, low-cost chemicals and plant extracts as precursors are used, several of which have advanced chemical and physical properties [3]. Cu NPs are among the most useful elements in medical sciences that can be used in numerous therapeutic effects, such as anti-inflammatory, anticancer, analgesic and antimicrobial effects [6]. Cu NPs have greater applications in heat transfer systems, such as sensors as well as catalysts [7]. Nanotechnology has greater applications in research area. In the past, chemical methods of the synthesis of Cu NPs were used which are known to be expensive

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and toxic due to usage of expensive hazardous chemicals, thus posing a threat to health as well as the environment issue. This has led to the utilization of safe methods of NP synthesis, such as the biological method through which various plant extracts can be used as precursors in the green synthesis. According to literature survey, Cu/CuO NPs were biosynthesized using *Neriumoleander, Punicagranatum*, *Aegle marmelos*, *Ocimum sanctum* and *Zingiber officinale*. As-synthesized Cu NPs were studied against gram +ve bacteria, like *Staphylococcus aureus,* and showed good results. [4] NPs are recognized for their large surface area to volume ratio, small size and other physicochemical parameters which make them useful to man in applications, such as dye removal [5], antioxidant, antidiabetic, anti-inflammatory [6] and antibacterial activities [8]. The Cu NPs also possess remarkable properties due to their specific qualities, like tunable size, shape, and distribution as compared to bigger particles. Nanoparticles generally possess remarkable catalytic, optical, magnetic, electronic and thermal properties. Amongst the various noble ionic-based NPs, Cu NPs remain the most explored and have potential in catalysis. Similarly, silver is one of the common antimicrobial agents like copper owing to its strong toxicity against various microorganisms [9]. However, Cu NPs attract a great deal of attention due to the availability of the Cu precursor and their distinguished exceptional properties, as mentioned earlier, in addition to their versatile applicability in many fields, including - but not limited to - agricultural, industrial, environmental and medical applications [10]. Synthesis methodologies are considered of utmost importance in the field of nanotechnology. In this regard, the methodologies which have been adopted in the synthesis of Cu NPs using plant extracts are shown in (Fig. 1) [11].

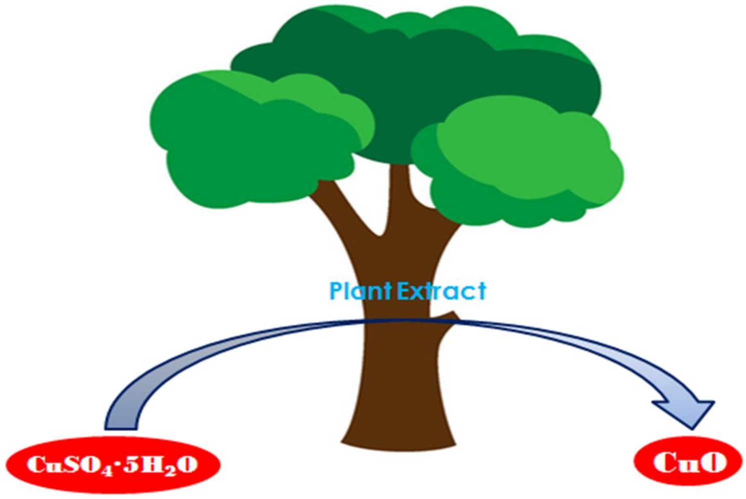

FIG. 1. Fabrication of Cu NPs from various zinc salts employing different plant extracts.

Plant-mediated Biosynthesis of Cu/Cuo Nps

The objective of the present work is the introduction of a quick and simple literature survey on the biosynthesis of Cu NPs. The green methodologies' utilization has increased considerably in the last few decades [12-14]. The literature survey reveals that the eco-friendly preparation methods using different plant species and their properties and potential applications serve as a good alternative in nanotechnology. The development of this new approach and the significant interest in it are mainly related to the absence of toxic chemicals or high-energy applied methods to the biological synthesis, which led to develop methods which are more environmentally friendly and cost-effective. This review enumerates the classification of nanomaterials in general, green biosynthesis of NPs using plant extracts and its advantages over using bacteria and fungi. Many researches in the literature indicate that the biosynthesis of metal oxides reduced to metallic nanoparticles is more eco-friendly than the conventional physiochemical methods used presently. Therefore, these biological methods have become more popular as green synthesis. The recent developments of plant-mediated biosynthesis of Cu NPs have been dissected in the subsequent paragraphs and are listed in Table 1.

