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Biomedical applications of copper nanoparticles: An up-to-date overview

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A B S T R A C T

Copper nanoparticles (CuNPs) have garnered significant attention in biomedicine due to their various properties and potential applications. These nanoparticles exhibit promising antimicrobial, anticancer, and antioxidant activities, which enhance their value in nanomedicine applications. Their properties, shaped by the fabrication techniques, facilitate their application in drug delivery, cancer therapy, tissue engineering, and dental applications uses. Nevertheless, obstacles persist in attaining biocompatibility and regulated release, which are vital for effective clinical transference. Toxicological evaluations are essential to ensure the secure utilization of CuNPs. Additionally, studies are ongoing to find creative solutions to address these challenges and fully harness the medical potential of CuNPs.

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1. Introduction

When nanotechnology first emerged, it transformed several industries, most notably healthcare, where the unique properties of nanoparticles were utilized in innovative ways [1-3]. Copper nanoparticles (CuNPs) have attracted significant attention due to their numerous applications in drug delivery, wound healing, cancer treatment [4].

CuNPs is an excellent choice for various biomedical applications because of its intrinsic qualities, including biocompatibility and antibacterial effectiveness [5]. As antibiotic resistance becomes an increasing concern, recent studies have demonstrated that CuNPs exhibit potent antibacterial activity against various pathogens, including bacteria and fungi [6, 7]. Among these, the synthesis of copper nanoparticles has evolved, with green synthesis methods gaining popularity for being cost-effective and environmentally sustainable [8]. Producing CuNPs using plant extracts preserves their therapeutic biocompatibility, making them suitable for medical applications [9]. CuNPs are superior to conventional antibacterial agents due to their large surface area-to-volume ratio, enhancing their reactivity and antimicrobial effectiveness [10].

CuNPs have been investigated for their potential use in tissue engineering and regenerative medicine and their antibacterial qualities. CuNPs may aid tissue regeneration and repair because they stimulate angiogenesis and improve wound healing processes [11]. CuNPs may be added to biomaterials for implants and prostheses to increase their functional performance and biocompatibility, which would benefit patients [12]. Furthermore, CuNPs' adaptability goes beyond only their antibacterial qualities. They have been investigated for use in biosensing technologies, where their localized surface plasmon resonance (SPR) may be adjusted to detect different biomolecules with greater sensitivity and specificity [13, 14]. As research continues to disclose the numerous possibilities of copper nanoparticles in biomedicine, it is vital to solve the problems connected with their utilization. To guarantee the safe and efficient use of CuNPs in clinical settings, issues with toxicity, environmental impact, and the requirement for standardized synthesis processes must be carefully considered [12].

A comprehensive understanding of copper's toxicity mechanisms and cell-affecting effects is essential, given the metal's recent widespread use and research. This study aims to provide a comprehensive overview of the state of copper nanoparticle research, focusing on potential future directions and biological applications.

2. Synthesis and properties copper nanoparticles

Several methods exist to create copper nanoparticles, including physical, chemical, and green synthesis techniques. The following sections will cover all of these methods. Methods and properties of CuNPs is shown in Table 1.

2.1. Physical methods

Physical getting techniques are less common than chemical or environmentally friendly procedures due to their drawbacks, which include the need for costly equipment and considerable energy consumption [15].

The reduction of metal ions in solution (chemical reduction method) is the primary chemical technique for creating metal nanoparticles due to its ease of usage [16]. Because it is easy to use, has a high production efficiency, and requires little equipment, the chemical reduction technique is frequently employed to produce CuNPs. Chemical-reducing agents are used in chemical reduction, as the name suggests. There are several options for their production because this technique may be further categorized based on the energy source or reaction device [17].

The usage of hazardous compounds during the synthesis stage is one significant disadvantage. The development of environmentally friendly procedures is crucial, given the growing use of nanoparticles and their increased interaction with humans [18]. Surface-active microarrays formed by immiscible water-oil, oil-water, and water supercritical carbon dioxide are used in the microemulsion reduction process, also known as colloidal synthesis [19].

