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Exploring the potential of copper oxide biogenic synthesis: a review article on the biomedical and dental implementations

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Abstract

Purpose – In the developing field of nano-materials synthesis, copper oxide nanoparticles (NPs) are deemed to be one of the most significant transition metal oxides because of their intriguing characteristics. Its synthesis employing green chemistry principles has become a key source for next-generation antibiotics attributed to its features such as environmental friendliness, ease of use and affordability. Because they are more environmentally benign, plants have been employed to create metallic NPs. These plant extracts serve as capping, stabilising or hydrolytic agents and enable a regulated synthesis as well.

Design/methodology/approach – Organic chemical solvents are harmful and entail intense conditions during nanoparticle synthesis. The copper oxide NPs (CuO-NPs) synthesised by employing the green chemistry principle showed potential antitumor properties. Green synthesised CuO-NPs are regarded to be a strong contender for applications in the pharmacological, biomedical and environmental fields.

Findings – The aim of this study is to evaluate the anticancer potential of CuO-NPs plant extracts to isolate and characterise the active anticancer principles as well as to yield more effective, affordable, and safer cancer therapies.

Originality/value – This review article highlights the copper oxide nanoparticle's biomedical applications such as anticancer, antimicrobial, dental and drug delivery properties, future research perspectives and direction are also discussed.

Keywords CuO-NPs, Biomedical activity, Dentistry applications

Paper type General review

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1. Background

Nanoscience is a domain of science which encompasses the analysis of properties of matter at the nanoscale, and it especially concentrates on the distinctive, size-dependent features of solid-state materials (Mulvaney, 2015). The field of study known as nanotechnology deals with the creation, engineering and application of nanomaterials, i.e. materials with a size between one and 100 nanometres (Hasan, 2015).

Nanotechnology has entered our daily lives during the past few years. With an integrated approach, this ground-breaking technology has been used in numerous fields. There are now more products and applications that either claim to use nanoparticles (NPs) or contain them. The same thing takes place in pharmaceutical research (Tinkle *et al.*, 2014). The use of nanotechnology for illness diagnosis, control, monitoring, prevention and therapy is known as nanomedicine, which is the application of nanotechnology for medical reasons.

The best course of action is to manufacture and apply nanotechnology using green processes to reduce the risks involved. The development of engineered nanomaterials is one of the most important developments in materials science and nanotechnology (Motahharifar, Nasrollahzadeh, Taheri-Kafrani, Varma, & Shokouhimehr, 2020). Several industries, including drug delivery and other biomedicinal uses, have been influenced by nanotechnology (Mahmood, Abbass, Razali, Al-Saffar, & Al-Obaidi, 2021; Mahmood *et al.*, 2022; Mamidi, Delgadillo, Barrera, Ramakrishna, & Annabi, 2022). There is no question that NPs pose a health risk that needs to be addressed right away, and their production and usage are largely unregulated. While risk is minimally considered in the design of new chemical processes, a set of fundamentals is used to reduce or completely remove dangerous substances. This is a fundamental aspect of the emerging field of green chemistry (Hassan *et al.*, 2021).

Due to their numerous applications and physiochemical properties, appropriate synthetic methods for producing NPs have taken a lot of time and effort to develop (Ahmed *et al.*, 2021). Unfortunately, many physiochemical methods to create metal NPs are constrained by environmental pollution brought on by heavy metals. Because of its repeatability, nontoxicity, simplicity in scaling up, and well-defined structure, the production of NPs by biological means has become a new trend in the business. Researchers have discovered that new resources like plants and bacteria exhibit the greatest potential for generating NPs (Hou *et al.*, 2022). Several microbes, such as fungi, bacteria and yeast, as well as plants, have been used to create metal NPs. By developing trustworthy, viable and environmentally friendly synthesis methods, 'green synthesis' can be pursued to stop the production of undesired or unsafe by-products. Metallic NPs have been produced sustainably to include a variety of biological elements, including fungi, bacteria, algae and plant extracts. In comparison to bacteria- and/or fungal-assisted synthesis, which is one of the most used greenways for making metal/metal oxide NPs using plant extracts is an easy approach to make NPs in large quantities. Together, these substances are known as biogenic NPs (Abu Hajleh, Abu-Huwaij, AL-Samydai, Al-Halaseh, & Al-Dujaili, 2021). Figure 1 shows the categorisation of several nanoparticle creation techniques and their uses.

2. Classification of nanomaterials

Nanomaterials are the main components of nanotechnology. Materials which have at least one dimension that is in the nanoscale, or less than 100 nm, are referred to as nanomaterials (Kolahalam *et al.*, 2019). Nanomaterials are categorised into four groups based on their dimensions, as shown in Figure 2.

