



Copper Oxide Nanoparticles Application in Prosthodontics

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Abstract

Objectives: To assess current knowledge about copper oxide nanoparticles and their applications in prosthetic dental technology. **Materials and Methods:** On this topic, an electronic systematic review was conducted in various databases (Google Scholar research, Science Direct reports, PubMed studies, and Web of Science data), as well as a hand search of the scientific literature. From 2015 to 2022, published work was collected, analyses, and relevant articles were chosen for inclusion in this review. Copper oxide nanoparticles and their applications in prosthetic dental technology have been reported in several studies. More than 30 papers were chosen for this review based on their applicability. **Results:** The findings suggest that current knowledge is adequate to recommend copper oxide nanoparticles and their applications in prosthetic dental technology for routine laboratory use, with improvements in each of the current nano materials and procedures for prosthetic dental technology. **Conclusion:** Because of their physical and chemical properties, copper oxide nanoparticles are suitable for prosthetic restorations; however, careful processing methods, nano materials, laboratory skill, and a strict protocol for prosthetic restoration are required to improve the mechanical and physical properties.

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Introduction

Copper oxide has a monoclinic structure and is a semiconductor. Because of its physical properties, copper oxide has a wide range of applications [1]. Because it is a p-type semiconductor, it is widely used in a variety of applications such as field emission emitters, high-temperature superconductors, catalysis, sensors, and batteries [2]. Copper oxide (CuO) nanoparticles have recently been observed to have microbial activity and to cross the biological membrane to reach the respective organ [2]. Free form or complex form of copper has germicidal activity. In recent Studies, Copper nanoparticles are

used in the paint industry as the antifouling coating. Copper has also been used as a copper nanocomposite to control fungi [1]. Because of its antimicrobial properties and low toxicity, copper is a popular element in medical and dental research [3]. The antimicrobial activities are induced by either copper's metal ions or the oxidized cupric ions derived from copper nanoparticles (1–100 nm). Moreover, copper is readily available for the synthesis of copper nanoparticles, so it is cost effective [3]. Copper nanoparticles can be processed either naturally or via chemical synthesis [4]. Furthermore, they oxidize easily in air or water,

producing copper oxide nanoparticles. Copper particles, like most metal nanoparticles used in dentistry, have variable nano -sizes and forms, a distinct distribution, and a large surface-area-to-volume ratio. These properties improve the nanoparticles' bio-physio-chemical functionalization, antimicrobial activity, and biocompatibility. According to reports, copper oxide nanoparticles are antimicrobial and inhibit biofilm formation [5]. Copper nanoparticles can prevent root caries by inhibiting the growth and colonization of *S. mutans* on the surface of the tooth root. Copper oxide nanoparticles are less expensive than silver nanoparticles. They have

desirable physical properties, such as a large surface area and a crystalline structure. According to a review, copper oxide nanoparticles are bactericidal against cariogenic bacteria. Furthermore, copper oxide nanoparticles' antimicrobial activity is dose dependent. Copper oxide nanoparticles are easily mixed into polymers to create composites with distinct physiochemical properties [6]. Copper oxide (CuO) is an important bactericidal and antifungal agent. It is the most basic element of Cu compounds, revealing a variety of potential physical properties such as high-temperature superconductivity, spin dynamics, and electron correlation effects [7]. Copper oxide nanoparticles (CuONPs) are well known for their optical, magnetic, and electrical conductivity due to their small size. Despite the fact that copper oxide nanoparticles are well known for their biological properties, particularly their antimicrobial activity, cytotoxic properties were well estimated in both *in vitro* and *in vivo* models [8]. Copper is a trace element that is essential for humans because it promotes angiogenesis, bone formation, wound healing, and the activity of various enzymes [9]. It also promotes the formation of crosslinks in collagen and elastin precursors [10].

Table 1. Nomenclature and Symbols.

Nomenclature	
CuO	copper oxide
CuONPs	copper oxide nanoparticles
Ref	Reference
NPS	Nanoparticles
<i>F. oxysporum</i>	<i>Fusarium oxysporum</i>
<i>F. graminearum</i>	<i>Fusarium graminearum</i>

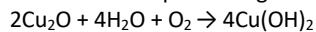
Material and Methods

Google Scholar, PubMed, Science Direct, and Z-library were used to conduct a search for the uses and applications of copper oxide nanoparticles in prosthetic dental technology. The inclusion criteria included, among other things, research articles about copper oxide nanoparticles published between 2015 and 2022, articles about additive effects, and articles about dental applications or biomaterials implants. The current work attempts to present research challenges and future directions in addition to reviewing the existing literature on copper oxide nanoparticles. The current copper oxide nanoparticles study will be useful for practitioners interested in conducting additional

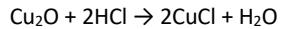
research in all areas of dentistry, particularly prosthetic dental technology.