Ultrasonic waves with a frequency of around 20 kHz to 10 MHz are the basis of sonochemical reduction; acoustic cavitation, a physical phenomenon, drives the reaction [20]. Cu NPs may now be produced with consistent particle size and shape using hydrothermal treatment and microwaves [21]. The electromagnetic energy used in microwave technology has frequencies between 300 MHz and 300 GHz [22].

2.2. Chemical methods

Compared to chemical synthesis, physical synthesis produces nanoparticles with homogeneous distribution and no solvent contamination [23]. Unconventional physical procedures, including those requiring vacuum or plasma, can occasionally produce low-quality nanoparticles.

In order to remove or extract atoms from a bulk surface by emitting a laser beam, a number of physical approaches are used before or after a chemical process. For instance, laser ablation necessitates a colloidal solution, which reduces the possibility of oxidation on the nanoparticles' surface and must be put in a vacuum chamber. This method is not practical because of the intricacy of the apparatus and the high energy required for the laser [24].

Two crucial factors in determining the particle size are the duration of exposure and the quantity of laser beam pulses used. In contrast to previous physical methods, the ions are implanted on a solid substrate using a pulsed electrical current in the Pulsed Wire Discharge (PWD) process [25]. Physical getting techniques are less common than chemical or environmentally friendly procedures due to their drawbacks, which include the need for costly equipment and considerable energy consumption [26].

Table 1
Methods and properties of CuNPs.

Synthesis	Methods	Properties	Refs.
Chemical	Thermal decomposition	Production of stable nanoparticle and antibacterial activity	[44]
	Chemical reduction	Controlled size and morphology	[15]
	Microwave technique	Regular particle size and morphology	[21]
Physical	Evaporation–condensation	Small nanoparticles	[23]
	Laser beam	Complexity of the equipment	[24]
	Aerosol technique	Controlled size and morphology	[45]
Green synthesis	Plant and fruit extract mediated	Antimicrobial and antiviral activity	[46, 47]
	Bacterial and fungal-mediated	Antimicrobial, antioxidant, and cytotoxic activity	[48]
	Algal mediated	Economical, eco-friendly, energy-efficient and less-toxic	[49]

2.3. Green synthesis

Green synthesis is often used as a safe method for producing metallic nanoparticles. This technique utilizes reducing agent molecules present in microorganisms, such as fungi and bacteria, as well as in plants [27]. Compared to chemical synthesis, it is less expensive, simpler, faster, and more sustainable. It also uses more environmentally acceptable resources. Given the incredible difficulty in maintaining cell cultures, it is preferred to employ plant extracts rather than microorganisms to produce nanoparticles [28]. The biomolecules found in plants, including proteins, amino acids, vitamins, alkaloids, terpenoids, flavones, ketones, aldehydes, tannins, phenolics, saponins, and polysaccharides, are essential for the reduction of metals [29]. Plant biomass is utilized as an extract or as a powder. They are combined with the metal solution of choice. The steps of the synthesis are shown in Fig.1.

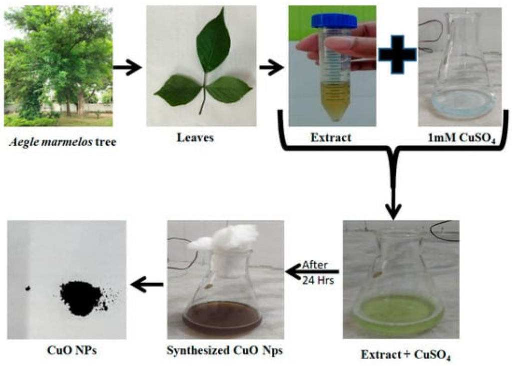

Fig. 1. Schematic illustration of the synthesis of CuNPs by plants [32].