Dry nanotechnology focuses on the creation of inorganic materials including carbon and silicon, as well as surface science, and chemical and physical qualities. Computational nanotechnology involves the simulation and modelling of intricate nanometre-scale

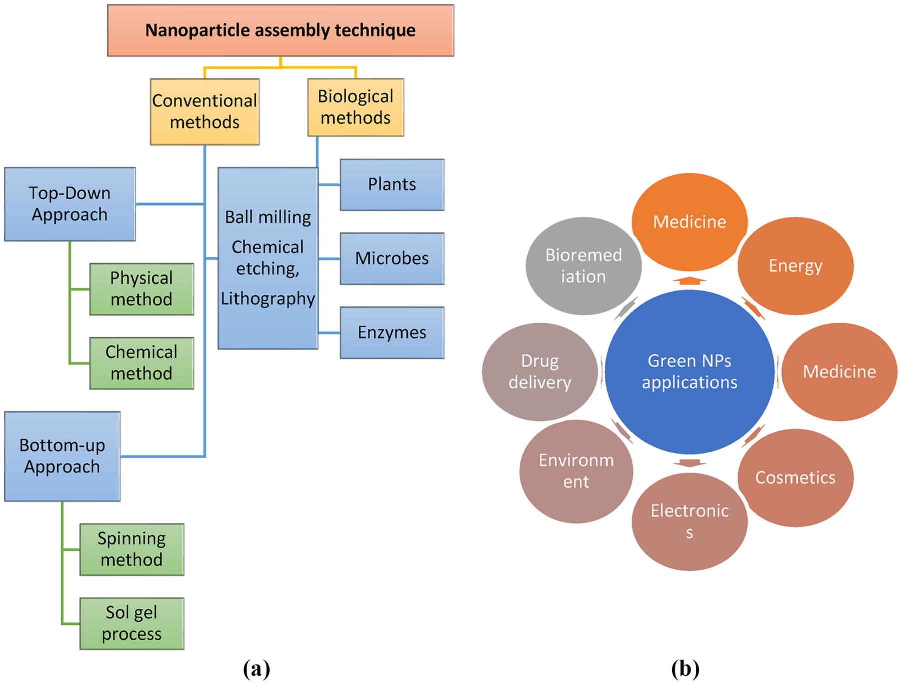


Figure 1.
Classification of different nanoparticle synthesis methods (a) and their applications (b)

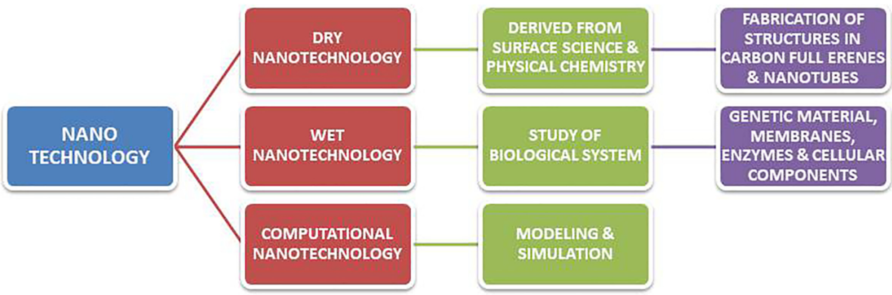
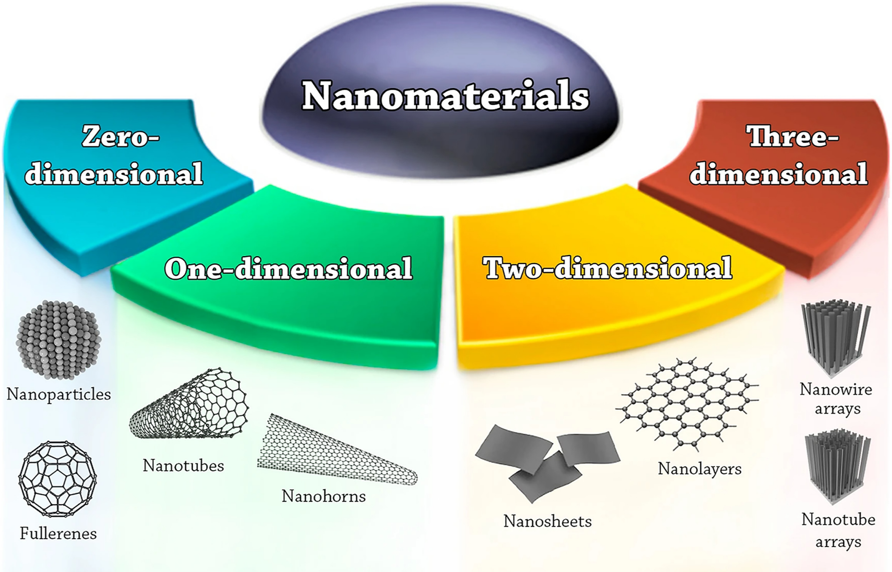


Figure 2.
Nanomaterials classification based on dimensionality

structures (Sinha *et al.*, 2009). As demonstrated in Figure 3, these three disciplines have been integrated to deliver the best performance. As it is possible to recognise nanoscale compounds based on specific characteristics, there has been the introduction of a broad range of applications and new avenues of scientific inquiry (Rai, Yadav, & Gade, 2008). Some of the industries that use nanoproducts are pharmaceuticals, dietary supplements for use in healthcare products, consumer items, diagnostics, smart delivery systems, bioremediation, biosensors, growth inhibitors of biofilm development and electronics (Al-Obaidi *et al.*, 2021).

