A COMPREHENSIVE REVISION ON THE BIOMEDICAL APPLICATION OF COPPER OXIDE NANOPARTICLES

Mary Sheloni Missier
Department of Orthodontics, Saveetha Dental College and Hospital, Saveetha University, Chennai, Tamil Nadu, Email: shelonibds@gmail.com

S.P Saravana Dinesh
Department of Orthodontics, Saveetha Dental College and Hospital, Saveetha University, Chennai, Tamil Nadu, Email: drsaravanadinesh@gmail.com

M.I. Niyas Ahamed
Department of Biochemistry, Sacred Heart College (Autonomous), Tirupattur, Tamil NaduEmail: driniyasahamed@shctpt.edu

SK. Jasmine Shahina
Department of Microbiology, Justice Basheer Ahmed Sayeed College for Women, Chennai, Tamil Nadu,Email: jasmine.shahina@jbascollege.edu.in

Summera Rafiq
Department of Microbiology, Justice Basheer Ahmed Sayeed College for Women, Chennai, Tamil NaduEmail: summerarafiq@jbascollege.edu.in

Radhika G Deshmukh
Department of Physics, Shri Shivaji Science College, Amravati, Maharashtra.,
Email: radhikadeshmukh35@gmail.com

Abstract

Recent advances in nanoscience and nanotechnology have facilitated the widespread use of metal and metal oxide nanoparticles in a variety of fields of science, research institutes, and industries. Copper oxide nanoparticles (CuO NPs) have received the most attention among all metal oxides due to their unique properties and applications. The use of CuO nanoparticles in topical formulations, dressings, and coated textiles is gaining popularity in medical settings and elsewhere (i.e., cosmetics, textile industry etc.). The primary application of such nanoformulations is their antimicrobial ability, which enables the development of a wide range of products, ranging from antimicrobial solutions used to disinfect surfaces and medical devices to antimicrobial wound dressings, textiles, and coatings.

Keywords: Copper oxide nanoparticles, CuO NPs, Antimicrobial effects, Antifungal activity

DOI Number: 10.14704/nq.2022.20.9.NQ44181 **Neuro Quantology 2022; 20(9):1566-1573**

Introduction

The ability of nanotechnology to modify the properties of materials at the nanoscale has increased its use. Materials at the nanoscale have properties that are extremely distinct from those found at the macroscale or microscale [1]. Nanomaterials are widely used in many fields of research due to their astonishingly unique properties [2]. Because of their extremely optimal properties, nanomaterials have seen an increase in demand in the academic field [3]. Copper Oxide nanoparticles' semi conductivity at high temperatures, photovoltaic properties, and antimicrobial properties in general are said to be novel in nanotechnology [4].

Copper Oxide Nanoparticle Applications

Copper Oxide nanoparticles (CuO NPs) have been reported to have a wide range of applications. As illustrated in Figure 1,

