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Nature-Inspired Synthesis of Copper Nanoparticles for Oncological Applications and Characterization – A Review

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ABSTRACT

Copper nanoparticles (CuNPs) have recently been of great interest because of their unique properties and versatility in applications across various industries, especially in medicine and dentistry. High surface-area-to-volume ratios, bio-physio-chemical functionalization, and antimicrobial and therapeutic capabilities make them effective in various biomedical applications, such as dental materials, wound healing, and cancer treatment. Recent developments in the approach of the green synthesis using extracts of plants and microorganisms have shown significant improvement toward ecofriendliness, biocompatibility, and enhancement of CuNPs functionalities, alleviating concerns about their sustainability and safety. CuNPs has shown promising anticancer effects through various mechanisms like ROS production, mitochondrial disruption, and inhibition of signaling pathways. They also provide tremendous action against microbial resistance and stimulate rapid healing of chronic wounds because of angiogenesis and tissue repair. Multifunctional hydrogels and functionalized scaffolds are the other innovative developments that emphasize the antioxidative, anti-inflammatory, and antibacterial properties of CuNPs. This review focuses on the properties, synthesis, and therapeutic applications of CuNPs, which have a potential to overcome global health challenges and transform clinical and industrial practices

Keywords: *Copper, Nanoparticles, Anticancer, Therapeutic.*

1. INTRODUCTION

Copper nanoparticles, or CuNPs, have lately gained attention due to their impressive properties and versatility in different industries, including medicine and dentistry. Copper is naturally available and inexpensive and is known as an antimicrobial compound and has therapeutic uses. [1] With all recent advancements in nanotechnology, copper nanoparticles became to be considered as versatile material with characteristic traits like high surface-area-to-volume ratios, enhanced bio-physio-chemical functionalization as well as shape-dependent property. All these attributes make CuNPs particularly effective within any biomedical and clinical area. [2]CuNPs have been added in various dental materials like dental amalgams, restorative cements, adhesives, resins, endodontic-irrigation solutions, and orthodontic devices for enhanced physical and chemical properties of the dental materials. [3]The antimicrobial effect of CuNPs helps control the growth of oral pathogens, thereby enhancing the shelf life and efficiency of the dental materials. Furthermore, it is also known for its role in wound healing, especially chronic wounds. Copper nanoparticles have been found to induce angiogenesis, regenerate skin, and heal faster by inducing the expression of vascular endothelial growth factor (VEGF) and hypoxia-induced factor-1-alpha (HIF-1α), making it very useful in wound dressing applications.[4]

More recently, CuNPs are explored in the treatment of cancer, utilising the different copper metabolism occurring within the malignant cells as a mode of targeted oncotherapeutic treatment. The unique ability of CuNPs to influence cellular processes such as oxidation, protein regulation, and inflammation further underscores their potential in treating drug-resistant cancer cells.[5] The growing body of research also emphasizes the role of CuNPs in combating microbial resistance, particularly in the context of bacterial and fungal infections, where they disrupt cell membranes, accumulate ions, and induce DNA damage.[6] A significant advantage of copper nanoparticles lies in their biogenic synthesis, which utilizes environmentally friendly plant extracts or microorganisms as reducing and stabilizing agents. This environmentally friendly synthesis pathway has gained much attention owing to its eco-friendliness, low toxicity, and cost-effectiveness compared with the traditional chemical synthesis route.[7] Bioactive compounds of various medicinal plants that help synthesize copper nanoparticles with improved biocompatibility and functionalities are used. The research is in line with the current trend of eco-friendly and sustainable materials in the pharmaceutical and medical industries. [8,9,10]

Green synthesis of nanoparticles (NPs) has recently been projected as highly sustainable and eco-friendly with the use of plants, fungi, bacteria, and algae as biological resources in the production of various nanoparticles.[11] Environmentally friendly, it does not use toxic chemicals typically used in conventional methods of synthesis. The biological agents used in green synthesis offer several advantages: low toxicity, cost-effectiveness, and tailor-made nanoparticles toward special applications.[12] Natural extracts rich in bioactive compounds serve as reducing as well as stabilizing agents for efficient and rapid inorganic nanoparticle formation, such as selenium, silver, carbon, iron oxide, and others. The use of plant extracts, fungi, and microorganisms ensures the sustainability of the process while increasing the biocompatibility and functional properties of the synthesized nanoparticles.[13] Green-synthesized nanoparticles have gained much attention in all fields, especially in medicine, where their antimicrobial, anticancer, anti-inflammatory, antioxidant, and antiviral properties are being explored. In recent times, interest in these nanoparticles has been observed due to their potential in solving some of the world's major health issues, such as antimicrobial resistance and chronic diseases, including cancer and inflammation. In biomedicine, for instance, nanoparticles synthesized through green synthesis are used in wound healing, drug delivery, and prevention and treatment as agents. The natural synthesis methods also provide control over the size, shape, and surface charge of nanoparticles that play an important role for its applications. [14,15]