S. Nasreen *et al.* have synthesized low-cost eco-friendly Cu NPs. A naturally available precursor with the help of plant extract *Aloe barbedensis* was used to develop the biocompatible NPs and the antibacterial activity was evaluated against gram-negative and gram-positive pathogens. Also, the results found more enhanced activity towards the gram-negative bacteria [15].

T. Saleh *et al.* used a biological extract of *Cynomorium coccineum* for the synthesis of Cu NPs using copper sulphate as a starting material and reported 14.2 nm as the size of the NPs [16].

Nadri *et al.* used *C. spinosa* fruits extract to prepare Cu NPs and obtained particle size between 17 and 41 nm. The results demonstrated the analgesic effects of Cu NPs, especially in combination with morphine and provided a new strategy for producing new antinociceptive medications in the future [17].

Bharadvaja *et al.* have synthesized environment-friendly Cu NPs with size of 1.54 nm which were also cost-efficient at different concentrations with the help of plant leaves of *Centella asiatica* and produced spherical shape of 323 nm size [18].

Ji-Ming Song *et al.* synthesized Cu NPs through biological route and environmentally friendly approach using *Camellia japonica* plant leaf extract, which were tested for antimicrobial properties against *Pneumoniae*, *Streptococcus pneumonia*, *Bacillus subtilis* and gram-negative (*Escherichia coli, Salmonella typhimurium*) bacterial pathogens as well as fungal strains of *Aspergillus flavus, Aspergillus fumigates*, *Aspergillus niger* and *Candida albicans* [19].

A. Mohamed reported a green method for synthesis of Cu NPs using the extract of seedless dates, which is simple, cost-effective and environment-friendly, obtaining spherical-shaped particles with size of 78 nm [20].

N. Ildiz *et al.* have demonstrated the plant-mediated synthesis of Cu NPs using a plant extract and enhanced antimicrobial activities towards standard bacterial (*E.coli, S.typhi, P.aeruginosa* and *S.aureus*) and fungal pathogens (*C.albicans*) compared to other extracts and reported flower-shaped 11±1 and 8±1nm nano-size particles. The results suggest that green synthesis of NPs presents a promising potential for development of eco-friendly antimicrobial agents for specific nasocomial human pathogens [21].

A. Zangeneh *et al.* performed biosynthesis of Cu NPs using *A. biebersteinii* leaf aqueous extract and reported crystal-shaped NPs of 10.1 nm and 23.4 nm size. According to these results, it seems that Cu NPs could be administrated as a neuroprotective supplement or drug for the treatment of central nervous system disorders in clinical trials and have shown antispermatogenic, antidiabetic, antibacterial, antiviral, antiparasitic, antifungal, antiulcer, anti-inflammatory, antispasmodic and especially neuroprotective effects [22].

Li,Burn *et al.* also reported a biosynthesis of Cu NPs from the bioreduction of $CuSO_4$ solutions using *A. eriophyllum* leaf extracts and produced spherical-shaped NPs of 31.34 nm size. The environment-friendly method used also indicated high antifungal, antibacterial, antibiotic, antiviral and antiparasitic effects against all the tested fungi and bacteria species [23].

Similarly, Al. Haddad *et al.* developed a cost-effective, non-toxic green technique to produce high-quality Cu NPs. This green synthesis of Cu bimetallic NPs was performed using extracts from date palm tree (*Phoenix dactylifera*) leaves. The results showed the FCC structure of 26 nm size having significant pharmacological and antibacterial activities against *Bacillus subtilis* (gram-positive) and *Escherichia coli* (gram-negative) bacteria [24].