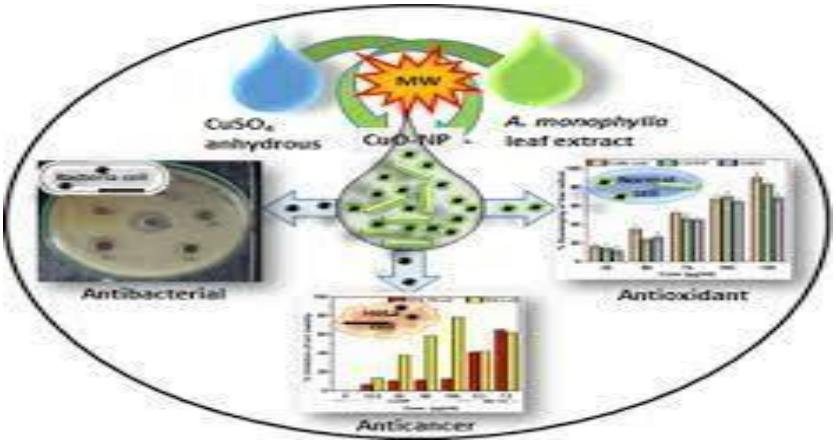

Figure1: Some applications of Copper Oxide nanoparticles

Antibacterial application of Copper Oxide nanoparticles

The antibacterial activity of biosynthesized CuONPs against both gram-positive and gram-negative bacterial strains has been investigated [5]. The antibacterial activities of phytosynthesized CuONPs derived from *Tecoma castanifolia* leaf extract demonstrated consistent bactericidal activity that may be useful in biomedical applications [6]. Previous research has shown that plant extract biomolecules used in CuONPs synthesis promote greater antibacterial efficacy against Gram-positive and Gram-negative bacterial strains. The biomolecule (terpenoids) found in the extract during the capping process has been linked to an increase in the antibacterial efficacy of CuONPs [7]. The antibacterial analysis of CuONPs obtained from the agar well diffusion technique against gram positive bacteria (*Streptococcus mutans and Staphylococcus aureus*) and gram-negative bacteria (*Pseudomonas aeruginosa, Klebsiella pneumonia*, and *Escherichia coli*) demonstrated the toxicity of CuONPs in destroying the growth of tested pathogens. CuONPs' bactericidal activity has been linked to the formation of highly reactive oxygen species on their surfaces, such as (OH, H2O2, and O2-), which kills bacteria (Figure 2).