Chemical Properties of Copper(I) Oxide – Cu₂O

Copper(I) oxide reacts with water in the presence of oxygen, forms copper (II) hydroxide. The chemical equation is given below:



Copper(I) oxide reacts with hydrogen chloride forms Copper(I) chloride and water. The chemical equation is given below:



Synthesis of copper oxide nanoparticles

Many researchers have reported various methods of synthesizing CuONPs, including hydrothermal ultrasound irradiation, biosynthesis approaches, electron beam lithography, solid-state reaction, sol-gel, template methods using surfactants, microwave-assisted proto-col, copper acetate decomposition, and sonochemical synthesis [11-13]. It has also been reported that the method of synthesis of CuONPs influences their morphological properties and toxicity behavior. The flowchart representing the various methods of CuONPs synthesis is shown in Figure 1.

Chemical approach

This method involves the use of some chemicals/regents to reduce copper ions during the synthesis of CuONPs [15].

The chemical approach to the formation of nanoparticles is classified into two types: green chemical approach and traditional approach. Chemicals synthesized from organic materials such as ascorbic acid are used in the green chemical approach, whereas inorganic compounds such as sodium borohydride and potassium borohydride are used in the traditional approach. Ascorbic acid has been reported to be used as a reducing agent in the synthesis of CuONPs [16]. The use of potassium borohydride in formation of CuONPs has also been established. Several studies have found that high energy consumption, environmental pollution, the use of high pressure and temperature, and the use of expensive and toxic chemicals are all significant limitations of the chemical method of producing CuONPs and other transitional metal oxide NPs [17].

Physical method

This method employs electric current as an electron source in the generation of required electrons during CuONPs synthesis [18]. Electro-spraying, laser pyrolysis, laser ablation, and evaporation-condensation are the most used techniques in the physical approach to CuONPs synthesis. Among the physical approaches, the pulsed laser induced ablation technique has gained popularity because it is simple, eco-friendly, and produces uniform nanoparticles [19]. High power pulsed laser is the cogent and

essential requirement for ablation on the surface of the sample in the synthesis of CuONPs via laser ablation [20]. Variation of some parameters, such as pulse width, wavelength, laser source repetition rate, ablation time, and temperature, enables the formation of nanoparticles with desired morphological identities [21].

Biological approach synthesis

The biological approach to nanoparticle synthesis includes the use of organisms (bacteria, yeast, and fungi) and extracts from various parts of plants as metal ion reducing agents [22]. The biosynthesis of CuONPs using the following bacteria *Phormidium cyanobacterium*, *Morganella morganii*, and *Escherichia coli* [23] had been reported. Despite the environmental benefits of creating nanoparticles from microorganisms, the following are their limitations: Some bacteria are toxic, and the isolation and incubation processes are difficult [24]. Plant extract biomolecules act as both reducing and stabilizing agents during the synthesis of CuONPs and other metal nanoparticles [25]. Flavonoids, proteins, tannins, phenols, and terpenoids have been reported to be effective reducing and stabilizing agents for CuONPs synthesis [26].

Copper Nanoparticles in Dental Materials

Copper nanoparticles have antimicrobial, biophysiological, and chemical properties. They increase the material pool to reduce the scarcity of dental materials in various clinical applications. Copper nanoparticles are commonly found in dental metals and alloys, dental polymers and resins, dental cements, and other dental materials (Table 3).