Moreover, extensive work was published on copper oxide nanoparticles (CuO NPs) for various clinical applications. The CuO NPs were biosynthesized by M.T. Pelegrino *et al.* using green tea extract, which acts as a reducing and capping agent and reported NPs with the size of 6.6 nm. CuO NPs were highly stable in aqueous suspension. Toxicity of bioassays has shown that at low concentrations (up to 40 µg mL^{-1}), the CuO NPs did not affect or even enhance seed germination enhancing plant growth and the involvement of nitric oxide signaled the phytotoxic effects induced by high concentrations of this formulation [25].

Next, Karunakaran *et al.* have demonstrated flower extract-mediated biosynthesis of CuO using *Hylotelephium telephium*. The study confirmed the formation of spherical-shaped of size 83nm NPs and found great antioxidant and antimicrobial activities on the tested bacteria. It is cleared that *H.telephium* flower extract-mediated biosynthesis of NPs is a new approach with prospects for eco-friendly NP synthesis [26].

Similarly, S. Shah *et al.* have reported green synthesis of nano-sized CuO NPs using *Carica papaya* leaves extract. They obtained a growth of crystalline-shaped with size of 270 nm nanoparticles. The CuO NPs-coated cotton fabric displays greater antibacterial activity against *E.coli* and exhibits superior antimicrobial activity, indicating that it has a higher potential to be employed in medical textile to avoid cross-infection within a clinical environment. The NPs also exhibited good antimicrobial activity against gram-negative *E.coli* [27].

Likewise, Chandrasekaran *et al.* have studied the green synthesis of CuO NPs using an aqueous extract of *Beta vulgaris* beetroots. The synthesized NPs appeared crystalline in shape with a range of 35-95 nm size. Subsequently, anticancer efficacy of the CuO NPs was studied in A549 cells through cell viability assay. The CuO NPs induced apoptosis in the A549 cell line with an IC_{50} value of 25 lg/mL, as revealed by cytometer analysis. Therefore, it is presumed that CuO NPs could be developed as a nano-drug for infectious diseases and tumor studies [28].

S. Suresh *et al.* have revealed the biosynthesis of CuO nanostructures, which were synthesized using *Cynodon dactylon* and *Cyperus rotundus* grass extracts. The reported NPs had clusters of sponge-like shape with 500 nm size, having a significant antibacterial activity against bacterial species *B.cereus*, *S.aureus*, *E.coli* and *K.pneumoniae* [29].

Moreover, Lin Yuanhua *et al.* used the peels extract to mediate the synthesis of Cu NPs (ETP-Cu NPs) using *Citrus reticulata* (tangerine) and obtained round shape with 54 and 72 nm particles. The crystal structure, morphology, surface and chemical properties were experimentally confirmed. The nano-formulation was found to inhibit both acid and microbial corrosion of X80 steel [30].

Getu Weldegebrie has revealed the study of biosynthesis of CuO NPs using *Verbascum thapsus* extract and their characteristics study showed NPs having a spherical shape with 219 to 500nm size. They also exhibited antibacterial properties against both *S.aureus* and *E.coli* bacteria [31].

J. Sackey *et al.* have revealed that CuO NPs were successfully synthesized *via* a cost-effective approach using aqueous extracts obtained from red flowers of *Euphorbia pulcherrima* and further characterization study of NPs showed a cubic shape with 153.7 and 16.3nm particle size [32].

D. Padmanabhan Nambiar *et al.* synthesized CuO NPs using *Caesalpinia bonducella* seed extract *via* a green synthetic pathway. The study introduces a convenient and inexpensive method to synthesize CuO NPs as a novel reducing and stabilizing agent. They obtained rice-shaped NPs with 3.13−56.3 nm particle size. The antibacterial properties of CuO NPs were investigated against *S.aureus* gram-positive and gram-negative bacteria by the agar diffusion method. Each bacterial strain was smeared evenly on the sterilized agar Petri plates and allowed to dry the synthesized nano-particles, thus proving to be an interesting material for electrochemical and biological studies (Fig. 2) [33].

Fatih Erci *et al.* prepared cost-effective and environment friendly Cu NPs by biogenic reduction of $CuSO_4.5H_2O$ solution through deionized water and ethanol mixed extract of leaf powder of *Thymbra spicata*. They have produced spherical-shaped and 26.8 nm and 21 nm size nanoparticles. The bacterial inhibition of the developed NPs against *S.typhi* and biofilm activity against *S.aureus* showed promising results. In addition, the reported particles showed a significant anti-oxidant property [34].