This review comprises properties, synthesis, and applications of copper nanoparticles (CuNPs) with special reference to biogenic synthesis employing natural sources such as plant extracts, fungi, and microorganisms. It provides an integrated overview of current research in CuNPs, with emphasis on their potential in various applications, such as antimicrobial agents, wound healing, and cancer therapy. The discussion also focuses on the environmental and health benefits of green synthesis, which emphasize sustainability, safety, and efficacy. In addition, this paper also assesses the challenges and prospects concerning the use of CuNPs in clinics and industries, particularly in biomedicine, in its current significance towards medical and dental uses. Therefore, eco-friendly synthesis approaches enhance sustainability, efficiency, and safety of nanoparticles to be used in therapeutic and industrial use.

2. METHODS FOR COPPER NANOPARTICLES SYNTHESIS

Cu-NPs have attracted enormous attention due to their multiple features like high electrical conductivity, catalytic activity, and even antimicrobial effects.[16] There are several methods that can be used to synthesize Cu-NPs. The approach selected depends on the size, shape, and application of the nanoparticles to be obtained. These methods have broadly been categorized into three major approaches: physical, chemical, and biological approaches.[17]

The physical method methods include laser ablation, PVD, and electron beam lithography. Laser ablation is the process that breaks down a copper target using a laser in a liquid medium to create nanoparticles.[18] PVD is done through the vaporization of copper in a vacuum, whereby the vapor condenses on the surface. Electron beam lithography is used to produce patterned nanoparticles. These methods, although possible with exact control over size and shape, are often too expensive for mass production. [19] The most common method is chemical reduction: in which copper salts such as copper acetate or copper sulfate are reduced by various reducing agents such as sodium borohydride or hydrazine. This process can be easily scaled up, making it suitable for large-scale production, but it may involve toxic chemicals. Other chemical methods include the sol-gel process, microwave-assisted synthesis, and hydrothermal methods. These approaches allow for precise control over the nanoparticles' size and structure but often require high temperatures or pressures.[20] Green synthesis of Cu-NPs using plant extracts has gained popularity due to its eco-friendly nature and simplicity. Phytochemicals in plant extracts, such as polyphenols, flavonoids, and proteins, act as reducing and stabilizing agents, leading to formation of nanoparticles. This method is inexpensive, green, and easily scalable but can have optimization to control the size and stability of the particles. Microbial synthesis by bacteria, fungi, or algae is another biological approach, with the advantages again being environmentally benign production, but the rates are usually slow compared to chemical methods. [21]

Many approaches of synthesizing CuONPs have been reported by various researchers. These include ultrasound irradiation hydrothermal, biosynthesis approaches, electron beam lithography, solid-state reaction, sol-gel, template methods using surfactants, microwave-assisted protocol, decomposition of copper acetate and sonochemical synthesis. It has also been depicted that the synthesis method of CuONPs impacts their morphology properties and toxicity behavior[22]. The green approach for CuONPs synthesized from the use of plant extract as a source of generating electrons to reduce the copper salt exhibits some benefits over microbe use in that this method does not involve the expensive culture of cells and, thus can be scaled for mass production[23]. The CuONPs preparation occurs with a noticeable variation in color of the extracts after the addition of a copper salt. Many studies have shown that the phytochemicals in the plant extracts first form complexes with the iron salts and then reduce the ions to form nanoparticles. The biomolecules in the plants extracts usually react with copper ion to cause reduction which subsequently transform into CuONPs. [24]

3. GREEN SYNTHESIS OF COPPER NANOPARTICLES

The term green synthesis of copper nanoparticles, or CuNPs, refers to an environmentally friendly approach to reducing copper salts into nanoparticles utilizing plant extracts, microorganisms, or other biological materials. It is rapidly gaining popularity because it is simple, less expensive, and most importantly, more environmental-friendly than the traditional chemical synthesis, which normally contains toxic reagents.