Copper Nanoparticles in Dental Polymers and Resins

A heat-cured thermoset denture base containing copper oxide nanoparticles effectively inhibits the growth of *Candida albicans*, the main cause of denture stomatitis [4]. Furthermore, another study discovered that copper oxide nanoparticles released ions when mixed with various resin formulations (heat-cured acrylic resin denture, chemically cured soft liner, and cream-type adhesive). This ion release could be controlled and used in the delivery of therapeutic drugs for the treatment of oral diseases. However, the release of these ions can differ. According to one study, the denture base and adhesive had higher releases than the denture line [30]. For the best clinical outcome, researchers may investigate the controlled and optimal therapeutic release of copper ions. According to one study, copper-doped mesoporous bioactive glass nanosphere-incorporated resin exhibited antimicrobial, mechanical, and aging resistance properties [31]. An etch-and-rinse adhesive containing copper nanoparticles

demonstrated antimicrobial activity and prevented adhesive interface degradation without affecting mechanical properties [32]. In another study, polyacrylic acid-coated copper iodide nanoparticles were used as an antibacterial additive to adhesive, with no effect on bonding strength or biocompatibility [33]. Another study found that adding copper nanoparticles to an adhesive improved shear bond strength and antibacterial properties while causing no cytotoxicity [34].

Application of CuO NPs

NPs are widely used as catalysts in cosmetics, textiles, photonics, agriculture, and heavy industries in the modern era. Furthermore, the use of NPs in medicine has been expanded. According to the available data, CuO NPs can be used as antimicrobial, antifungal, anticancer, anti-inflammatory, and wound healing agents. The following sections will go into more detail on these, including the mechanism.

Antibacterial

CuO NPs have been shown in studies to inhibit the growth of Gram-negative and Gram-positive bacteria. CuO-NPs were found to be significantly effective against *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Propionibacterium acnes*, and *Salmonella typhi* in vitro antimicrobial activity tests. However, among the plant pathogenic fungi tested, *Fusarium culmorum* was found to be the most sensitive, followed by *Fusarium oxysporum* (*F. oxysporum*) and *Fusarium graminearum* (*F. graminearum*) [35]. Their antibacterial efficacy was higher than that exhibited by standard antibiotic, streptomycin [36]. These particles were discovered to be more effective against *Staphylococcus aureus* and *Bacillus subtilis* (gram-positive bacteria) than against *Pseudomonas aeruginosa* and *E. coli* (gram-negative). Efficacy was found to be dependent on the size of NPs [37], the thickness of bacterial cell wall and incubation time. Smaller particles were more toxic than larger ones even if they do not penetrate the bacterial cell wall.

Antifungal

Direct contact with fungi can result in human infection. When spoiled food is consumed, *A. flavus*, a pathogenic fungus, causes liver cancer in humans. If *A. fumigatus* spores are inhaled, they can cause chronic lung disease. *C. albicans*, which is found in our bodies at the mouth and vagina, can cause infections if it grows too quickly [38]. The fungus's cell wall contains multiple layers of lipids, making NP entry into the organism difficult [39]. CuO NPs synthesized can be exhibited an antioxidant activity

that may contribute to the anti-fungal property [40].

Anticancer

The anticancer investigation of CuONPs biosynthesized using black bean extract revealed some changes in mitochondrial structure when incubated with CuONPs, and the growth of cervical carcinoma cells was also greatly reduced when treated with CuONPs [41]. The report on the invitro toxicity investigation of phytosynthesized CuONPs reveals that they exhibit better toxicity efficacy that is beneficial in biomedical application when compared to chemically synthesized nanoparticles, emphasizing the importance of toxicity analysis in selecting non-toxic nanoparticles with distinct biological activities [42]. Several studies have shown the cytotoxicity of CuONPs against cancer cell growth [43].

Toxicity of CuO NP

The complications that result from misinterpreting toxicity are due to CuO NPs binding, interaction with living cells, and subsequent change in surface chemistry. To understand the toxicity of CuO NPs, it is necessary to first understand the characterization and surface modification of CuO NPs, as well as the routes of exposure and the mechanisms or pathways involved in toxicity. The complications that result from misinterpreting toxicity are based on the fact that NPs bind, interact with living cells, and cause a change in surface chemistry. To understand the toxicity of nanomaterials, it is necessary to first understand the characterization and surface modification of NPs, as well as the routes of exposure and the mechanisms or pathways involved in toxicity [44].

Characterization

Characterization of CuO NPs includes particle size, shape, and charge. There is a relationship between the size of the NPs and the surface-to-volume ratio; the smaller the size, the greater the surface-to-volume ratio, and vice versa. The size of a particle determines its penetration and reactivity. However, it has been proposed that NPs larger than 100 nm can enter cells by crossing the cell membrane, whereas NPs smaller than 40 nm can enter blood and reach cell nuclei [44].