Jaswanth Seetha *et al.* have reported the biosynthesis of CuO NPs with the help of de-ionized water extract of fresh leaves of *Moringa oliefiera* (MO) by utilization of precursor $CuSO_4.5H_2O$ as a reductant for bioreduction. This research resulted in the growth of spherical-shaped, 110 nm NPs having a significant pharmacological activity against *S. aureus* and pathogenic bacteria *Klebsiella pneumonia* (*K.pneumonia*) in a disc diffusion test [35]. D. Balakrishnan *et al.* have demonstrated the flora-mediated generation of CuO NPs through water and alcohol extraction method of the leaves of *Euphorbia cyathophora*. The NPs were spherical-shaped with 40 nm to 55 nm size range. The developed nanoparticles showed promising antioxidant capacity [36].

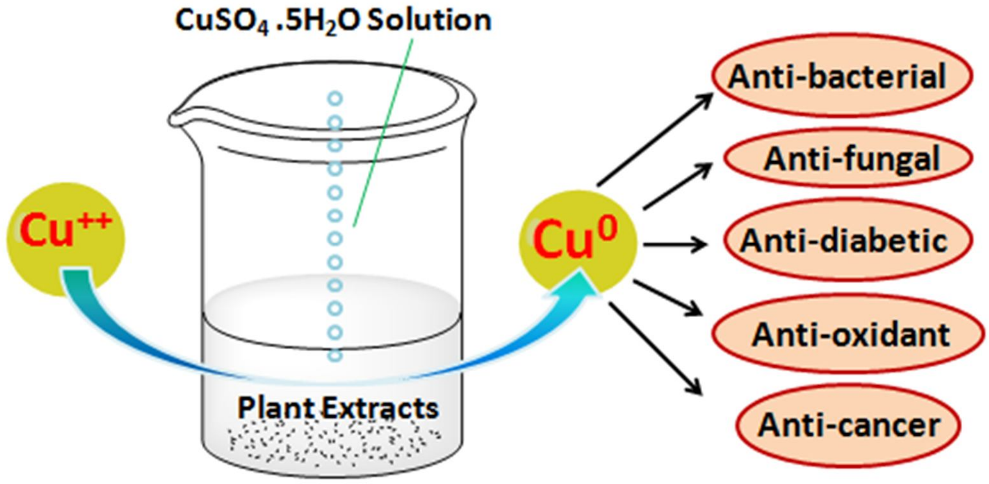

FIG. 2. Biosynthesis of Cu NPs and their pharmacological applications.

Similarly, A.M. Awwad *et al*. have revealed interesting facts about biosynthesis of CuO NPs in the presence of aqueous solution of *Ailanthus altissima* leaf extract with copper acetate initiator. Spherical-shaped NPs with 20 nm size were produced. The CuO NPs have revealed antibacterial activity against *S.aureus* using chloromphenical as a control for the antimicrobial agent in a disc diffusion method [37].

Sharmila Pradhan Amatya *et al*. have studied the green synthesis of CuO NPs with the help of *Euphorbia hirta* leaves extract as reducing and capping agent with $CuSO_4 \cdot 5H_2O$ as the precursor of the reaction. The newly formed Cu NPs were spherical-shaped with size between 20-25 nm. The synthesized NPs appeared to be effective against various standard strains of micropathogens, like *S.aureus* and *E.Coli* by taking ofloxacin as a standard for zone of inhibition [38].

Adeyemi, D. K. *et al*. have reported the biosynthesis of CuO NPs by using *Spondias mombin* leaves extract with copper acetate as reductant of the reaction. The reported NPs have a triangular shape with 65-90 nm size. The newly synthesized NPs were found to have exceptional pharmacological activity, like antibacterial inhibition towards common micropathogens *E.Coli*, *Pseudomonas aeruginosa* and *S. aureus* against standard drug ciprofloxacin [39-40].