For over a century, metallic NPs have captivated scientists and are now broadly employed in biological sciences and engineering fields (Lespes, Faucher, & Slaveykova, 2020). In nanotechnology, the synthesis of metal NPs is regarded to be a crucial topic of research due to



Source(s): Rai *et al.*, 2008

Figure 3. Nanotechnology disciplines

its shape-dependent properties, unusual size (maximum lengths of 200 nm) and appealing applications in biofuel manufacturing, electronics, biotechnology, medicine and catalysis (Ganesan, Narasimhalu, Joseph, & Pugazhendhi, 2020). Thus, biogenic synthesis is regarded to be a significant tool for decreasing the undesirable impacts of NPs that are commonly employed in laboratories and industry for traditional synthesis techniques.

In recent years, nanotechnology has offered broad applicability (Mamidi & Flores Otero, 2023). Metal-containing NPs find applicability in electronics, biology, physics, medicine and chemistry (Alishah, Pourseyedi, Ebrahimipour, Mahani, & Rafiei, 2016). The NPs' considerable exposed surface-to-volume ratio enables them to be used for magnetism, optics, sensing, biology and as catalysts. The copper-containing NPs display special properties versus their bulk material (Kanhed *et al.*, 2014). Copper oxide NPs (CuO-NPs) are categorised as p-type semiconductors as they have a band gap of 1.7 eV (Debbichi, Marco de Lucas, Pierson, & Krüger, 2012).

In the pharmaceutical and organic fields, a commonly used product is 3,4-dihydropyrimidinones-2(1H)-one (DHPM) Biginelli product (Bhuyan, Saikia, Saikia, & Materials, 2018). Employing strong acid catalysts is done for the one-pot, three-component cyclo condensation on an aldehyde, urea and b-ketoester to yield various dihydropyrimidinones (Barbero, Cadamuro, & Dughera, 2017), which possess significant pharmacological attributes, like calcium antagonists, antiviral, antihypertensive, antimalarial, hepatitis B virus replication inhibitors and applicability in various other activities (Puripat *et al.*, 2015). For this reaction, as a catalyst, mineral acid or Lewis acid is employed typically; however, there has also been the discovery of different newly developed heterogeneous catalysts. These include nano zinc oxide ZnO (Tamaddon & Moradi, 2013), SiO-$CuCl_2$ (Kour, Gupta, Paul, & Gupta, 2014), MnO2-MWCNT (Safari & Gandomi-Ravandi, 2013), CuO@mTiO_2@CF (Ghosh *et al.*, 2017), CuS QDs (Chaudhary, Bansal, & Mehta, 2014) and sulfonated-phenylacetic acid coated Fe_3O_4 (Prakash *et al.*, 2014). These catalysts are highly loaded, tough to recover, difficult to synthesise, less reusable, costlier, low rate of product creation, inadequate yield and subject to adverse reaction conditions (Elhamifar, Mofatehnia, & Faal, 2017).

Copper is regarded to be an essential trace element for plants, animals and humans (Raha, Mallick, Basak, & Duttaroy, 2020). For a human, it is needed only in minor quantities (Bost *et al.*, 2016). A typical adult individual weighing 70 kg has roughly 100 mg of copper in his/her body (Shabbir *et al.*, 2020). In humans, copper plays a range of functions, including regulating cell signalling pathways, improving antioxidant defence, acting as a cofactor for several enzymes during the synthesis of neuropeptides, and supporting the actions of immune cells in humans which help in removing pathogens (Waris *et al.*, 2021). The immune cells, which comprise macrophages, neutrophils and helper T cells, are crucial for the immune system's upkeep (Georgopoulos, Roy, Yonone-Lioy, Opiekun, & Lioy, 2001). For optimum plant growth, copper is regarded to be a crucial trace element (Ghaderian & Ghotbi Ravandi, 2012). It is important to carry out the normal operation of several essential proteins, including membrane oxidases and plastocyanin (Sifri, Burke, & Enfield, 2016).