Surface modification

CuO NPs have a wide range of applications due to their high surface reactivity, chemical stability, and thermoelectric properties [45]. The higher the surface reactivity, the higher the production of reactive oxygen species (ROS), and vice versa. The relationship between the surface chemistry (capping agents) of Cu NPs and the generation of ROS is well established [46]. Three surface modifiers, 8-mercaptopoctanoic acid (MOA), 12- mercaptododecanoic acid (MDA), and 16-mercaptophexadecanoic

acid (MDA), were used, followed by water dispersion, demonstrating the strong affinity of Cu NPs to thiolated functional groups when compared to carboxylic acids. Cu-NPs treated with 8-mercaptopoctanoic exhibited significant ROS activity. The findings revealed that the ability to generate ROS decreased dramatically as the length of the chain increase.

Exposure route of Cu NP

The primary source of NP exposure is improper raw material and equipment handling by workers during lab-scale production. Another major source of NP exposure is commercial nanomaterial synthesis. Other types of NP exposure routes include errors that occur during the classification, packing, and transportation of nanomaterials. On the contrary, the use and consumption of nanomaterials-based products can be fatal. NPs enter the body primarily through inhalation, ingestion, or through the skin and bloodstream [47]. After entering the body, NPs are transported to other parts of the body via the blood circulatory system, where they cause toxic effects at various sites [48]. The main indicator that influences the toxicological outcomes of Cu NPs is the route of exposure. Cu NPs can easily translocate through tissue interstitially (between cells), pass through cell membranes, and eventually enter the blood circulatory system due to their small size. The circulatory and lymphatic systems play an important role in the translocation of NPs from the exposure site to downstream effects, culminating in accumulation in the body organ.

Discussion

CuO NPs have emerged as an important class of nanomaterials for a wide range of applications (medicinal, environmental, industrial) that have potential risks to organisms and environment. In this review, an overview about CuO NPs synthetic methods, their, applications, exposure routes, toxicological evaluations, immunotoxicity, cytotoxicity and genotoxicity and factors affecting the toxicity of CuO NPs are discussed. The factors that influence the toxicity of CuO NPs are shape, size, surface modification, morphology and concentration [49]. Copper oxide is a member of the copper compound family with useful physical properties such as high-temperature superconductivity, electron correlation effects, and spin dynamics. It is relatively inexpensive, easily mixed with polar liquids and polymers, and has a relatively stable chemical and physical activity. Previous research has shown that CuO NPs have a significant antimicrobial effect [50]. CuO nanoparticles are effective antibacterial, antifungal, and antiviral agents and antioxidant

material which control microbe effectively CuO penetrates membranes due to its high surface area. CuO nanoparticles are used in food packaging because they are biocompatible. It prevents bacterial growth. CuO acts as a drug carrier in nanomedicine. In the field of nanomedicine, drugs based on nanomaterials have been developed to selectively kill cancerous cells in target cancer therapy. Modified CuO nanocrystals with specific ligand interact with specific receptors on the tumor cell. CuO nanoparticles have the potential to detect a wide range of diseases, including cardiac syndrome, neurological disorders, tumors, stress, and diabetes [1]. Mahmoud et al [51] showed highest values of human neuronal cell genotoxicity at copper oxide nanoparticles concentrations 15ug/ml, and highest values apoptosis at 40 ug/ml. Ivast et al [52] showed mice fibroblasts toxicity when copper oxide nanoparticles concentration is 49.9 ug/ml. Transmission electron microscopic analysis study by Wang et al [53] showed copper oxide nanoparticles toxicity to lung epithelial cells lysosomes, mitochondria, and nucleus occur when copper oxide nanoparticles release is 15 ug/ml. Copper nanoparticles are alternative for silver and gold nanoparticles which are currently used in inkjet printing of conductive patterns because of the low price and high electrical conductivity [54]. Suleiman M, et al. concluded that CuO nanoparticles can be synthesized by different ways and synthesis factors such as method, solvents, surfactants starting precursors and temperature are used to control the shape and size of desired nanoparticles [55]. Lanje AS, et al. studied that CuO nanoparticles are rectangular in shape with average size of 5-6 nm with monoclinic structure are synthesized by aqueous precipitation method [56]. Copper oxide nanoparticles were prepared by modified sol-gel technique using sodium dodecyl sulphate as a surfactant [57]. Effect of calcination temperature on particle size, band-gap, crystallinity and morphology of the nanoparticles.

