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A Review on Copper oxide Nanoparticles: Green Synthesis, Characteristics and its Application in Oral and Maxillofacial Surgery

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ABSTRACT

Herbal extract-derived copper oxide nanoparticles, which combine the therapeutic advantages of medicinal plants with the special qualities of nanoscale materials, have become a advancing field of study. The synthesis, characteristics, and properties of nanoparticles made from herbal extracts are reviewed. These green synthesis techniques create copper oxide nanoparticles that are more biocompatible and less poisonous. Unique physicochemical characteristics, such as improved solubility, stability, and controlled release of active chemicals are displayed by the resultant nanoparticles. This comprehensive review aims to provide insights into the current state of research on copper oxide nanoparticles derived from herbal extracts, offering a valuable reference for further studies and applications in oral and maxillofacial surgery.

Keyword: *copper oxide nanoparticle, Green synthesis, OMFS, Antioxidant, Antimicrobial, Toxicity, Wound healing*

1. INTRODUCTION

Numerous scientific disciplines have seen radical change because of nanotechnology, which has also significantly advanced medicine. Nanoparticles, which have dimensions measured in nanometers and distinct physical, chemical, and biological capabilities, are at the center of this revolution [1]. These characteristics provide nanoparticles the ability to interact at the molecular level with biological systems, creating new avenues for disease detection, therapy, prevention and management.

Nanoparticles are used in medicine for several purposes, such as targeted medication administration and improved diagnostic precision using imaging agents. Because of their tiny size, they can pass through biological barriers, allowing for more targeted, efficient treatments with fewer adverse effects [2].

Nanoparticles provide novel approaches to the diagnosis, management, and prevention of oral health issues. Furthermore, while bacterial infections are a prevalent cause of oral diseases, nanoparticles have demonstrated potential in this regard [3]. By facilitating greater integration and quicker healing, nanoparticles can also enhance the results of bone regeneration and dental implant treatments.

The use of nanoparticles represents a change toward more specialized and individualized treatment. There has been an exponential increase in research and development in nanotechnology due to its immense potential and wide range of applications [4]. Nanoparticles, which are essential to this technology, have special qualities because of their nanoscale size.

There are concerns to the environment and human health when using hazardous chemicals and high energy needs in traditional nanoparticle synthesis processes. By using natural materials and procedures to create nanoparticles, green synthesis has emerged as an eco-friendly and sustainable solution to these issues.

Herbal preparations with nanoparticles mark a new frontier in contemporary biomedicine by fusing the potent therapeutic effects of traditional herbal therapy with the cutting-edge capabilities of nanotechnology. By using nanoparticles, these

formulations improve the targeted distribution, bioavailability, and effectiveness of herbal bioactive components [1,2].

Copper oxide has gained significant attention in recent years due to its multifunctional properties. It exhibits excellent chemical stability, low cost, and strong antimicrobial, catalytic, and photoconductive capabilities. These attributes make CuO nanoparticles particularly promising in biomedical applications, especially in antimicrobial formulations, where their ability to generate reactive oxygen species (ROS) and disrupt microbial membranes plays a pivotal role. Moreover, its eco-friendly synthesis potential further enhances its appeal for sustainable nanotechnology solutions [4].

This article provides an extensive exploration of copper oxide nanoparticle herbal preparations, focusing on their characterization techniques, methods to evaluate antioxidant, anti-inflammatory, antimicrobial, and wound healing properties, along with its application in oral and maxillofacial surgery.

HERBAL FORMULATION PREPARATION:

Three primary elements are usually involved in the green production of nanoparticles:

- Enzymes, plant extracts, and microorganisms (fungi, bacteria, and algae) are examples of biological reducing agents.
- Metal Precursors: Metal salts, such as Copper sulphate.
- Solvent: A typical green solvent is water.