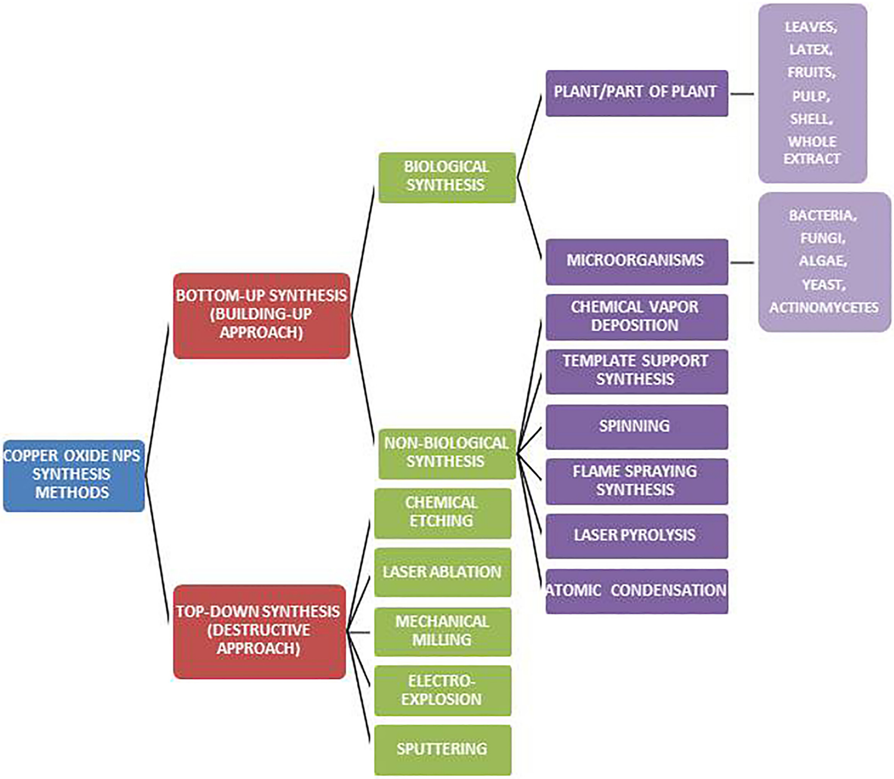
Due to their distinctive thermal, optical, chemical, electrical and biological attributes, copper oxide NPs are becoming more and more popular (Bhattacharjee & Ahmaruzzaman, 2016). The creation of sensors, supercapacitors, storage devices and infrared filters, as well as applications in the environmental and health sectors, are all made possible by these features (Dagher, Haik, Ayesh, & Tit, 2014). Additionally, CuO-NPs are excellent candidates to be employed as therapeutic agents due to their antimicrobial properties (Nations *et al.*, 2015). To address drug resistance, researchers are currently up against a significant hurdle in the healthcare industry. Physical, biological, and chemical processes are among the various enhanced synthesis methodologies that are being developed in this area (Soomro *et al.*, 2014). Thus, the "green chemistry" concept, which employs natural sources such as microbes and plants for synthesising products, could be a promising solution to deal with these shortcomings (Kiranmai *et al.*, 2017).

3. Biogenic synthesis of CuO-NPs

A range of physical, chemical and biological techniques are employed for synthesising copper oxide NPs. These techniques encompass precipitation, sonochemical, chemical reduction, hydrothermal approach, electrothermal, non-vacuum and sol-gel spin coating, chemical bath deposition and green chemistry mode (Sackey *et al.*, 2020). These techniques can be divided into two groups: bottom-up and top-down approaches (Khan, Saeed, & Khan, 2019) as presented in Figure 4. In the bottom-up method, miniature atomic scale particles get combined to yield nanoscale particles, but in the top-down method, the larger molecules are fragmented into smaller ones, and these tiny molecules start developing into appropriate nanomaterials (Khan *et al.*, 2019). Copper oxide NPs that have been synthesised employing green methods are deemed to be more stable, durable, cost-efficient, safe and possess a longer shelf life. A range of biotic resources has been employed to synthesise copper oxide NPsNPs (Buazar, Sweidi, Badri, Kroushawi, & synthesis, 2019). Table 1 shows some of the biogenic techniques reported for the production of CuO-NPs.