Suresh Ghotekarb *et al*. have revealed some interesting facts about flora-mediated synthesis of CuO NPs in aqueous extract of *Moringa oleifera* leaf by utilising copper acetate monohydrate as the precursor. The synthesized NPs, as observed, were quasi-spherical-shaped with 35-95 nm size. The newly reported particles have interesting antifungal activity against some selected strains (*C.albicans*, *A.niger*, *A.clavatus*, *T.mentographyte* and *E.floccosum*) with reference standard of griseofulvin [41].

Akhilesh Kumar Singh *et al*. have synthesized eco-friendly CuO NPs by utilizing $CuSO_4$ as reductant with the help of aqueous extract of leaf of *Mangifera indica* (L.). The synthesized NPs were spherical-shaped and 4-7 nm size. They have found to be efficient in the detection of cysteine and NADH. The newly synthesized NPs have revealed antimicrobial inhibition against *E.coli* KT45/45A and *S.aureus* KT68, as well as antioxidant activity [42].

Anbuvannan Mari *et al.* have reported the flora-mediated synthesis of CuO NPs with the help of aqueous extract of fresh leaves of *Catharanthus roseus* by utilization of copper nitrate used as the precursor. The research revealed the development of rod-shape 23-nm nanoparticles having promising anti-micropathogenic activity against *E.coli* [43].

Rakesh Chowdhury *et al.* have reported the synthesis of CuO NPs by an alkaline hydrolysis process in the presence of the flower extract of *Lantana camara*, an invasive weed, followed by calcination in air at 400 ^{o}C. They noted crystalline shape with 10 nm size [44].

Olga Długosz1 *et al.* have revealed a green method for synthesis of Cu NPs using extract of hawthorn dried fruit having been reported for the reduction of copper ions. The synthesized NPs have a spherical shape and 200 nm size. The NPs showed roughly similar antibacterial activity against the tested pathogenic microorganisms, *A.niger*, *E.coli* and *S.cerevisiae* (below 100 mg/l) [45].

Elias E. Elemike *et al.* have reported the synthesis of Cu_2O/CuO NPs, prepared using *Alchornea cordifolia* leaf extract. The average size of the NPs in the composites was estimated at 3.54 nm having spherical shape and toxicity against cervical cancer using MTT assay method. The *in vitro* cytotoxicity tests of the nanomaterials was conducted on cervical *Hela* cell lines [46].

T. Venkatappa Rao *et al.* reported a green synthesis of Cu NPs, with aqueous extract of *Curcuma longa* powder by using a simple and cost-effective method. The size of the particles was in the range of 5–20 nm having a crystalline structure. The antibacterial activity of the obtained Cu NPs is tested for both gram-positive and gram-negative microorganisms. The zone of inhibition of Cu NPs for gram-negative bacteria is higher as compared to that for gram-positive bacteria due to their distinct cell wall structure. The cell wall of negative bacteria does not have an outer membrane envelope. The NPs equally showed antimicrobial, antifungal and anticancer activity [47].

Sukumar Kayalvizhi *et al.* have explored eco-friendly green synthesis of CuO NPs using *Annona muricata* leaf extract to investigate cytotoxic property on human breast cancer cell lines (MCF-7) *via in-vitro* studies. The NPs were exposed to cancer cells in a dose-dependent manner. The synthesized CuO NPs showed 30-40 nm particle size range and spherical shape [48].

R M. Mahmoud *et al.* have explored an efficient biosynthesis of CuO NPs by utilizing two precursors of waste plant extracts; namely, pomegranate peel and date stones. The biogenic CuO NPs as cytotoxic agent were applied against human breast cancer (MCF7) cell lines and compared with the normal BJ1 cell line. The synthesized Cu NPs were reported to be crystalline in nature having particle size of 6 to 20 nm [49].

Abu-Yousef *et al.* in their study revealed the biosynthesis of Cu NPs using an extract of *M.oleifera* leaves treated with $CuSO_4.5H_2O$ solution. This *oleifera* leaves extract exerts considerable anti-bacterial activity against *E.coli*, *Klebsiella pneumoniae*, *S.aureus* and *Enterococcus faecalis* and anti-fungal activity against *A.niger*, *A.flavus*, *Candida albicans* and *Candida glabrata*. Besides, it reported antioxidant, anti-bacterial and anti-fungal activities [50].