Common precursor copper salts employed in the production of Cu NPs include copper (II) sulfate pentahydrate ($CuSO_4.5H_20$), cupric acetate (monohydrate) (CH_3COO) ($2Cu{\cdot}H_2O$), copper (II) nitrate (Cu $(NO_3)_2$), and others. Typically, the extract is combined with a metal salt solution at room temperature and the appropriate pH, either with or without stirring. The synthesis of NPs will be finished in a short period [30, 31]. Due to their high metal resistance and ease of handling, several fungi have been used for the biogenic production of copper nanoparticles. They produce a range of extracellular enzymes that are crucial to the manufacture of metallic nanoparticles. CuNPs were synthesized using Aspergillus niger because of its capacity to bioaccumulate metals. The common filamentous fungus A. niger has a range of enzymes, including hydrolytic and oxidative enzymes, that allow metal ions to be absorbed from aqueous solutions [33]. Algae are a varied collection of plants being investigated for potential use in nanotechnology. In addition to producing NPs, algae are being investigated for their nutritional value, ability to increase bio-diesel, and extensive potential for medicinal use. Compared to chemically manufactured silver nanoparticles, their documented antibacterial action against bacteria recovered from the sick silkworm was found to be more effective, and it is anticipated that they would be biocompatible [34].

3. Biomedical application of copper

Together with other metallic NPs like silver (Ag) [35] and gold (Au) [36], Cu nanoparticle may be used as appealing substitutes in nanomedicine because of their possible antiviral properties, low toxicity, antifungal and antibacterial activity, excellent biocompatibility, oxidation resistance, and better availability at cheaper prices [37]. Table 2 provides information on the characteristics and uses of copper nanoparticles.

3.1. Drug delivery systems

Effectively targeting tissues with therapeutic molecules remains one of the most significant challenges in drug discovery [38, 39]. Copper nanoparticles have gained popularity as drug delivery vehicles due to their vast surface area-to-volume ratio, changeable surface chemistry, and ability to encapsulate a wide range of medications [40]. Several methods, such as surface functionalization, encapsulation in polymeric matrices, and stimuli-responsive drug release procedures, have been used to construct CuNPs-based drug delivery systems [41].

Table 2
Properties, applications, and synthesis methods of copper nanoparticle.

Types of copper nanoparticles	Methods of synthesis	Properties	Applications	Ref.
CuNPs	Green synthesis (M. Oleifera leaves)	Improve anti-bacterial and anti-fungal activities	Treatment of various bacterial, and particularly, fungal infections	[62]
CuNPs	Green synthesis (Crataegus rose fruits)	The relevance of biosafety enhancing the antitumor	Cancer therapy	[63]
CuONPs	Green synthesis (Melia azedarach leaves)	Optimizing the uptake and increasing potential of gene therapy	Cancer therapy	[52]
CuNPs	Green synthesis (musa sapientum plant)	Better anti-inflammatory activity and less biotoxic	Anti-inflammatory	[64]
CuNPs	Chemical method	Development of antimicrobial agents	Drug delivery	[65]
CuNPs/NGO	Chemical method	Outstanding catalytic activity	Electrocatalytic activity	[14]
CuO/CuNps	Chemical method	Size reduction	Biosensor applications	[13]
CuO/AgNPs	Chemical method	Increasing the antibacterial effect up to six times	Treat infected wounds	[66]
CuNPs	Green synthesis (S. Didymobotrya methanolic root extract)	Better antimicrobial activity against E. Coli and S. Aureus	Antimicrobial activity	[67]
CuNPs	Chemical and Green synthesis	Cunps that are prepared using green synthesis have smaller nanoparticle size	Antimicrobial activity	[68]
CuO/NPs	Green synthesis	Excellent antifungal activity against C. Albicans	Antifungal activity	[69]
CuO/NPs	Chemical method	Acceptable antimicrobial effects against E. Faecalis, P. Aeruginosa, and C. Albicans	Tissue engineering	[59]
CuNPs	Green synthesis (black tea leaves	Antibacterial capabilities, environmentally friendly and cost-effective	Biomedical applications	[70]
CuNPs	Green synthesis (Nigella sativa seeds extract)	Less toxicity properties and antibacterial activity	Therapeutic applications	[71]
CuNPs	Green synthesis (ginger and garlic)	Antimicrobial properties	Anticancer activity	[72]
CuNPs with adhesive resin	Green synthesis	Antimicrobial properties	Dental adhesive	[73]

The surface functionalization of CuNPs with targeting ligands, such as peptides or antibodies, enables targeted cell attachment and recognition, increasing the efficacy of drug delivery [42]. According to Assadi et al. [43], CuNPs interacts with antibiotics and functions as a transporter of tetracycline, enhancing its accumulation in bacteria.

