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Copper nanoparticles: Synthesis, characterization, and their applications in medicine

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Abstract

Copper nanoparticles (CuNPs) have emerged as versatile nanomaterials with significant biomedical potential owing to their unique optical, electrical, thermal, and catalytic properties. As an essential trace element, copper plays a pivotal role in various physiological processes, including metabolism, cardiovascular health, and tissue regeneration, making its nanoscale forms particularly relevant for medical applications. This review offers a thorough synthesis of existing research on CuNPs. Encompassing their preparation via chemical, physical, and biologically mediated (green) approaches, alongside detailed characterization techniques essential for correlating size, morphology, and surface chemistry with biological performance. Special emphasis is placed on their multifunctional roles in antimicrobial therapy, targeted drug delivery, cancer treatment, and imaging-guided diagnostics, as well as their integration into theranostic platforms. The toxicological profile of CuNPs, including their cellular interactions, generation of reactive oxygen species (ROS), and potential environmental impact, is critically discussed. Furthermore, the review outlines recent advances and future perspectives, highlighting the importance of precise synthesis control, advanced characterization, and rigorous safety evaluation to facilitate the safe and effective clinical translation of these technologies. This review aims to link synthesis strategies, physicochemical properties, and biomedical functionalities of CuNPs while identifying challenges and research priorities that can accelerate their translation from laboratory to clinical practice.

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Keywords: Copper nanoparticles; green synthesis; nanomedicine; antimicrobial activity; drug delivery; cancer therapy; toxicity assessment.

1. Introduction

Copper nanoparticles (CuNPs) have garnered persistent scientific interest as novel nanomaterials for extensive medical applications. Copper is a crucial trace metal integral to numerous metabolic processes, encompassing glucose, cholesterol, and iron metabolism, and is needed for cardiovascular function, lung elasticity, bone development, and red blood cell production. Excessive copper can result in hepatic damage and gastrointestinal complaints, while a shortage may significantly impair cardiovascular health, induce anemia, cause tissue damage, and result in skeletal anomalies [1], [2], [3], [4], [5].

Despite these hazards, the controlled application of copper nanomaterials holds significant promise in medicine, alongside a suite of other biomedical technologies. Copper-based nanostructures exhibit excellent effectiveness against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus*, *Bacillus subtilis*, *Proteus vulgaris*, and *Escherichia coli*, and often surpass the potency of silver nanoparticles. Consequently, copper nanostructures have been widely investigated to measure and optimize their properties for biomedical uses [6], [7], [8], [9].

This review aims to provide a comprehensive overview linking synthesis strategies, physicochemical properties, and biomedical applications of CuNPs, while critically addressing their toxicity and safety. It seeks to highlight current challenges, recent advances, and future research priorities that can accelerate their translation from laboratory research to safe and effective clinical use.

2. Synthesis of Copper Nanoparticles

Copper nanoparticles are a class of particles with diameters ranging from 1 to 100 nm. Various synthesis and stabilisation methods have been reported, yielding highly monodisperse copper nanoparticles with excellent morphology and tunable size, which have numerous applications spanning various industrial and biological processes [10], [11], [12], [13].

Several physical, chemical, and biological approaches have been used for their synthesis; however, these approaches have drawbacks such as high-energy requirements, high cost, and the use of toxic chemicals. To overcome the limitations of the physical and chemical methods, different biological methods have been employed for the synthesis of copper nanoparticles using plants to increase the antioxidant activity and control of the particle size in biomedical applications [14], [15], [16], [17], [18].

These methods are simple, non-toxic, eco-friendly, sustainable, biocompatible, and cost-effective. As such, copper nanoparticles have an important role in life medicine and diagnostics. Various chemical routes have been used for producing copper nanoparticles, including chemical reduction, microemulsions, and sonochemical synthesis. They have been produced from dimethyl copper $(\text{CH}_3)_2\text{Cu}$, copper hydrazine carboxylate, copper carbonyl clusters, metallic copper, and Cu (II) complexes as precursors. Copper nanopowders have been proven to manufacture high-density sintered compacts from metallic copper powders and have been used in fabricating copper nanotubes using the sacrificial template method [11], [19], [20], [21], [22].

Chemistry-informed techniques employed in the synthesis of nanoparticles include the sol-gel method, solvothermal technique, chemical vapor deposition, microemulsion, hydrothermal method, and chemical reduction [14], [23], [24].

Characterization techniques encompass UV-vis spectroscopy, Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), and dynamic light scattering (DLS). [12], [25], [26].

Chemical reduction is one of the most preferred techniques for the synthesis of copper nanoparticles, as it is simple and allows controlled manipulation of particle size [27], [28], [29].

Copper salt and polymers with a reducing agent are the primary materials required for synthesis; copper salts such as copper chloride, copper acetate, copper sulfate, copper nitrate, copper carbonate, and copper phosphate have been used, with copper sulfate being preferred [15], [30].

Polyvinylpyrrolidone (PVP), cetyltrimethylammonium bromide (CTAB), polyaniline (PAN), and polyethylene glycol (PEG) have been employed as polymers because of their ability to prevent aggregation of the nanoparticles [31], [32].