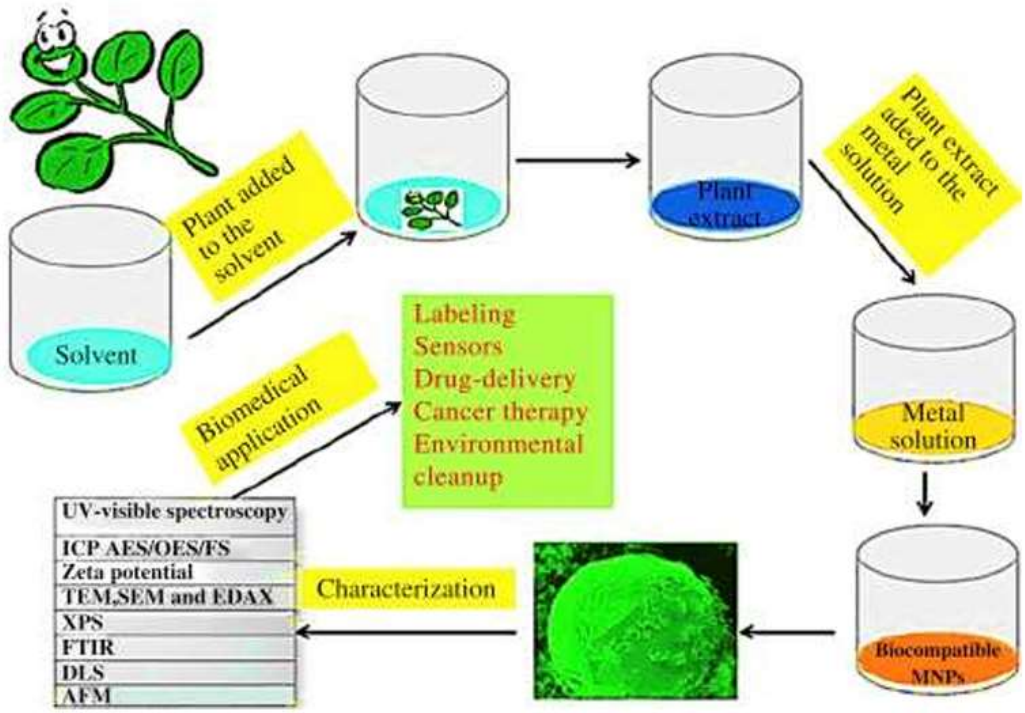
Preparation of copper oxide nanoparticles involve following steps:

1.1. Preparation of Plant Extract: choose a plant with a high concentration of reducing agents, such as polyphenols, or one with proven therapeutic qualities. Wash the plant material well, cut into little pieces, and boil in distilled water. To get rid of the solid waste, filter the mixture.

1.2. Copper oxide Nanoparticle Synthesis [4]:Add the plant extract in a predetermined ratio to an aqueous solution of copper sulphate. Depending on the required size and form of the nanoparticles, different concentrations of the metal salt and extract can be used. Stir the mixture at room temperature or slightly above it to provide proper reaction conditions. The reduction process, which causes the colour to change to signal the production of nanoparticles, might take a few minutes to many hours.

To separate the nanoparticles, centrifuge the mixture. Use ethanol and distilled water to wash away any contaminants or unreacted materials. The nanoparticles can be dried in an oven or in a vacuum.

FIGURE 1: Depicts the green synthesis of nanoparticles



2. CHARACTERIZATION OF COPPER OXIDE NANOPARTICLE HERBAL PREPARATION

Characterization plays a pivotal role in understanding the physicochemical properties, structure, stability, and interactions of green synthesised copper oxide nanoparticle. Advanced analytical techniques are employed to assess these formulations comprehensively.

2.1. Particle size and morphology analysis [2,3]: The size of nanoparticles, which can vary from 1 to 100 nanometers, affects both their biological activity and therapeutic potential. Techniques for characterization consist of:

• Dynamic Light Scattering (DLS): This technique provides information on particle stability and aggregation by measuring the hydrodynamic diameter and size distribution of nanoparticles in solution.

• Transmission Electron Microscopy (TEM): This technique uses high-resolution visualization to assess the homogeneity, morphology, and shape of nanoparticles.

• Scanning Electron Microscopy (SEM): This technique offers precise pictures of the surfaces and cross-sections of nanoparticles, revealing details on the size, shape, and surface properties of the particles.

• Atomic Force Microscopy (AFM): This technique examines the surfaces of nanoparticles to provide topographical pictures that show surface interactions and roughness.