In a different study, Verma et al. [50] produced mupirocin-paired copper nanoparticles to overcome drug resistance in Staphylococcus aureus, which causes dermal skin infections. They found that a gel comprising Mupirocin and Cu NPs was more effective against S. aureus due to its sustained release than a pure drug.

Phull et al. [51] synthesized the CuO-Fu-NPs. MTT, TUNEL, and western blot tests showed that the CuO-Fu-NPs could influence apoptosis and growth signaling molecules and had anti-proliferative and genotoxic effects on the cancer cells. The study's findings highlight the importance of using naturally occurring compounds to increase the amount of organic and inorganic metallic nanoparticles in natural product medication development, which may have therapeutic benefits and anticancer drug delivery potential. The anticancer mechanism of the produced fucoidan-capped copper oxide nanoparticles is depicted in Fig.2.

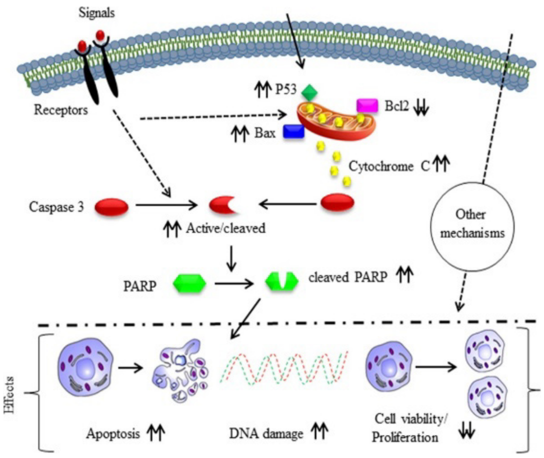

Fig. 2. Anticancer mechanism of the synthesized fucoidan-capped copper oxide nanoparticles (CuO-Fu-NPs) [51].

3.2. Cancer therapy

With their many advantages, such as drug stability, appropriate biodistribution, enhanced therapeutic index, and active agent delivery to the precise location (active or passive targeting), copper and copper oxide nanoparticles have attracted much interest in the biomedical domains [52, 53]. Copper-based nanomaterials (Hc-CuO NPs) were created by Chen et al. [54] and comprised of herbal extract of Houttuynia cordata (Hc) and copper oxide (II) nanoparticles, which range in size from 40 to 45 nm. By targeting PI3K/Akt (the phosphatidylinositol 3-kinase/protein kinase B) signaling pathways in cancer cells, the scientists demonstrated that Hc-CuO NPs suppressed the growth of cervical cancer in vitro by overproducing ROS and inducing death. Copper oxide (II) nanoparticles coated with fucoidan from Undaria pinnatifida algae showed genotoxic and antiproliferative effects on HeLa cells, according to Abdelhakm et al. [55].

A potent antibacterial effect is often produced by photothermal treatment, which is directly influenced by particle concentration and laser strength. In Tao et al. [56] study, methacrylate-modified gelatin was used to polymerize CuNPs drastically chelated with N, N-bis(acryloyl)-cystamine (BACA) CuNP proximity resulted in a localized surface plasmon with resonance at 808 nm, creating a three-dimensional network. Depending on the laser intensity and copper concentration, the CuNPs-hydrogel may raise the temperature by up to 40 degrees in 4 minutes at this wavelength. In a different study, Cabral et al. [57] showed that PL-based hydrogels with CuO NPs or GSNO had a good chance of killing cancer cells. This creates a new therapy option for skin cancer.

3.3. Tissue engineering

Their exceptional cost-effectiveness justifies the use of copper nanoparticles over other metal nanoparticles [58]. Because copper nanoparticles have antibacterial qualities, using them with fabric softeners is highly advantageous, especially considering the many drawbacks of different fabric softener additions [59]. Incorporating antimicrobial compounds into tissue conditioner structures has been the subject of several attempts. These additions include antibacterial nanoparticles, essential and herbal oils, and antibiotics [60].