In recent decades, it has attracted much interest in green nanotechnology for the synthesis of metallic nanoparticles due to their cost-effectiveness, simple steps of preparation, and environmentally friendly nature. In the present research work, CuO NPs were synthesized using Parthenium hysterophorus whole plant aqueous extract as reducing, stabilizing, and capping agent. [25] The present discussion is related to the synthesis of CuO NPs using the aqueous extract of Morinda citrifolia as a stabilizing agent. The synthesized CuO NPs were found highly stable, spherical and particles size from 20 to 50 nm. [26] Furthermore, the as-formed CuO NPs have also revealed strong antibacterial activity against the Gram-positive bacteria Bacillus subtilis, and Staphylococcus aureus, and Gram-negative bacteria Escherichia coli. The CuO NPs revealed similar trend was analyzed for antifungal activity. This paper documents a simple and eco-friendly procedure for the synthesis of bimetallic nanoparticles, zinc oxide along with copper oxide using Sambucus nigra L. extract. The findings have shown that polygonal ZnO NPs of hexagonal phase and spherical CuO NPs of monoclinic phase are present in the NPs. [26] The synthesized bimetallic NPs have been checked for anticancer activity in terms of MTT assay against lung and human melanoma cell lines. Recently, the utilization of green methods of nanoparticles by plant extracts has increased. In the last decades, CuO NPs have been widely applied in various fields. Preparation of CuO NPs in the aqueous extract of Morinda citrifolia as stabilizing agent is reported here in this paper. Leaf extract of Morinda citrifolia mixed with a solution of copper sulphate ($CuSO_4 \cdot 5H_2O$) and sodium hydroxide as a catalyst.[27]

4. CHARACTERIZATION OF COPPER NANOPARTICLES CU NPS

The characterization of copper nanoparticles CuNPs is important for knowing the size, shape, structure, and surface properties, which directly impact their functionality and potential applications.

Several techniques are commonly used for CuNP characterization. UV-Vis spectroscopy is often the first step, confirming the formation of CuNPs by detecting the surface plasmon resonance (SPR) peak, usually around 560 nm for copper nanoparticles, indicating successful reduction of copper ions. SEM and TEM are very informative for the morphology and size of nanoparticles, showing spherical or irregular shapes and size distributions. [21] The crystal structure of CuNPs can be confirmed by XRD; purity and crystallinity are thus assured. Fourier transform infrared spectroscopy (FTIR) identifies the functional groups existing in the biomolecules that act as a capping agent, and it helps stabilize the nanoparticles. Energy dispersive X-ray (EDX) analysis correlates these techniques, providing the elemental compositions and confirming the existence of copper in the nanoparticles. These characterization methods together provide ample understanding of CuNPs, which are necessary to apply them in diverse fields such as catalysis, medicine, and environmental remediation. Copper oxide nanoparticles (CuO NPs) were synthesized by using Parthenium hysterophorus whole plant aqueous extract as a reducing, stabilizing, and capping agent. [25]

UV–Vis Spectroscopy, Fourier Transform Infrared Spectroscopy (FTIR), powder X-Ray Diffraction (XRD), Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), and Dynamic Light Scattering (DLS) were applied for characterizing the CuO NPs. Surface plasmonic resonance bands were at 340 nm for CuO NPs. FTIR analysis demonstrated that there is the presence of secondary metabolites on the surface of CuO NPs. The characteristic band of Cu–O stretching was identified at 522 cm^{-1}. Scanning electron micrographs and transmission electron micrographs showed that CuO NPs were nearly spherical; an average particle of 59.99 nm is obtained from the SEM micrograph. The monoclinic crystalline structure of CuO NPs was confirmed through XRD and the calculated size of crystallite by using the Scherrer-Debye equation is 31.58 nm.[25] The article shows the synthesis of CuO NPs by using the aqueous extract of Morinda citrifolia as stabilizer.[26] Leaf extract of Morinda citrifolia was mixed with the solution of copper sulphate ($CuSO_4 \cdot 5H_2O$) along with sodium hydroxide as catalyst. UV–visible spectroscopy, FTIR, XRD, SEM, TEM, and EDAX analysis have been carried out to analyze the synthesized CuO NPs. The particle size distribution of the synthesized CuO NPs was measured with dynamic light scattering. The CuO NPs synthesized were highly stable, sphere-like, and have size of particles from 20 to 50 nm.[27]

5. THERAPEUTIC POTENTIAL OF COPPER NANOPARTICLES

Due to these properties like biocompatibility at high levels, antioxidant activity, and good efficacy of the particles as antimicrobials, CuNPs have tremendous scope in therapeutics. They are good scavengers for reactive oxygen species, with values for the management of oxidative stress-related disorders. Moreover, their antibacterial and antifungal efficacies are very potent. They could be used in infections mediated by drug-resistant microbial strains. CuNPs also have potential in anticancer activity since they induce apoptosis and inhibit proliferation of cells. They are applied in wound healing as they assist in regenerative cell repair without causing infection. For drug delivery applications, CuNPs enhance the bioavailability of drug agents while managing targeted release to a specific location without inducing side effects. Because of their anti-inflammatory property, they find an application in chronic inflammatory disease. The natural origin of plant-extract-derived CuNPs ensures decreased toxicity and meets the growing demand for green therapeutic solutions.