3.1 Plant-mediated nanoparticle synthesis

Plant-mediated nanoparticle synthesis is more advantageous than bacteria-, algae- and fungi-mediated nanoparticle production since the latter are time-consuming due to the high maintenance culture and continuous sterile conditions required (Chandraker, Ghosh, Lal, & Shukla, 2021). Because plant parts including the stem, leaves, roots and fruit contain phytochemicals that help with the bio-reduction of metallic ions, they have been used in the green manufacturing of NPs (Iwuozor, Ogunfowora, & Oyekunle, 2021). It was discovered



Source(s): Khan *et al*., 2019

Figure 4.
Several methods for synthesising copper oxide nanoparticles

that the therapeutic characteristics of the plant extract covered the NPs that were created from it, and they might be used in medication, cosmetic applications and targeted drug delivery (Saranyaadevi, Subha, Ravindran, & Renganathan, 2014). The leaves of the olive tree have multiple potentially bioactive compounds that may have antiatherogenic (Harwood, Yaqoob, & Technology, 2002), antioxidant (El & Karakaya, 2009) and anti-inflammatory properties (Sulaiman, Tawfeeq, & Jaaffer, 2018). Oleuropein, hydroxytyrosol and other flavonoids, the most prevalent class of polyphenolics in the human diet, are thought to represent the main medicinal components of olive leaves. Olive leaves' anti-oxidant properties shield the body from free radicals' ongoing activity (Yoneyama *et al*., 2003).

A great amount of reducing agents is present in fruit extracts. For instance, fruits such as blackberries, *Cornus mas L., blueberries, Citrullus lanatus, grape, Terminalia arjuna and Punica granatum L.*, have a high number of anthocyanins, phenolic compounds, ascorbic acid, flavonoids, saccharides and other vitamins (Timoszyk, 2018). Cantaloupe peels also showed potential for the synthesis of CuO-NPs (Saleh *et al*., 2022). An additional benefit is provided when NPs are prepared from fruits versus NPs prepared based on the biological method. Microbes mediate the biological method during the synthesis of NP, and these microbes must be pure strains and maintained in an uncontaminated environment. In addition, during downstream processing, it is challenging to separate NPs from a microbial broth culture. Transformation of the metallic salts (soluble) into the elemental oxide/ elemental NPs requires time (Kumar *et al*., 2020). For biosynthesising CuO-NPs, employing

Biogenic source of CuO-NPs	Particle size of CuO-NPs	Application	Reference
Malva sylvestris leaf	5–30 nm	Antimicrobial activity	Kuppusamy, Yusoff, Maniam, and Govindan (2016)
Gloriosa superba L	5–10 nm	Antimicrobial activity	Naika *et al.* (2015)
Black soya bean (Glycine max)	26.6 nm	HeLa cells	Nagajyothi, Muthuraman, Sreekanth, Kim, and Shim (2017)
Centella asiatica leaves	27.65–8.19 nm	Photo catalytic degradation of Methyl Orange	Markus *et al.* (2016)
Eucalyptus Globoulus leaf extract	88 nm	–	Alhalili (2022)
Nilgirianthus ciliatus plant extract	20 nm	Antimicrobial activity Anticancer activity	Rajamma, Gopalakrishnan Nair, Abdul Khadar, and Baskaran (2020)
Annona muricata L plant extract	33.24 ± 6.49 nm	Anticancer activity	Mahmood *et al.* (2022)
Lactobacillus casei subsp. casei	30 nm to 75 nm	Antimicrobial activity Anticancer activity	Kouhkan, Ahangar, Babaganjeh, and Allahyari-Devin (2020)
Syzygium alternifolium stem bark	17.2 nm	Antimicrobial activity Anticancer activity	Yugandhar, Vasavi, Uma Maheswari Devi, and Savithramma (2017)
Camellia sinensis extract and *Prunus africana* bark extract	3 to 192 nm 4–576 nm	Antimicrobial, Antioxidant and Photocatalytic Performances	Ssekatawa *et al.* (2022)
Prunus dulcis (gum)	16 nm–25 nm	Antimicrobial effects	Nithiyavathi *et al.* (2021)
Brevibacillus brevis PI-5	2–28 nm	Antimicrobial activity Anticancer activity	Fouda *et al.* (2022)
Aerva javanica plant leaf extract	15–23 nm range	Antimicrobial, antifungal, and cytotoxic activitiy	Amin *et al.* (2021)
Populus ciliate leaf extract	50 to 60 nm	antimicrobial activity	Hafeez *et al.* (2019)

Table 1. Example of biogenic approaches reported for the synthesis of CuO-NPs

banana peel extract to act as a stabilising and reducing agent is regarded to be a simple and environment-friendly method. As per the results, employing the banana peel extract to synthesise CuO-NPs has yielded high purity with an average particle size of 60 nm (Aminuzzaman, Kei, & Liang, 2017). In addition, sweet lime peel extract has also been employed for synthesising CuO-NPs.