Joy Sarkar *et al.* have reported the biosynthesis of CuO NPs with the help of de-ionized water extract *Adiantum lunulatum* whole plant extract by utilization of precursor $CuSO_4.5H_2O$ as a reductant for bioreduction. This research resulted in the growth of spherical-shaped, 6.5 - 1.5 nm NPs. The NPs have significant antioxidant activity [51].

Ashutosh Sharma *et al.* conducted a study to prepare cost-effective and environment-friendly CuO NPs by biogenic reduction of $CuSO_4.5H_2O$ solution through de-ionized water and ethanol mixed extract of leaf and flower powder of *Galphimia glauca*. They have produced spherical-shaped and 5-10 nm sized particles. The cytotoxicity assays of developed nanoparticles were also determined using MRC-5 and HeLa cell lines for CuO NPs and it was found that the NPs are non-toxic to the normal cells and are relatively toxic to cancer cells [52].

Mehran Moradi *et al.* have reported the biosynthesis of CuO NPs with the help of deionized water extract of fresh fruit of mulberry (*Morus alba* L.) by utilization of precursor copper nitrate trihydrate ($Cu(NO_3)_2{\cdot}3H_2O$) as a reductant for bioreduction. The research resulted in the growth of spherical-shaped, 50 to 200 nm NPs having a significant pharmacological activity and superior antibacterial activity against *E.coli* O157:H7 and *Listeria monocytogenes* [53].

D Renuga *et al.* prepared cost-effective and environment-friendly CuO NPs by biogenic reduction of copper (II) acetate solution through deionized water and ethanol mixed extract of leaf powder of *Brassica oleracea.* They have produced spherical-shaped and 26-nm size particles. The bacterial inhibition of the developed NPs against *E.coli* showed enhanced effect. Likewise, the nanocomposites exhibited strongest antifungal activity against *Aspergillus niger* and *Candida albicans* (Table 1) [54].

TABLE 1. Plant-mediated synthesis of Cu/CuO NPs.

S/ No.	Plants	Family	Part Used	Average Size of Cu/CuO NPs (nm)	Shape	Characterizations	Therapeutic Applications	Ref.
1	*Aloe barbedensis*	Apiaceae	Plant	NA	--	SEM-EDX, FTIR	Antibacterial	[12]
2	*Cynomorium coccineum*	Balanophoraceae	Whole plant	14.2	--	FTIR, SEM, EDX, XRD, TG	Biosorption, Water purification, Photocayalysis, Textile printing	[13]
3	*Copperas spinosa*	Capparaceae	Fruit	NA	--	FTIR, EDX, SEM	Anti-nociceptive	[14]
4	*Centella asiatica*	Mackinlayaceae		323	Spherical	SEM. UV	NA	[15]
5	*Camellia japonica*	Theaceae	Leaf	1.54	--	UV–Vis, FTIR, XRD, SEM, TEM	Antimicrobial, Antifungal	[16]
6	*Seedless dates*	Palmaceae	NA	78	Spherical	TEM, DLS, XRD, UV-Vis, FTIR	NA	[17]
7	*Artemisia*	Asteraceae	Whole Plant	11±1, 8±1	Flower	FTIR, SEM, XRD, EDX	Antimicrobial activity, Antibacterial, Antifungal	[18]
8	*Achillea biebersteinii*	*Achillea*	Leaves	10.1,23.4	Crystalline	FTIR, EDS, SEM, TEM	Antispermatogenic, Antidiabetic, Antibacterial, Antiviral, Antiparasitic, Antifungal, Antiulcer, Anti-inflammatory, Antispasmodic	[19]
9	*Allium eriophyllum*	Asteraceae	Leaf	crystal size of 31.34	Spherical	UV–Vis, FE-SEM, TEM	Antioxidant, Antibacterial, Antiviral, Anti-Parasitic	[20]
10	*Date palm tree*	Arecaceae	Leaves	26	FCC structures	SEM, EDX, XRD	Antibacterial	[21]
11	*Lactuca sativa L.*	Asteraceae	Commercial green tea	6.6	NA	NA	Antioxidant activity	[22]
12	*Hylotelephium telephium*	Crassulaceae	Flower	83	Spherical	SEM and TEM, XRD	Antioxidant, Antibacterial	[23]
13	*Carica papaya*	Caricaceae	Leaves	270	Crystalline nature	UV–Visible, FTIR, XRD, SEM, TEM	Antioxidant, Antibacterial	[24]
14	*Beta vulgaris*	Amaranthaceae.	Beetroot	310	NA	FTIR, TEM EDAX,AFM,	Anticancer, Antibacterial	[25]
15	*Cynodon dactylon*	Poaceae	Grass	500	Clusters of sponge-like	FTIR, TEM EDAX, XRD	Antibacterial	[26]
16	*Citrus reticulata*	Rutaceae	Peels	54, 72	Round	UV–Vis, FTIR, XRD, SEM/EDAX, TEM	Inhibition of acid and bio-corrosion in the oil field	[27]
18	*Verbascum thapsus*	Scrophulariaceae	Leaves	219-500	Spherical	UV–Vis, FTIR, SEM	Photocatalytic, Antibacterial	[28]
19	*Euphorbia pulcherrima.*	Euphorbiaceae	Red flowers	153.7, 16.3	Cubic	XRD (SEM) OPM, HRTEM EDS (FTIR/ATR) (XPS DR UV–Vis, PL CV, EIS)	NA	[29]
20	*Caesalpinia bonducella*	Caesalpiniaceae	Seed	3.13−56.3	Rice shape	UV–Vis, FTIR, XRD, SEM/EDAX, TEM XPES,SEM	Antibacterial	[30]