The various key properties of Nano Cu are enlisted in the subsequent sections, and they are also enumerated in the table (Table 1).

Table 1. Properties and Biomedical Applications of Plant-Extract-Derived Copper Nanoparticles

Sl. No	Plant extract	Properties of copper nanoparticles	Biomedical Application	References
1	Millettia pinnata (*Millettia pinnata (L.) Panigrahi*) flower extract	These nanoparticles effectively inhibited the growth of a variety of microbial pathogens, including bacteria and fungi, making them useful for infection control	Antimicrobial, Antioxidant, And Anticancer Properties	[28]
2	Magnolia kobus leaf extract	The size of the nanoparticles was crucial for their therapeutic efficacy, and they were shown to be stable and non-toxic. These CuNPs can also serve in targeted drug delivery systems.	Antimicrobial And Anticancer Activities.	[29]
3	Eucalyptus (Eucalyptus spp.) leaf extract	the extract also enhanced the stability of CuNPs, reducing their aggregation. Their high antioxidant activity was linked to the phenolic compounds present in the extract.	Antibacterial, Antifungal, And Anticancer Properties	[30]
4	**Azadirachta indica** (Neem) leaf extract	The biocompatibility and eco-friendly synthesis make these CuNPs ideal candidates for drug delivery and wound healing applications.	Anticancer And Antimicrobial Effects	[31]
5	Lawsonia inermis (Henna) leaf extract	These CuNPs were also used in cancer therapy and wound healing due to their excellent biocompatibility and therapeutic potential.	Antimicrobial And Antioxidant Properties	[32]
6	**Coriandrum sativum** (Coriander) leaf extract	CuNPs from *Coriandrum sativum* leaf extract demonstrated strong antimicrobial activity and antioxidant properties, which	Antimicrobial Activity And Antioxidant Properties	[33]

		are valuable in pharmaceutical and food preservation applications.		
7	**Citrus limon** (Lemon)	These nanoparticles were also evaluated for their anticancer potential, particularly against liver cancer cells, and displayed significant cytotoxic effects.	Antimicrobial And Antioxidant Activities	[34]
8	Allium sativum (garlic)	The garlic extract contributed to the reduction of copper ions and enhanced the biological activities of the nanoparticles.	Antibacterial, Antifungal, And Anticancer Activities	[35]
9	Bacopa monnieri (Brahmi) leaf extract	These nanoparticles are explored for neuroprotective applications, and their potential in treating neurodegenerative diseases is under investigation.	Antioxidant And Anti-Inflammatory Properties	[36]
10	**Salvia rosmarinus** (Rosmarinus officinalis) leaf extract	Their potential in treating bacterial infections and in cancer therapy is supported by their stability and biocompatibility.	Antioxidant, Antimicrobial, And Anticancer Activities.	[37]

Table 2. Mechanisms of copper nanoparticles in Targeting Various Cancer Cell Types

Type Of Cancer Cell	**Mechanism**	**Effects**	**References**
Liver Cancer	CuO nanoparticles modulate gene expression in **HepG2 cells (**human liver cancer). They alter both **mRNA** and **small RNA (miRNA)** profiles, affecting pathways related to cell cycle, apoptosis, and oxidative stress.	Induced significant changes in gene expression linked to tumor suppression and stress responses. Highlighted potential toxic effects in a dose-dependent manner, which may limit therapeutic application or require careful dosing strategies.	[38]
Cervical Cancer	CuO nanoparticles derived from *Houttuynia cordata* act by inhibiting the **PI3K/AKT/mTOR signaling pathway,** which is crucial for cell proliferation, survival, and metabolism. This pathway's inhibition triggers apoptotic pathways in cervical cancer cells, leading to reduced tumor growth.	Significant attenuation of cervical cancer cell proliferation. Enhanced induction of apoptosis in cancer cells. Potential therapeutic application in targeting specific oncogenic pathways.	[39]
Breast Cancer	CuO nanoparticles synthesized using walnut shell extracts exert size-dependent anticancer	Effective against breast cell lines. Smaller nanoparticles showed higher cytotoxicity due to increased surface	[40]