Conclusions

1- Copper nanoparticles play a dual role in the development of the properties of dental materials. The inclusion of copper nanoparticles may improve the physio-mechanical properties and introduce or enhance the antimicrobial activities of various dental materials. It is expected that researchers and clinicians will focus on the perspective of cost-effective copper nanoparticles in dentistry. This will reveal potentials and limitations, as well as open a new door to dental biomaterials research for the use of copper nanoparticles in clinical dental practice.

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methods of CuONPs synthesis is shown in Figure 1.

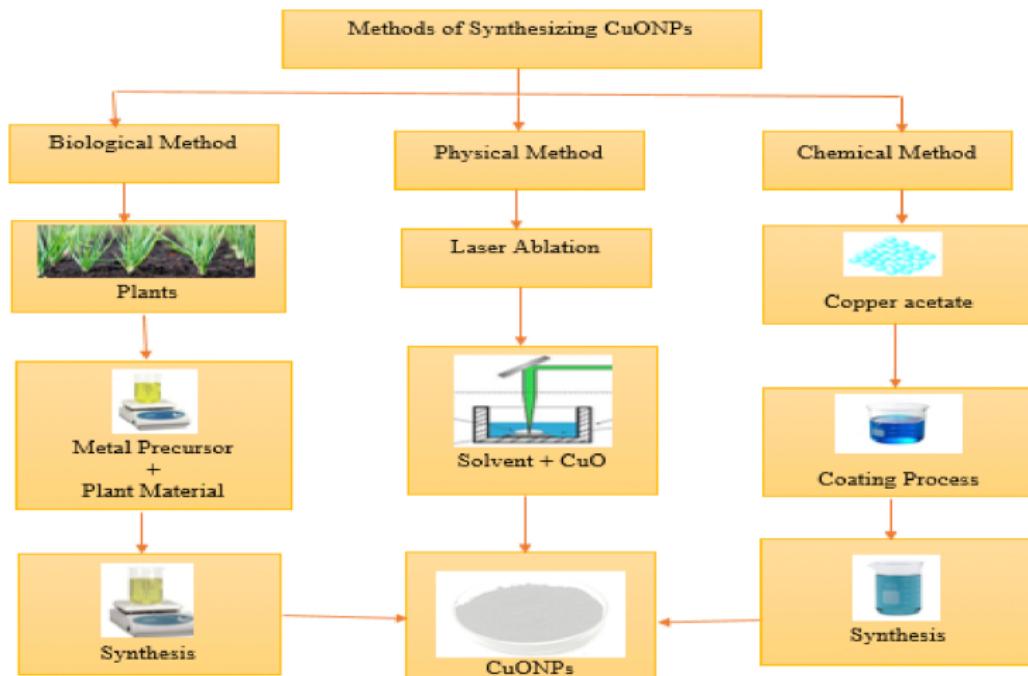


Figure 1. Flowchart representing the various methods of synthesis of CuONPs [14].

Table 2. Advantages and disadvantages of different methods of CuONPs synthesis.

Methods	Advantages	Disadvantages	Reference
Chemical	It enhances large scale production	Its energy-intensive processes, use of toxic solvents as reducing and stabilizing agents, and production of non-ecofriendly products.	[27]
Physical	Control crystallinity, shape and production of CuONPs with uniform, controlled sized and high purity are achievable	high capital costs and high energy consumption	[28]
Biological	This method is cost effectiveness, non-use of toxic materials and simple.	The use of microorganisms is unappealing due to the need for aseptic cultivation and increased production costs on an industrial scale.	[29]

Table 3. Dental polymers and resins.

Materials	Properties and Functions	Applications	Ref.
Copper-nanoparticle incorporated acrylic resin	Offer antimicrobial properties, Prevent stomatitis	Denture soft liner	[30]
Copper-doped mesoporous bioactive glass nanosphere acrylic resin	Facilitate copper-ion release Offer antimicrobial properties Prevent stomatitis.	Denture acrylic base	[31]
Copper nanoparticles with adhesive Resin	Offer antimicrobial properties, Prevent secondary caries	Dental adhesive	[32]
Polyacrylic acid-copper iodide nanoparticles with adhesive resin	Offer antimicrobial properties, Prevent secondary caries.	Dental adhesive	[33]