S/ No.	Plants	Family	Part Used	Average Size of Cu/CuO NPs (nm)	Shape	Characterizations	Therapeutic Applications	Ref.
21	*Thymbra spicata*	Lamiaceae	Leaf	26.8, 21	Spherical	UV-Vis,XE,AFM, FTIR, EDX, SEM, TEM	Antibacterial Antibiofilm	[31]
22	*Moringa oliefiera*	Moringaceae	Leaf	NA	Globular	FTIR, XRD, SEM, EDAX,	Antibacterial.	[32]
23	*Euphorbia cyathophora*	Euphorbiaceae	Leaf	40-55	Spherical	UV-Vis, FTIR, SEM	Antioxidant	[33]
24	*Ailanthus altissima*	Simaroubaceae	Aqueous leaf	20	Spherical	UV-Vis, SEM, TEM, FTIR	Antibacterial, Antimicrobial	[34]
25	*liliales*	Alliaceae	Garlic *Allium sativum*	NA	---	UV-Vis,XE,AFM, FTIR, EDX	Antibacterial, Antifungal, Antiparasitic, Antiviral, Antioxidant, Anti-cancerous	[35]
27	*Spondias mombin*	Anacardiaceae	Leaf	65-90	Triangular	UV-Vis, FTIR, SEM	Anxiolytic, Antiepileptic, Antipsychotic, Antioxidant, Antimicrobial	[37]
28	*Moringa oleifera*	Moringaceae	Leaf exract	35-95	Grain size	XRD, SEM, EDS. UV-DRS, PL	Antiatherosclerotic, Antioxidant,Anti-inflammatory, Anticancer, Antimicrobial	[38]
29	*Phyllanthus Reticulatus/Conyza Bonariensis*	Euphorbiaceous	Leaf	4-14	Microspher	UV-Vis, XRD, FTIR, XPS, BET	Antibacterial, Antioxidant	[39]
32	*Catharanthus roseus*	Apocynaceae	Leaf	23	Crystalline	UV-Vis-DRS PL, XRD, FTIR, SEM-EDS,TEM	Antibacterial, Antimicrobial	[40]
33	*Lantana camara*	Verbenaceae	Flower	10	Crystalline	XRD, FTIR, SEM,TEM,XPS,BET	NA	[41]
34	*Hawthorn*	Rosaceae	Fruits	200	Spherical	UV–Vis, LSPR, DLS, SEM, STEM	Antioxidant, Antimicrobial	[42]
35	*Alchornea cordifolia*	Euphorbiaceae	Leaf	3.54	Spherical	UV-Vis, XRD, FTIR, SEM, EDX, TEM	Anticancer	[43]
37	*Curcuma longa*	Zingiberaceae	*Curcuma longa* powder	5-20	Crystalline	FTIR, FE-SEM, EDS, XRD, TEM	Antimicrobial, Antifungal, Anticancer	[44]
38	*Annona muricata*	Annonaceae	Leaf	30-40	Spherical	UV-Vis, XRD, FTIR, SEM, EDX, BIO-TEM	Cytotoxic	[45]
39	*pomegranate peel*	Lythraceae	Peels	6.0-20	Crystal	FTIR, XRD, SEM, TEM,TGA, SPSS, TGA, DTA, Zetasizer	Cytotoxic inhibition of cancer cell growth	[46]
40	*Moringa oleifera*	Moringaceae	Leaves	35.8-49.2	Amorphous	UV-Vis, XRD, SEM,TEM, ALPHA-E, FTIR, FEG, HRTEM	Antioxidant, Anti-bacterial,Anti-fungal	[47]
41	*Adiantum lunulatum.*	Adiantaceae	Whole plant	6.5-1.5	Quasi-spherical	UV-Vis, XRD, FTIR, TEM, DLS, EDX, BIO-TEM	Antioxidative enzyme	[48]
42	*Galphimia glauca*	Malpighiaceae	Leaves and flowers	5-10	Crystalline	FTIR, TEM,XRD,GCMS	Anticancer	[49]