3.2 Fungal-mediated synthesis of CuO-NPs

Attention to a range of fungi species has been given to the green production of copper oxide and other metal NPs (Chakraborty *et al.*, 2022). Fungi have a high potential in synthesising NPs in numerous ways in comparison to other microorganisms. Fungi can withstand bioreactor conditions such as high pressure and temperature in comparison to bacteria. Cell-free microorganism extracts take on the role of agents that reduce, catalyse or cap the NPs' biogenic fabrication (Narayanan, Sakthivel, & science, 2010). *Trichoderma,* a well-known species of fungi, generates various bioactive metabolites, such as pyrones, terpenes, polyketides, glycolipids, diketopiperazine and enzymes. However, these metabolites have nothing to do with synthesising copper oxide NPs (Fayaz *et al.*, 2010). There are two primary pathways by which fungi synthesise NPs: intracellular as well as extracellular. The size of the nanoparticle produced inside the fungal species is much smaller and possesses good dimensions and dispersity versus the ones synthesised via the extracellular pathway (Mukherjee *et al*., 2001). There is a chance that the synthesised NPs are not contaminated by cell components. For the synthesis of NPsNPs, the fungi's extracellular pathway is broadly employed as the fungi secrete different metabolites, which can help to decrease and stabilise the process of nanoparticle synthesis (Shankar, Ahmad, Pasricha, & Sastry, 2003).

3.3 Bacterial-mediated synthesis of CuO-NPs

Bacteria have immense potential in nanoparticle synthesis. They have short generation times and are easy to manipulate at the genetic level. Large energy requirements for metallic reduction are met by molecules like enzymes that are well characterised in their roles as oxidoreductases. Enzymatic proteins that have an affinity for inorganic surfaces have been well studied in the case of gold crystals and their specific feature which is a repetitive sequence of amino acids, has been identified. These proteins possess catalytic properties and gold-binding properties. At the same time, the amphipathic nature of lipids makes them a promising role as capping agents (Brown, Sarikaya, & Johnson, 2000).

A study reported employing cell-free culture supernatant of MHM38, a marine *Streptomyces sp*., to synthesise CuO-NPs. Considerable increase was seen in the enzymatic and nonenzymatic antioxidants of the CuO-NP groups in GSH and SOD levels, while exceptionally low levels of nitric oxide and malondialdehyde were seen for the paracetamol group (Bukhari *et al*., 2021).

Marine entophytic actinomycetes were employed as stabilising and reducing agents based on the biological route to prepare CuO-NPs. This study concluded that excellent biomedical applications were displayed by the actinomycetes-mediated CuO-NPs versus biofilm-yielding bacteria and cancer cells, and these can also be employed for future studies about different biomedical applications (Zhao *et al*., 2022).

For stabilising and reducing CuO-NPs, *Brevibacillus brevis* PI-5 was employed as a biocatalyst. The small-sized CuO-NPs that were synthesised showed highly orientated activity for breast cancer cell lines (T47D), even at a lower dose, versus activity towards normal cell lines. Finally, high mortality percentages were shown by bacteria-mediated CuO-NPs, which lied in the range of 86.9% $\pm$ 2.1% to 53.1% $\pm$ 1.4% with regards to instar larvae of *Culex antennatus* (Fouda *et al*., 2022).

4. Anticancer activity of CuO-NPs

Cancer diseases involve abnormal cell growth, which may also spread to other body parts (Shamsee, Al-Saffar, Al-Shanon, & Al-Obaidi, 2019). The CuO-NPs that are green synthesised exhibited promising anticancer activity vis-a-vis various cancer cell lines. Green synthesised CuO-NPs have been proven to be effective in pharmaceutical, environmental and biomedical applications.

To assess the anti-cancer properties of copper CuO-NPs, research was conducted utilising an easy bio-synthesis method and plant extract from *A. muricata*. According to a study, treatment with CuO-NPs increased the formation of lactate dehydrogenase (LDH), which was most likely brought on by cell membrane disruption that led to leaks containing cellular components including lactate dehydrogenase. Therefore, according to research findings, the produced CuO-NPs triggered anti-proliferative effects by inducing cell death via apoptosis (Mahmood *et al*., 2022).

CuO-NPs aid in the positive regulation of the caspase cascade pathway for mitochondrial and death receptor-mediated apoptosis in A549 cells (Kalaiarasi *et al*., 2018).

A decline in dose-dependent cell viability was exhibited by the biogenic CuO-NPs with a 50% inhibitory concentration (IC_{50}) at 20 µg/ml. In the breast tumour cell line, CuO-NPs displayed a significant potential to fight against cancer (Zughaibi *et al.*, 2022).

The green-synthesised CuO-NPs exhibited high potential for treating a few types of cancer such as breast (MCF-7, HBL-100 and AMJ-13 cell lines) (Thamer & Barakat, 2019), gastric cancer (human adenocarcinoma AGS cell line), colon (HCT-116), cancer (A549),

Cytotoxic behaviour on human lung cancer cell edge (A549) conducted using CuO-NPs confirmed the considerable anticancer behaviour of the CuO-NPs prepared (Shwetha *et al.*, 2021).