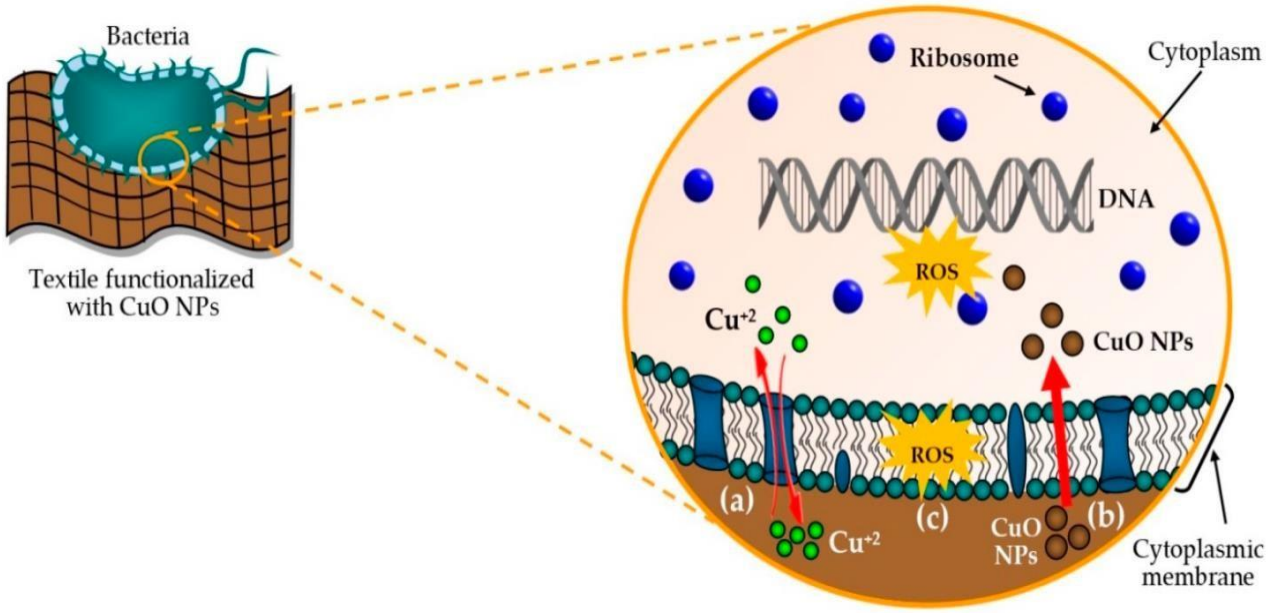

Figure2: Antibacterial application of Copper Oxide nanoparticles

Antifungal activity and crop protection of Copper Oxide nanoparticles

In today's medical world, fungal disease has become a serious health threat, with many patients dying each year, particularly those with weakened immune systems. Despite the fact that several antifungal drugs are available on the market, drug resistance is a serious threat. Several studies have shown that CuNPs can be used as an antifungal agent because they can inhibit a variety of pathogenic fungi in both humans and plants. More research is needed, however, to determine the precise antifungal mechanisms of CuNPs and their future use as an antifungal agent. *Fusarium oxysporum* Schltdl., *Alternaria solani* (Ellis & G. Martin) L.R. Jones, *Aspergillus niger* Tiegh., and *Penicillium citrinum* Thom can all be controlled by green CuNPs. CuNPs derived from Chitosan demonstrated antifungal activity against the tomato plant pathogens *A. solani* and *F. oxysporum*. CuNPs synthesized chemically are extremely effective against *Candida albicans*, *Berkhout* and *Aspergillus flavus* Link. [8]. In another study, CuNPs were found to have antifungal activity against crop pathogens such as *Alternaria alternata* (Fr.) Keissl., *Curvularia lunata* (Wakker) Boedijn, and *Phoma destructiva* Plowr. [9]. Green CuNPs synthesised with *Syzygium alternifolium* (Wight) Walp. have antifungal activity against some plant pathogens. CuNPs have the potential to be used in the formulation of nanofungicides. Cu-based fungicides were found to be more effective than other agrochemicals against the tomato pathogen *Phytophthora infestans* (Mont.) de Bary in a field study [10]. Because CuNP has antimicrobial and antifungal properties, it could be used in food preservation and packaging. Copper at high concentrations is toxic to a variety of food spoilage microbes and fungi (Figure 3).

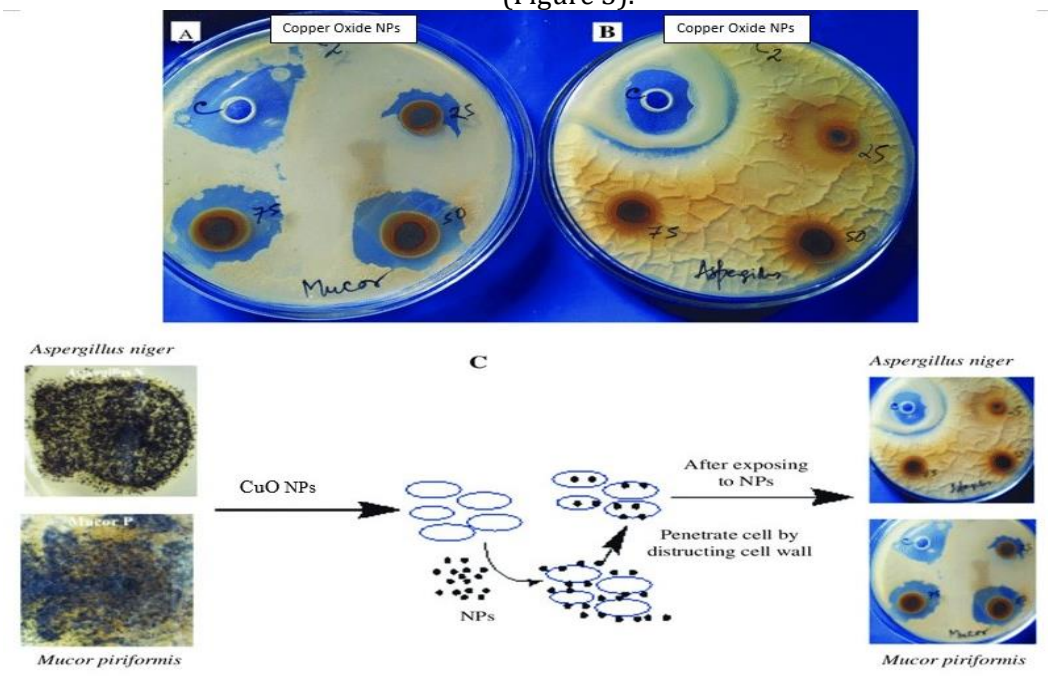

Figure 3: Antifungal activity of CuO NPs

Probable mechanism for the toxicity of CuONPs against bacteria

CuO produces reactive oxygen species that interact with the bacterial cell membrane, allowing CuONPs to enter the bacterial cell. The disturbances caused by CuONPs in the bacterial cell membrane cause some malfunctions in the bacterial cell, which results in the inhibition of the bacterial species' growth, which may eventually lead to their death [11]. CuONPs' smaller size (nanometer) in comparison to bacterial cell pore size (micrometer) allows CuONPs to easily penetrate the cell membrane without interference [12]. CuONPs could destroy bacterial membranes by producing reactive oxygen species and radicals, or by causing direct

cell damage because metal oxides (CuO) produce superoxide and hydroxyl radicals [13]. The presence of carboxyl and

Amine groups on bacterial cell surfaces may attract Cu2 ions to the cell [14,15]. As a result, the likely antibacterial mechanism can be linked to gene toxicity, mechanical damage, or oxidative injury. Figure 3 depicts the likely antibacterial toxicity (Figure 4).