	effects by: Inducing oxidative stress via ROS generation. Triggering apoptosis by disrupting mitochondrial membrane potential and activating caspase-dependent pathways.	area and ROS production. Demonstrated biocompatibility, making them suitable for green and sustainable cancer therapies.	
Brain Cancer	CuO nanoparticles target glioma cells through cytotoxic effects mediated by the production of **reactive oxygen species (ROS),** which leads to oxidative stress and DNA damage. These nanoparticles disrupt tumor cell homeostasis both ***in vitro*** and ***in vivo.***	Decreased viability of glioma cells in cell cultures. Inhibited tumor growth in glioma-bearing animal models. Highlighted as a promising agent for glioma therapy due to selective cytotoxicity.	[41]
Colorectal Cancer	CuO nanoparticles synthesized using walnut shell extracts exert size-dependent anticancer effects by: Inducing oxidative stress via ROS generation. Triggering apoptosis by disrupting mitochondrial membrane potential and activating caspase-dependent pathways.	Effective against colorectal cancer cell lines. Smaller nanoparticles showed higher cytotoxicity due to increased surface area and ROS production. Demonstrated biocompatibility, making them suitable for green and sustainable cancer therapies.	[40]

6. ANTIOXIDANT PROPERTIES

Copper nanoparticles (Cu NPs) have received much attention for their anticancer properties in the last few years. These nanoparticles primarily exert their action by enhancing ROS production, which finally causes oxidative stress, mitochondrial damage, and DNA damage in cancerous cells. For example, Tian et al., 2024 demonstrated that CuO nanoparticles are highly potent in the treatment of glioma through ROS-induced cytotoxicity and disrupting tumor cell homeostasis both in vitro and in vivo. In the same direction, Abdollahzadeh et al., 2024 demonstrated size-dependent anticancer effects of CuO nanoparticles synthesized using the green methods, such as walnut shell extracts, against human cancer cell lines namely, breast and colorectal cancer cells. These nanoparticles induced apoptosis through mitochondrial membrane potential disruption and caspase activation. Besides, Chen et al. (2021) also showed that CuO nanoparticles isolated from Houttuynia cordata suppressed the PI3K/AKT/mTOR signaling pathway, which is an important regulator of cell proliferation in cancer cells, thereby inhibiting cervical cancer cell growth. Taken collectively, these studies and their results clearly indicate the versatile potential of Cu NPs as potent anticancer agents based on mechanisms involving generation of oxidative stress, activation of an apoptotic pathway, and inhibition of various signaling pathways.

The mechanism of action of Cu NPs against several types of cancer is summarized in the table below (Table 2). The work presents a tissue-adhesive F127 hydrogel loaded with copper-selenide nanoparticles as a treatment for dry eye disease. CuSe NPs possess strong antioxidative properties through scavenging reactive oxygen species in the ocular environment. These nanoparticles protect tissues in the eyes from oxidative stress-induced damage by reducing inflammation and providing an environment that promotes tissue repair, which are key factors in the effective management of dry eye disease.[42] The effectiveness of a multifunctional photothermally responsive hydrogel for chronic diabetic wound healing is showcased. This hydrogel contains antioxidative agents that control the levels of ROS in the wound microenvironment. By reducing oxidative stress, the hydrogel not only accelerates tissue repair but also prevents excessive inflammation, ensuring a balanced healing process for chronic wounds.[43]

This paper focuses on collagen scaffolds functionalized with Cu^{2+}-chelated EGCG nanoparticles, which have strong antioxidative activity. The nanoparticles neutralize ROS, which reduces oxidative stress in the wound area. This action is complemented by their anti-inflammatory and antibacterial properties, which together enhance vascularization and facilitate rapid wound healing.[44]This research introduces Ir@Cu/Zn-MOF nanoparticles designed to sequentially regulate ROS levels in infected wound environments. The nanoparticles scavenge excess ROS to minimize oxidative damage and then create controlled levels of ROS for their antimicrobial activity. This ensures effective infection management and promotes wound healing while protecting the tissue from oxidative stress.[45]

7. CONCLUSION

Copper nanoparticles (CuNPs) are versatile materials with unique properties like high surface area and bio-physio-chemical functionalization, making them valuable in medicine for antimicrobial, anticancer, anti-inflammatory, and antioxidative applications. Green synthesis methods using natural resources enhance their sustainability and safety, reducing environmental and health risks. CuNPs show potential in cancer therapy, wound healing, and combating oxidative stress through mechanisms like ROS scavenging and apoptosis activation. Advances in nanotechnology, such as hydrogels and collagen scaffolds, have expanded their therapeutic applications, though challenges like toxicity and scalability require further research

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