2.2. Surface Chemistry and Functionalization [5,6]:

Herbal nanoparticle formulations with modified surfaces have improved stability, biocompatibility, and targeting abilities. Techniques for characterization consist of:

• Fourier-Transform Infrared Spectroscopy (FTIR): Verifies the presence of herbal ingredients and nanoparticle carriers by identifying functional groups and chemical bonds on nanoparticle surfaces.

• X-ray photoelectron spectroscopy (XPS): Clarifies surface chemistry and alterations by analyzing the elemental composition and oxidation states of nanoparticle surfaces.

2.3. Zeta Potential and Stability [7]:

- Zeta potential tests evaluate the colloidal stability and surface charge of nanoparticles in aqueous solutions. This technique also, establishes the electrostatic potential at the surface of nanoparticles, which affects their stability, dispersion, and interactions with biological membranes.

2.4. Composition and Crystallinity [7]:

X-ray diffraction (XRD) and energy-dispersive X-ray spectroscopy (EDS) are two methods used to study the composition and crystalline structure of nanoparticles.

• XRD: Determines the lattice parameters and crystallographic phases of nanoparticles, verifying the existence of herbal components and nanoparticle carriers.

• EDS: Offers elemental analysis of samples of nanoparticles, identifying and measuring the elemental distribution in nanoparticle compositions.

2.5. Stability Studies [6]:

Analyzing the stability of herbal preparations with nanoparticles across a range of environmental factors (such as pH and temperature) is essential for determining shelf life and storage needs:

• Long-Term Stability Testing: This method ensures the resilience and effectiveness of the formulation by tracking changes in particle size, aggregation, and chemical integrity over lengthy periods of time.

3. ANTIOXIDANT PROPERTY:

Copper oxide nanoparticle formulations helps shielding cells from oxidative damage [8]. A range of assays are utilized to assess the antioxidant property of copper oxide nanoparticles:

3.1. **DPPH Assay:** This test assesses antioxidants' potential to scavenge radicals by measuring their ability to neutralize the stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) [9].

3.2. **Hydrogen peroxides radical scavenging Assay:** This method provides quantitative assessments of antioxidant efficacy by measuring the absorbance of the reaction solution spectrophotometrically [10].

3.3. **The Ferric Reducing Antioxidant Power (FRAP) Assay** measures an antioxidant's power to donate electrons and its antioxidant potential by converting ferric ions (Fe^3+) to ferrous ions (Fe^2+) [11,12].

4. ANTIMICROBIAL ACTIVITY:

Copper oxide nanoparticles have strong antibacterial action against bacteria, fungi, and viruses, making them attractive options for the fight against infections that have developed resistance [13]. The following tests are used to gauge antimicrobial activity:

4.1. **The Inhibitory Zone Assay**: Agar Diffusion Method- This technique gauges the diameter of the clear zone encircling wells or discs coated with nanoparticles on agar plates that have been infected with microbial cultures. Increased antibiotic potency against susceptible organisms is shown by larger zones of inhibition [14].

4.2. **Time-Kill Kinetics Assay**: Dynamic Assessment of Microbial Viability- Tracks alterations in microbial colony-forming units (CFU) once they've been exposed to formulations of nanoparticles over time. The pace and degree of microbial growth inhibition or eradication are shown by time-kill curves, which show the kinetics of antimicrobial action [15].

4.3. **Cytoplasmic Leakage and Protein Leakage Analysis**: Evaluates the disruption of microbial cell membrane integrity following exposure to nanoparticle formulations. The extent of intracellular content release, such as nucleotides, proteins, or ions, is quantified to assess membrane damage. Elevated levels of leaked cytoplasmic materials indicate effective nanoparticle-induced lysis or permeabilization of microbial cells, serving as a mechanistic insight into their antimicrobial efficacy [16].

4.3. Assays for Biofilm Inhibition and Eradication [16]:

- **The Crystal Violet Staining Assay** measures the biomass of biofilms by using crystal violet dye to stain adhering microbial cells. By evaluating the optical density or fluorescence intensity of stained biofilms, nanoparticles are shown to either prevent the creation of new biofilms or eliminate existing ones.
- **Confocal Laser Scanning Microscopy (CLSM):** Utilizing fluorescent stains (e.g., SYTO 9, propidium iodide) to visualize biofilm architecture and vitality, CLSM evaluates the penetration and antibacterial activity of nanoparticles inside biofilms.