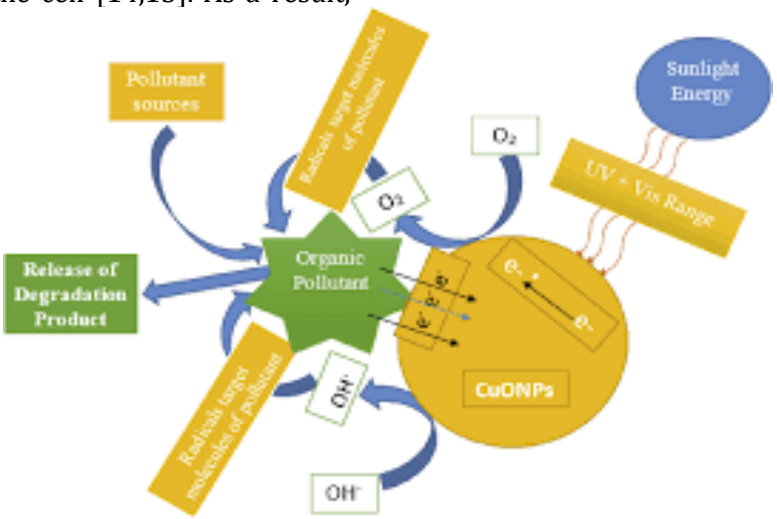

Figure 4: mechanism for the toxicity of CuONPs against bacteria

Anticancer activity of Copper Oxide nanoparticles

Cancer is currently the most dangerous and common disease, increasing the global mortality rate. There are currently no promising cancer treatments on the market. The most commonly used radiotherapy and chemotherapy have severe side effects and are both costly procedures. Several studies are still being conducted in order to find a nontoxic biological drug alternative. In this regard, it has been discovered that the emergence of nanotechnology aids in the effective treatment of various types of cancer. When tested against some human cancer cell lines, biologically synthesized Cu and CuO nanoparticles showed promising results (Figure 5).[16-22].