Several shortcomings have been noted for the instances under investigation, even though some of these tissue conditioners exhibit encouraging effects against bacteria. The unstable nature of the components supplied to the tissue conditioner and its detrimental impact on its mechanical qualities are two examples of these flaws. There are currently no commercially available antimicrobial tissue conditioners, even though antimicrobial compounds benefit tissue conditioners [61].

Tissue conditioners using copper oxide nanoparticles shown respectable antibacterial activity against E. faecalis, P. aeruginosa, and C. albicans in a study by Nikanjam et al. [59].

3.4. Dental applications

CuNPs have bio-physiochemical and antibacterial qualities. They enhance the material pool to reduce the scarcity of dental materials for various clinical applications. Dental metals and alloys, dental cement, dental polymers and resins, and other dental materials are typically made with copper nanoparticles [10]. According to Gomez et al. [74], covering dental implant healing caps with copper nanoparticles prevented the growth of germs and biofilms. However, another study by Liu et al. [75] showed that an implant made of titanium alloy containing copper has anti-infective qualities against oral bacteria. Additionally, they showed that titanium–copper alloy was biocompatible and prevented peri-implant infections. Different research by Torres et al. [76] demonstrated that adding copper nanoparticles to an adhesive enhanced its antibacterial qualities and shear bond strength without causing cytotoxicity.

4. Future perspectives

The research on copper nanoparticles and copper-based nanomaterials has been less comprehensive than other metallic nanoparticles like gold, silver, or platinum [12]. Broad and reliable information on biokinetics and biodistribution is generally lacking, and much less is known about long-term persistence in the environment and body. A logical design of copper-based nanocomposites and nanostructured materials is anticipated to become more critical in several applications, such as topical therapy, antivirals, antimicrobial tissues and surfaces, and cancer. The studies included in this review emphasize that copper is only harmful when it is more than what the body can process. Substantial control over the quantity of copper injected or discharged is essential to reducing the negative consequences. In order to maintain an adequate amount of copper for effective antibacterial action while preventing an overload, slow-releasing NPs may be crucial [77]. On the other hand, difficulties and safety issues might be a significant worry. Another challenge is developing reproducible and scalable synthesis methods for producing copper nanoparticles in an ecologically responsible manner. Even though a number of green synthesis techniques have been reported in the literature, producing consistent nanoparticle sizes, shapes, and dispersibility remains highly challenging [78]. In conclusion, despite the tremendous progress made in the last few decades in comprehending how Cu surfaces and NPs affect microbes, there are still a lot of unresolved issues about their antimicrobial properties [79].

5. Conclusion

Research on CuNPs for biomedical applications shows their significant potential in various therapeutic fields, including wound healing, antibacterial treatments, and cancer therapies. In term of to current research, CuNPs have exceptional antibacterial qualities that enable them to fight various diseases successfully, making them valuable tools for infection control and preventative measures. The unique physicochemical properties of CuNPs facilitate the targeted and controlled release of therapeutic agents, improving treatment effectiveness while reducing systemic toxicity. Their potential as drug delivery vehicles is similarly intriguing. Even though copper nanoparticles have great promise for use in biomedicine, further study is needed to understand the safety and effectiveness concerns fully.

Author contributions

Negin Khosravi: Conceptualization, Writing—Original Draft Preparation; **Alaa Alzufairi**: Investigation, Writing – review & editing; **Parisa Zahed:** Conceptualization. Writing – original draft, Writing – review & editing; **Aliasghar Abouchenari:** Writing – original draft, Writing – review & editing; **Sohrab Asgaran**: Visualization, Writing—Original Draft Preparation; **Setareh Reza-Soltani**: Writing—Original Draft Preparation, Writing – review & editing; **Zahra Moazzami**: Writing—Original Draft Preparation, Writing – review & editing.

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Conflict of interest

The authors declare no conflict of interest.

Data availability

No data is available.

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