5. WOUND HEALING PROPERTY OF COPPER NANOPARTICLES:

Multifunctional effects of copper oxide nanoparticles include improved angiogenesis, extracellular matrix formation, cell proliferation, and regulation of inflammatory responses, all of which aid in the healing processes of wounds. A range of in vitro and in vivo experiments are utilized to assess the ability of copper nanoparticle formulations to promote wound healing [17].

5.1. In Vitro Tests [17]: In vitro studies provide controlled testing in a laboratory setting and offer initial insights into the processes behind nanoparticle-mediated wound healing:

- Cell viability and proliferation assays: Use assays like MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) and BrdU (5-bromo-2'-deoxyuridine) incorporation to evaluate the cytotoxicity and proliferative effects of nanoparticles on pertinent cell types (fibroblasts, keratinocytes, etc.).
- Migration Assays: Employ methods such as scratch wound healing assays and transwell migration assays to assess how well nanoparticles can promote cell migration, an essential stage in wound closure.
- Angiogenesis tests: Endothelial cell tube creation tests, which mimic capillary-like structures and assess vascular network development crucial for wound healing, are used to evaluate the pro-angiogenic effects of nanoparticles.

5.2. In Vivo studies [18]:

By mimicking physiological circumstances and intricate tissue interactions, animal models offer a more thorough assessment of copper nanoparticle efficiency in wound healing:

• Incisional or Excisional Wound Models: To assess the impact of copper nanoparticle therapies on wound closure rate, epithelialization, and scar formation, create standardized wounds on animal skin (e.g., rats).

• Full-Thickness Wound Models: Create deeper, dermis-piercing wounds to evaluate how well nanoparticles encourage tissue regeneration and wound contraction.

• Histological Analysis: Collagen deposition, re-epithelialization, and inflammatory cell infiltration are evaluated in wound tissues by staining them with hematoxylin and eosin (H&E) and Masson's trichrome.

6. TOXICOLOGY OF COPPER NANOPARTICLES:

To ensure the clinical application of copper oxide nanoparticle formulations and minimize possible side effects, it is imperative to evaluate their safety and toxicological profiles. Comprehensive toxicological assessments evaluate the

interactions of copper oxide nanoparticles with biological systems and their systemic consequences using a variety of in vitro and in vivo research [19,20,21].

5.3. In Vitro Hazard Evaluation [19]:Using pertinent cell models, in vitro investigations assess the cytotoxicity, genotoxicity, and cellular responses generated by nanoparticles:

5.4. • Cell Viability Assays: Determine the cytotoxic effects by measuring the integrity of the cell membrane and metabolic activity using assays like Embryonic toxicology assay, LDH (lactate dehydrogenase) release tests.
• Genotoxicity tests: Evaluate the damage caused by nanoparticles to DNA by employing toxicology in fibroblast cell line assay, comet tests, micronucleus assays, and γH2AX staining to identify chromosomal abnormalities and breaks in DNA strands.

5.5. Inflammatory Responses: Assess the degree of inflammation caused by nanoparticles by monitoring the production of cytokines (like TNF-α and IL-6), as well as the activation of inflammatory pathways (like NF-κB), in the appropriate cell types.

5.6. Oxidative Stress [21]: Measure the formation of reactive oxygen species (ROS) and the activity of antioxidant enzymes (e.g., SOD, CAT) to evaluate the reactions to nanoparticle-induced oxidative stress.

7. ANTI INFLAMMATORY PROPERTY:

Numerous illnesses, such as cancer, cardiovascular disease, and autoimmune disorders are linked to chronic inflammation. The potential of tailored administration of anti-inflammatory medicines in nanoparticle formulations to modify and reduce inflammation is being studied. To evaluate the anti-inflammatory properties of copper oxide nanoparticles, various tests are utilized[22].

7.1. Assays conducted in vitro [22,23]: Egg Albumin Denaturation Assay: This assay evaluates the anti-inflammatory potential of nanoparticles by measuring their ability to inhibit heat-induced denaturation of egg albumin, a process linked to protein aggregation and inflammation. The degree of inhibition is indicative of the sample's capability to stabilize proteins under stress, mimicking anti-inflammatory effects in biological systems.