5. Antimicrobial activity of CuO-NP

The prepared CuO-NPs have been subjected to screening for their antimicrobial effectiveness against various strains of bacteria, like Gram-positive (*Bacillus subtilis* and *Staphylococcus aureus*) and Gram-negative (*Salmonella Paratyphi, Enterobacter aerogenes* and *Klebsiella pneumonia*). The synthesised NPs exhibited significant activity in curbing pathogenic bacteria (Jeronsia, Raj, Joseph, Rubini, & Das, 2016).

The CuO-NPs demonstrated significant antifungal inhibition activity against *Aspergillus flavus* and *Aspergillus niantimicrobialger* (3.0 ± 4.24 mm) (Alao, Oyekunle, Iwuozor, & Emenike, 2022).

Due to the therapeutic effects of the bacteria utilised in nanoparticle manufacturing, green-synthesized NPs display a protective effect against liver and kidney deterioration. These findings are congruent with those of Ghaffar *et al.* (Ghaffar *et al.*, 2014). CuO-NPs' protective action may be linked to their function in reducing cellular leakage and loss of functional membrane integrity in hepatocytes and kidneys.

In the tests against bacterial strains *Lactobacillus acidophilus*, *Salmonella typhi* and *Escherichia. coli,* it is indicated in the CuO-NPs quantum dots' *in vitro* antimicrobial activity that the NPs synthesised from fruit extracts demonstrate greater antimicrobial activity compared to the control (Zaman *et al.*, 2020).

CuO-NPs synthesised from *Catha edulis* extract in different concentrations were used to test its antimicrobial activities (Andualem, Sabir, Mohammed, Belay, & Gonfa, 2020).

Excellent antimicrobial activity was displayed by CuO-NPs against various strains of bacteria (*E. coli*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *E. faecalis*, *K. pneumonia*, *Shigella flexneri* and *S. aureus*) (Ahamed, Alhadlaq, Khan, Karuppiah, & Al-Dhabi, 2014).

CuO-NPs concentrated at 1-1000 µg/ml in TSB medium were applied to *C. albicans*, *Candida glabrata* and *Candida krusei* cells, resulting in a fungal growth decrease (Amiri, Etemadifar, Daneshkazemi, & Nateghi, 2017).

Against *E. coli,* CuO-NPs composite displayed the most significant Antimicrobial behaviour at 1000 µg mL^{-1}, the maximum concentration. Amoxicillin and CuO-NPs demonstrated a synergistic outcome that restrained the growth of *S. aureus* and *E. coli*; this effect was also observed when a good diffusion technique was employed (Khashan, Sulaiman, & Abdulameer, 2016).

Excellent antimicrobial activity was demonstrated by CuO-NPs against different bacterial strains, such as *P. aeruginosa and E. coli*. It was also detected that Cuo-NPs' antimicrobial activity is size dependent (Mohammed, Mubark, & Al-Haddad, 2018).

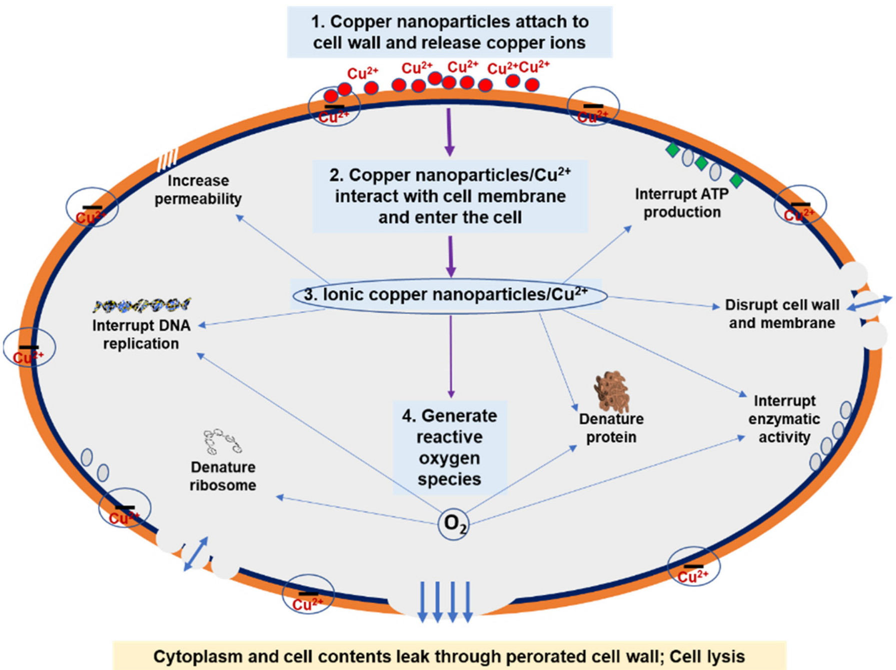
Orthodontic devices encourage the build-up of microbial plaque and increase the chance of creating white spot lesions. A study was conducted to elucidate the antimicrobial properties and bond strength of CuO-NPs. Based on that research, it was concluded that incorporating CuO-NPs into the adhesives of the orthodontic devices strengthened them with antimicrobial characteristics (Toodehzaeim, Zandi, Meshkani, & Firouzabadi, 2018).