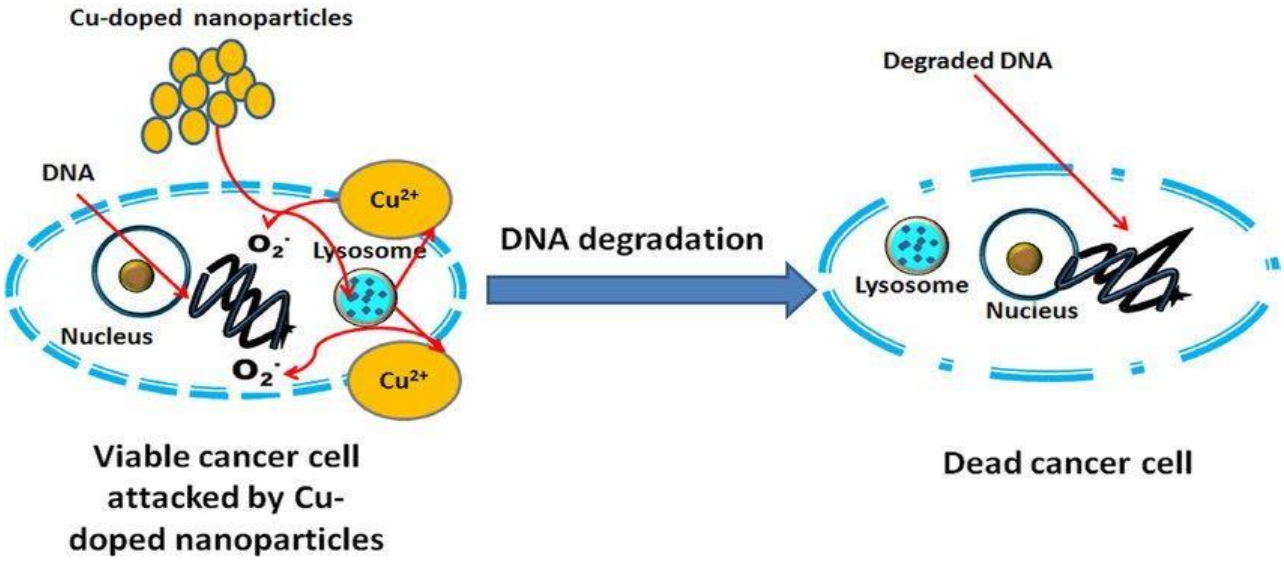

Figure 5: Anticancer activity of Copper Oxide nanoparticles

Plant growth, nutrients and defense booster of Copper Oxide nanoparticles

Plants require various minerals and nutrient elements for proper growth and development. Plant nutrients are classified as macronutrients or micronutrients. Macronutrients are generally needed in high concentrations, whereas micronutrients are needed in relatively low concentrations. Both macronutrients and micronutrients are required for plants to maintain structural integrity and normal growth. A lack of which causes disease and death in various plant parts [23]. Copper, as a micronutrient, is required in very low concentrations in plants. A high Cu concentration promotes toxicity and inhibits plant growth. Plant chloroplasts have the highest concentration of Cu because it aids in the synthesis of chloroplasts and other pigments. Cu deficiency causes several abnormal conditions in crop plants such as young leaf distortion, necrosis, stem bending, affects vegetative growth, and reduces grain quality [24]. Several factors influence CuNP-mediated plant growth responses, including particle concentration, size, plant species, and particle structure. CuNPs were found to stimulate root and shoot growth in *Phaseolus radiates* and *Triticum aestivum* in a study. The growth response typically varies with CuNP concentration. Wheat plants grew and yielded better when treated with CuNPs at concentrations of 20, 25, 30, and 35 ppm. Concentrations above 1000 ppm inhibited wheat growth, followed by a decrease in yield [25]. CuNPs at 20 g/ml concentrations were applied to *Allium cepa* and increased growth and mitotic index. The mitotic index decreased as CuNP concentrations increased [26]. CuONP applications stimulated shoot and root growth in *Zea mays* [27]. The use of CuONPs on transgenic cotton plants increased the expression of exogenous genes that code for Bt toxins in the leaves [28]. A high concentration of CuNPs, on the other hand, has a negative impact on plant growth. CuNPs in concentrations ranging from 200 to 1000 mg/l inhibited the growth of *Raphanus sativus, Triticum aestivum, Lolium perenne, and Phaseolus radiatus* [29]. CuONPs at higher concentrations inhibited root and shoot growth and decreased chlorophyll content in *Arabidopsis thaliana* seedlings [30]. We recently demonstrated that CuONP treatment significantly increases defense enzymes, total phenol, and other defense parameters, as well as plant vigour in Lens culinaris via the nitric oxide signaling pathway [31]. Figure 6 illustrates one possible mechanism (Figure 6).

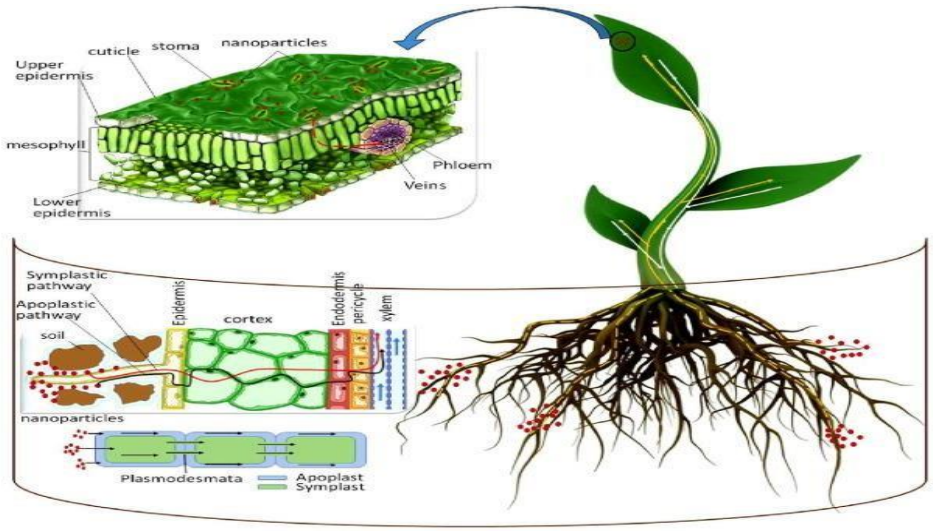

Figure 6: Plant growth, nutrients and defense booster of Copper Oxide nanoparticles