S/ No.	Plants	Family	Part Used	Average Size of Cu/CuO NPs (nm)	Shape	Characterizations	Therapeutic Applications	Ref.
44	*Mulberry*	*Moraceae*	Fruit	50-200	Spherical	UV-Vis, FTIR, TEM, DLS, ICP, OES	Antibacterial, Antimicrobial	[50]
45	*Brassica oleracea var. italic*	Brassicaceae	Whole plant	26	More or less uniform	FTIR, FESEM, EDAX, XRD, UV –Vis, FESEM	Antifungal activity	[51]

Applications of Cu/CuO NPs

Nanoparticles are generally synthesized in various sizes and shapes. Copper-based NPs, such as Cu NPs and CuO NPs are fabricated into varied shapes, like spherical, hexagonal, quasi-spherical, rod … etc. and demonstrated diverse pharmacological applications ranging between anti-fungal (*Aspergillus fumigatus*, *Aspergillus niger* and *Candida albicans*), anti-bacterial (*S.aureus*, *E.lmonella typhi* and *Pseudomonas aeruginosa*), anxiolytic, antiepileptic, antipsychotic, anti-oxidant, anti-inflammatory, anti-ulcer, anti-spasmodic, anti-viral, anti-parasitic, anti-spermatogenic, anti-diabetic, anti-biofilm, anti-atherosclerotic activities … etc.

A variety of plant parts was employed to biosynthesize Cu NPs and CuO NPs and their characterizations and applications are tabulated in Table 1.

Conclusion and Future Aspects

In conclusion, this article provided a perspective view on the active research area of biogenic synthesis, especially Cu NPs and CuO NPs for clinical applications. In the present work, we discussed the diverse morphologies (hexagonal, spherical, tetragonal, oval, cubic … etc.) of Cu NPs and CuO NPs which were obtained from different plant parts (leaf, stem, bark, fruit, flower, seed and trunk). Also, the pharmacological perspectives of these nanomaterials were discussed, like anti-oxidant, anti-inflammatory, anti-leishmanial, anti-diabetic, anti-bacterial, anti-fungal, anti-cancer, anti-viral, muscle relaxant, anti-nociceptive activities … etc. which opened new avenues in research for therapeutic applications. This literature opened new future perspectives for researchers in developing copper-based nanomaterials which will have multifarious applications. The future aspect of this technique is impactful. Moreover, more emphasis will be paid by young researchers as this technique is cheap and easy. Therefore, this technique could be sustainable, as it is eco-friendly, toxic-free, convenient and straightforward. Nonetheless, around the globe, researchers are always striving for green synthesis, as it is the best technique for nanomaterials' synthesis.

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