Combining CuO-NPs and ZnO-NPs in an adhesive exhibited anti-MMP (matrix metalloproteinases) and antimicrobial activities with no effect on the bond strength (Gutiérrez *et al.*, 2019). Because fluorine is extensively used in enhancing dentin and enamel remineralisation, Matsuda *et al.* earlier introduced new fluoride-containing nanocomposites of ZnO-NPs and CuO-NPs, which they found to exhibit strong properties as an antimicrobial (Matsuda *et al.*, 2019).

An investigation was conducted about the properties arising from a combination of adhesive dental materials with innovative zinc and copper nanocomposite that contains fluoride. It was established that anti-MMP (matrix metalloproteinase) properties were imparted when zinc and copper nanocomposites are added to the self-etch adhesive system. That study proposed that this novel nanocomposite could handily bring a novel additional uses to adhesive dental materials (Altankhishig *et al.*, 2022). Figure 5 demonstrates the mechanism of copper NPs' antimicrobial activities in bacterial cells.

6. Dental application of copper oxide nanoparticles

With regards to dental applications, metal and metallic oxides-based NPs have become a new trend. In dentistry, metal NPs are employed due to their exclusive shape-dependent characteristics, such as their different nanosizes and shape, large surface-area-to-volume ratio as well as unique distribution. These characteristics enhance the antimicrobial activity, bio-physio-chemical functionalisation as well as biocompatibility pertaining to the NPs. Copper NPs are also employed for improving the chemical and physical characteristics of different dental materials, like restorative cements, dental amalgam, obturation materials,



Source(s): Xu *et al.*, 2022

Figure 5. Antimicrobial mechanism of copper nanoparticles

adhesives, dental implants, endodontic-irrigation solutions, resins as well as orthodontic brackets and archwires (Xu *et al.*, 2022).

In the dental field, oral infections and denture-induced stomatitis can be addressed with removable and fixed partial denture framework designs incorporated with copper NPs (Grass, Rensing, Solioz, & microbiology, 2011). Earlier research studies have reported the titanium–copper alloy to possess anti-aging and antimicrobial characteristics. The research studies also showed that these antimicrobial characteristics could be adjusted by modifying the alloy composition's copper concentration (Koohkan, Hooshmand, Tahriri, & Mohebbi-Kalhori, 2018). A study reported that copper-containing mesoporous bio-glass decreased the microbial activity as well as biofilm formation due to release of copper ions (Astasov-Frauenhoffer *et al.*, 2019). Research reported a copper-bearing titanium alloy implant possessing anti-infective characteristics that could be used against oral bacteria. The research also showed that not only did titanium–copper alloy help in fighting against peri-implant infections but also exhibited good biocompatibility (Liu *et al.*, 2022). A study showed that oral bacteria were inhibited by a titanium–copper alloy as well as a titanium-copper ion-doped hydroxyapatite (Hameed, Ariffin, Luddin, Husein, & Research, 2018). With regards to orthodontic appliances, adding copper NPs to a nickel–titanium alloy provides various benefits. Loading stress was decreased when copper NPs were included in archwire, which offered a relatively high unloading stress (Thamer & Barakat, 2019).

7. Development of nanocomposite based on CuO-NPs

Nanocomposites possess both special properties of nanomaterials along with polymer advantages such as high conductivity, chemical resistance, elasticity and biocompatibility (Gholamali, Yadollahi, & Medicine, 2021). The recent advancements in scientific areas, like chemical engineering (Liu *et al.*, 2021), biochemistry (Joseph *et al.*, 2021) and physics (Noor *et al.*, 2021), entail the production of novel sensing techniques which combine lower power usage and miniaturisation with extremely tactile sensitivity. Moreover, these materials possess unique structures and optical properties that are not typically found in conventional composites (Al-Hossainy, Abdelaal, & El Sayed, 2021). Nanocomposite synthesis is considered as the primary step in building different electronic devices (Chen, Chen, Zhang, & Fuels, 2021), drug delivery systems (Sathishkumar *et al.*, 2021), biomedical and immunosensing applications (Beyene, Moniruzzaman, Karthikeyan, & Min, 2021).

Due to the diversity in its applications, copper oxide NPs attract much attention. It has different potential medical applications as antimicrobial, antioxidant, anticancer and drug delivery properties. Physicochemical and biological approaches have been applied to synthesise copper oxide NPs. The physicochemical methods are not only expensive but use toxic chemicals with a possibly hazardous effect. Aside from being cost-effective and environment-friendly, the biological approach is also stable and reliable; it also uses a straightforward method and has low energy consumption.

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