Wound healing activity of Copper Oxide nanoparticles

Several studies in recent years have demonstrated that CuNPs can be used as wound healing agents that also provide infection protection. Wounds and cuts on the body's surface are the most common route for infectious microorganisms to enter the body. It is critical to remove microbes from the wound site to avoid infection. CuNPs, as previously

discussed, may have antimicrobial and antifungal activity and thus be used in wound healing [32]. Cu stimulates the formation of new blood vessels at the site of the wound, resulting in angiogenesis. CuNPs also stimulates the expression of vascular endothelial growth factor (VEGF), which facilitates the transport of various nutrients and the formation of collagen, both of which are required for wound healing (Figure 11). Cu application can halt severe phosphorus burn through tissue remodeling. Cu helps to maintain the stability of fibrinogen and accumulates lysyl oxidase enzyme at the wound site. Green CuNPs synthesized from *Falcaria vulgaris* leaf extracts demonstrated potential cutaneous wound healing activity. A 500 mm cut was made on an anaesthetized animal in a study. Three different setups were created using biologically synthesized CuNP gel, nonbiologically synthesized CuNP and a control. After a few days, it was discovered that biologically synthesized CuNPs could reduce 92 percent of the wound. Furthermore, it promotes cell proliferation and migration while inhibiting the cyclooxygenase-2 enzyme at the wound site (Figure 7). [32].

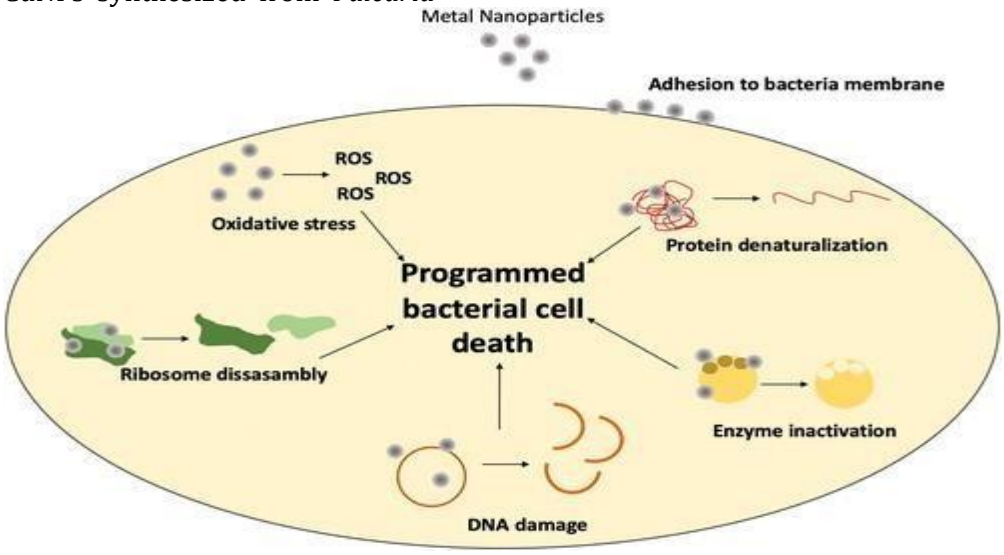

Figure 7: Wound healing activity of Copper Oxide nanoparticles

Conclusion

CuO nanoparticles can be synthesized using various methods and bulk materials, as well as coating agents, to produce various types of nanosystems with various applications. All of these factors may have a significant impact on their physicochemical and biological properties, as well as their biomedical applications. Due to the increased toxicity, the use of CuO nanoparticles in drug delivery formulations is still limited; however, other applications, such as topical formulations, dressings, and coated textiles, are of great interest among medical environments and others (i.e., cosmetics, textile industry etc.). The primary application of such nanoformulations is their antimicrobial ability, which enables the development of a wide range of products, ranging from antimicrobial solutions used to disinfect surfaces and medical devices to antimicrobial wound dressings, textiles, and coatings. To improve their biomedical applications, researchers are looking for optimal synthesis approaches that will reduce the toxicity of CuO NPs while maintaining or even improving their efficiency in diagnosis, therapy, and possibly even prophylaxis.

References

1. Grigore, M.E.; Biscu, E.R.; Holban, A.M.; Gestal, M.C.; Grumezescu, A.M. Methods of synthesis, propertiesand biomedical applications of CuO nanoparticles. Pharmaceuticals 2016, 9,75.
2. Grasso, G.; Zane, D.; Dragone, R. Microbial nanotechnology: Challenges and prospects

for green biocatalytic synthesis of nanoscale materials for sensoristic and biomedical applications. Nanomaterials 2020, 10.