Bovine Serum Albumin (BSA) Denaturation Assay: Similar to egg albumin, this assay tests the ability of nanoparticles to prevent heat-induced denaturation of BSA, a standard protein used in biochemical assays. Inhibition of denaturation reflects the nanoparticles' potential to interfere with the inflammatory cascade by preserving protein structure under physiological stress.

Membrane Stabilization Assay: This assay assesses the capacity of nanoparticles to stabilize erythrocyte (red blood cell) membranes exposed to hypotonic or heat-induced lysis. Since lysosomal membrane stabilization is a key mechanism in anti-inflammatory action, protection of red cell membranes serves as an indicator of anti-inflammatory potential Inflammatory effects in biological systems.

7.2. Models in vivo [24,25]: Animal-Based Inflammation Models: Use animal models (mice, rats) to study autoimmune diseases (rheumatoid arthritis models) or acute or chronic inflammation caused by chemical irritants (carrageenan, lipopolysaccharide). Biomarker tests (e.g., ELISA, PCR) and histological examination of tissue samples are used to measure inflammatory markers and evaluate how well copper oxide nanoparticle formulations reduce tissue inflammation.

8. APPLICATION OF COPPER OXIDE NANOPARTICLES IN OMFS:

Copper oxide nanoparticles (CuO NPs) have shown promising applications in the field of oral and maxillofacial surgery (OMFS) due to their antimicrobial properties, biocompatibility, and ability to promote tissue regeneration.

8.1. Wound Healing: CuO NPs have been observed to promote wound healing by enhancing fibroblast proliferation and collagen synthesis. Their ability to combat bacterial infections while supporting tissue regeneration makes them valuable for post-operative wound care in maxillofacial surgery (28).

8.2. Antibacterial Applications: CuO NPs have shown enhanced antimicrobial activity, reducing the risk of surgical site infections (SSIs) post-surgery. These nanoparticles are particularly useful in oral surgeries where the risk of infection is high due to the presence of diverse oral microflora (27).

8.3. Antiviral Applications: Given the high prevalence of viral infections in the oral cavity (e.g., herpes simplex virus), CuO NPs are being explored for antiviral coatings on dental instruments and prosthetics. Their antiviral properties can help in maintaining sterility and reducing cross-contamination during surgical procedures (33).

8.4. Oral Biofilm Management: CuO NPs can be integrated into oral hygiene products like mouthwashes, toothpaste, and gels to inhibit biofilm formation. This property is particularly beneficial in maintaining oral hygiene after maxillofacial surgery, where the presence of biofilms can delay healing and complicate outcomes (34).

8.5. Coatings for Implants: CuO NPs can be applied as coatings on dental implants and surgical plates to prevent bacterial colonization and biofilm formation, which are common causes of implant failures. Their broad-spectrum antimicrobial properties help in reducing infections and promoting successful implant integration (26).

8.6. Drug Delivery Systems: CuO NPs can be used as carriers for localized drug delivery, providing controlled release of antibiotics, anti-inflammatory agents, or growth factors. This application is particularly useful in reducing the systemic side effects of medications while enhancing local therapeutic effects during oral surgery (30).

8.7. Cancer Therapy (Oral Cancer): CuO NPs exhibit cytotoxic properties against cancer cells, and they have been studied for their potential in oral cancer treatment. They can be engineered to selectively target and kill cancer cells, thus offering a new approach to treating oral malignancies with minimal side effects (31).