3. Azam, A.; Ahmed, A.S.; Oves, M.; Khan, M.S.; Memic, A. Size-dependent antimicrobial properties of CuO nanoparticles against Gram-positive and -negative bacterial strains. International journal of nanomedicine 2012, 7.
4. Ponnar, M.; Thangamani, C.; Monisha, P.; Gomathi, S.S.; Pushpanathan, K. Influence of Ce doping on CuOnanoparticles synthesized by microwave irradiation method. Applied Surface Science ,2018, 449, 132–143.
5. A. Azam, A.S. Ahmed, M. Oves, M.S. Khan, A. Memic, Size-dependent antimicrobial properties of CuO nanoparticles against gram-positive and -negative bacterial strains, Int. J. Nanomed. 7 ,2012, 3527–3535.
6. G. Sharmila, M. Thirumarimurugan, V.M. Sivakumar, Optical, catalytic and antibacterial properties of phytofabricated CuO nanoparticles using Tecoma castanifolia leaf extract, Optik - Int. J. Light Elect. Opt. 127, 2016 7822–7828.
7. A. Khursheed, A. Bilal, M.A. Sabiha, S. Quaiser, A.A. Abdulaziz, D. Sourabh, A. Majed, S.K. Mohd, M. Javed, Comparative in situ ROS mediated killing of bacteria with bulk analogue, Eucalyptus leaf extract (ELE)-capped and bare surface copper oXide Nanoparticles, Mater. Sci. Eng. C 100 2019 747–758.
8. Ramyadevi, J.; Jeyasubramanian, K.; Marikani, A.; Rajakumar, G.; Rahuman, A.A.; Santhoshkumar, T.; Kirthi, A.V.; Jayaseelan, C.; Marimuthu, S. Copper Nanoparticles Synthesized by Polyol Process Used to Control Hematophagous Parasites. Parasitol. Res. 2011, 109, 1403–1415.
9. Kanhed, P.; Birla, S.; Gaikwad, S.; Gade, A.; Seabra, A.B.; Rubilar, O.; Duran, N.; Rai, M. In Vitro Antifungal Efficacy of Copper Nanoparticles Against Selected Crop Pathogenic Fungi. Mater. Lett. 2014, 115, 13–17. doi:10.1016/j.matlet.2013.10.011.
10. Kasana, R.C.; Panwar, N.R.; Kaul, R.K.; Kumar, P. Biosynthesis and Effects of Copper Nanoparticles on Plants. Environ. Chem. Lett. 2017, 15, 233–240. D. Das, B.C. Nath, P. Phukon, S.K. Dolui, Synthesis and evaluation of antioxidant and antibacterial behavior of CuO nanoparticles, Colloids Surf. B Biointerfaces 101 ,2013 430–433.
11. P. Sutradhar, M. Saha, D. Maiti, Microwave synthesis of copper oXide nanoparticles using tea leaf and coffee powder extracts and its antibacterial activity, J. Nanostruct. Chem. 4 (86) 2014, 1–6.
12. Y. Chang, M. Zhang, L. Xia, J. Zhang, G. Xing, The toXic effects and mechanisms of CuO and ZnO nanoparticles, Materials 5 ,2012 2850–2871.
13. S. Jaspreet, V. Kanchan, R. Naleeni, R. Padmaja, K.S. Vivek, K.M. Rohit, K. Vivek, K.T. Durgesh, S. Shivesh, Nanomaterials and microbes' interactions: a contemporary overview, 3 Biotech 9 ,2019, 68.
14. J.S. Kim, E. Kuk, K.N. Yu, et al., Antimicrobial effects of silver nanoparticles, Nanomedicine 3 ,2007, 95–101.
15. Waris, A.; Din, M.; Ali, A.; Ali, M.; Afridi, S.; Baset, A.; Ullah Khan, A. A Comprehensive Review of Green Synthesis of Copper Oxide Nanoparticles and Their Diverse Biomedical Applications. Inorg. Chem. Commun. 2021,
16. Emima Jeronsia, J.; Allwin Joseph, L.; Annie Vinosha, P.; Jerline Mary, A.; Jerome Das, S. Camellia Sinensis Leaf Extract Mediated Synthesis of Copper Oxide Nanostructures for Potential Biomedical Applications. In Materials Today: Proceedings; Elsevier Ltd, 2019; pp. 214–222.
17. Shankar, S.; Teng, X.; Rhim, J.W. Properties and Characterization of Agar/CuNP Bionanocomposite Films Prepared with Different Copper Salts and Reducing Agents. Carbohydr. Polym. 2014, 114, 484– 492.
18. Nagajyothi, P.C.; Muthuraman, P.; Sreekanth, T.V.M.; Kim, D.H.; Shim, J. Green Synthesis: In-Vitro Anticancer Activity of Copper Oxide Nanoparticles Against Human Cervical Carcinoma Cells. Arab. J. Chem. 2017, 10, 215.
19. Thamer, N.A.; Barakat, N.T. Cytotoxic Activity of Green Synthesis Copper Oxide

Nanoparticles Using cordia myxa L. aqueous Extract on Some Breast Cancer Cell Lines, Iopscience.Iop.Org (n.d.),

20. Harne, S.; Sharma, A.; Dhaygude, M.; Joglekar, S.; Kodam, K.; Hudlikar, M. Novel Route for Rapid Biosynthesis of Copper Nanoparticles Using Aqueous Extract of Calotropis Procera L. Latex and Their Cytotoxicity on Tumor Cells. Colloids Surf., B 2012, 95, 284–288.
21. Kouhkan,M.;Ahangar, P.;Babaganjeh, L.A.;Allahyari-Devin, M. Biosynthesis of Copper Oxide Nanoparticles Using Lactobacillus Casei Subsp. Casei and its Anticancer and Antibacterial Activities. Curr. Nanosci. 2019, 16, 101–111.
22. Banerjee, A.; Sarkar, A.; Acharya, K.; Chakraborty, N. Nanotechnology: An Emerging Hope in Crop Improvement. Lett. Appl. NanoBioScience. 2021, 10, 2784–2803.
23. Siddiqi, K.S.; Husen, A. Current Status of Plant Metabolite-Based Fabrication of Copper/Copper Oxide Nanoparticles and Their Applications: A Review. Biomater. Res. 2020, 24, 1–15.
24. Yasmeen, F.; Raja, N.I.; Razzaq, A.; Komatsu, S. Proteomic and Physiological Analyses of Wheat Seeds Exposed to Copper and Iron Nanoparticles. Biochim. Biophys. Acta Proteins Proteom. 2017, 1865, 28–42. doi:10.1016/j. bbapap.2016.10.001.
25. Nagaonkar, D.; Shende, S.; Rai, M. Biosynthesis of Copper Nanoparticles and its Effect on Actively Dividing Cells of Mitosis in Allium Cepa. Biotechnol. Prog. 2015, 31, 557– 565.
26. Maithreyee, M.N.; Gowda, R. Influence of Nanoparticles in Enhancing Seed Quality of Aged Seeds, 2015.
27. Kasana, R.C.; Panwar, N.R.; Kaul, R.K.; Kumar, P. Biosynthesis and Effects of Copper Nanoparticles on Plants. Environ. Chem. Lett. 2017, 15, 233–240.
28. Atha, D.H.; Wang, H.; Petersen, E.J.; Cleveland, D.; Holbrook, R.D.; Jaruga, P.; Dizdaroglu, M.; Xing, B.; Nelson, B.C. Copper Oxide Nanoparticle Mediated DNA Damage in Terrestrial Plant Models. Environ. Sci. Technol. 2012, 46, 1819–1827.
29. Nair, P.M.G.; Chung, I.M. Impact of Copper Oxide Nanoparticles Exposure on Arabidopsis ThalianaGrowth, Root System Development, Root Lignificaion, and Molecular Level Changes. Environ. Sci. Pollut. Res. 2014, 21, 12709–12722.
30. Sarkar, J.; Chakraborty, N.; Chatterjee, A.; Bhattacharjee, A.; Dasgupta, D.; Acharya, K. Green Synthesized Copper Oxide Nanoparticles Ameliorate Defence and Antioxidant Enzymes in Lens Culinaris. Nanomaterials 2020, 10, 312.
31. Powar, N.S.; Patel, V.J.; Pagare, P.K.; Pandav, R.S. Chemical Methodologies Cu Nanoparticle: Synthesis, Characterization and Application Graphical Abstract. Chem. Methodol. 2019, 3, 457–480.
32. Zangeneh, M.M.; Ghaneialvar, H.; Akbaribazm, M.; Ghanimatdan, M.; Abbasi, N.; Goorani, S.; Pirabbasi, E.; Zangeneh, A. Novel Synthesis of Falcaria vulgaris Leaf Extract Conjugated Copper Nanoparticles with Potent Cytotoxicity, Antioxidant, Antifungal, Antibacterial, and Cutaneous, Elsevier (n.d.), 2019.