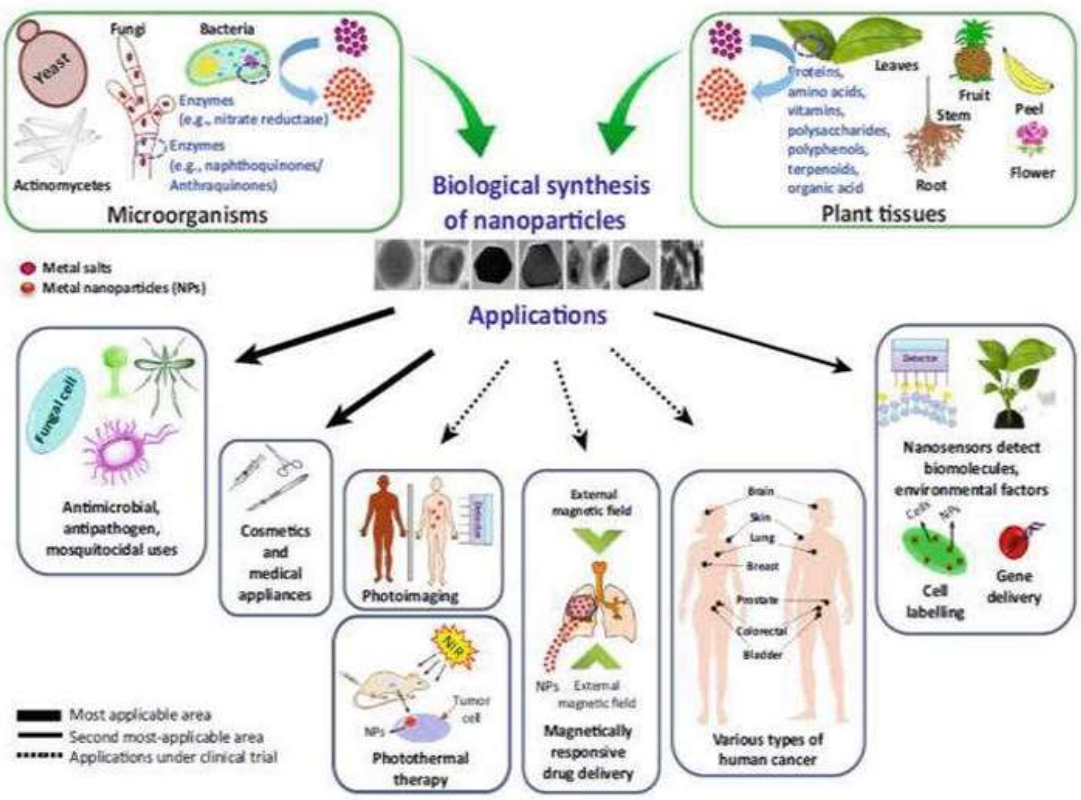
8.8. Photothermal Therapy: In combination with infrared light, CuO NPs can be used for photothermal therapy (PTT), where they generate heat that can selectively destroy diseased tissues, such as tumors or hyperplastic tissues, in the oral cavity. This non-invasive treatment method is gaining interest for its precision and minimal damage to surrounding healthy tissues (32).

8.9. Bone Tissue Engineering: CuO NPs can be incorporated into scaffolds for bone regeneration. They aid in the osteogenic differentiation of stem cells, making them useful for bone defects and fractures commonly treated in maxillofacial surgery. Their presence also promotes angiogenesis, crucial for bone healing (29).

8.10. 3D-Printed Scaffolds for Maxillofacial Reconstruction: CuO NPs can be embedded into 3D-printed scaffolds used for maxillofacial reconstruction. These scaffolds not only provide structural support but also have antimicrobial and osteogenic properties, aiding in the recovery of bone and soft tissues after extensive surgical procedures (35).

These applications demonstrate the versatile role of CuO NPs in enhancing surgical outcomes, improving healing, and addressing common challenges in oral and maxillofacial surgery.

FIGURE 2: Depicts biosynthesis and application of nanoparticles



9. CONCLUSION

Investigating the potential of copper oxide nanoparticles made from herbal preparations for a range of biological uses, such as wound healing, antibacterial, anti-inflammatory, and antioxidant capabilities, has shown promise. In addition to

guaranteeing biocompatibility and environmental sustainability, the green synthesis of these copper oxidenanoparticles makes use of the natural bioactive qualities of the herbal sources.

In conclusion, new opportunities for the development of multifunctional medicinal agents are created by the incorporation of herbal extracts into the nanoparticle production process. These nanoparticles combine effectiveness with less negative impacts on the environment and side effects, making them a viable substitute for traditional therapies. To completely achieve the therapeutic potential of these innovative nanomaterials, future research should concentrate on refining the synthesis procedures, comprehending the molecular pathways, and carrying out extensive in vivo investigations

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