Sodium borohydride, L-ascorbic acid, hydrazine, sodium citrate, and sodium hypophosphite have been utilized as reducing agents.

A typical reaction proceeds with the reduction of Cu^{2+} ions to copper (0) nanoparticles, where the copper ions first hydrolyze to copper hydroxide in an aqueous solution, followed by the production of copper nanoparticles triggered by a reducing agent. Generally, to prevent rapid reaction and sedimentation, the process is carried out in ice-cold conditions and under an inert gas [11], [33], as illustrated in Figure 1.

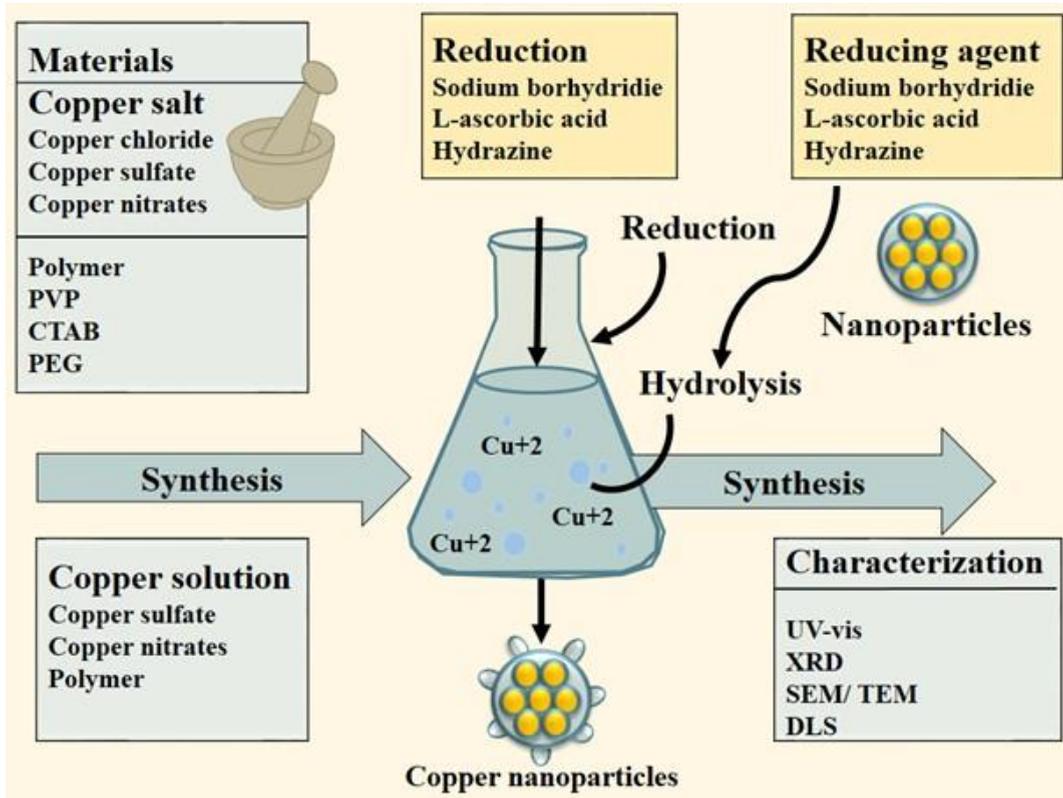


Fig 1. Chemical reduction process for CuNPs synthesis.

2.1. Chemical methods

Chemical methods involve commonly employed reduction techniques that use chemicals or reagents to convert copper ions into metallic copper nanoparticles. These methods achieve reduction through agents such as sodium ascorbate, elemental copper, sulfites, hydrazine, and sodium hypophosphite. The selection of the chemical reducer influences particle size, morphology, and distribution, along with concentrations of the metal precursor and stabilizer. Advantages include high efficiency, reproducibility, the synthesis of high-purity nanoparticles, cost-effectiveness, simplicity of methods, and scalability. The disadvantages include restricted production capacity, possible contamination from chemical residues, and an environmental impact resulting from toxic byproducts [14], [33], [34],

[35], [36], as summarized in Table 1.

Table 1. Summary of section 2.1. This table outlines key chemical reducing agents for CuNP synthesis, their mechanisms, typical particle sizes, and main pros and cons. Sodium ascorbate is eco-friendly with good size control but oxidation-prone; hydrazine yields ultra-small particles yet is highly toxic; sulfites are low-cost but risk sulfur contamination; sodium hypophosphite offers oxidation resistance, though may leave phosphorus residues; elemental copper avoids external reducers but lacks precise size control and is prone to oxidation.

Table 1. Overview of prevalent chemical techniques for the manufacture of copper nanoparticles (CuNPs) and their principal characteristics.

Chemical Reducing Agent	Reduction Mechanism	Typical Size & Shape	Advantages	Disadvantages
Sodium ascorbate	Electron donation converts Cu ²⁺ to Cu ⁰ in aqueous media	10–80 nm, mostly spherical	Eco-friendly, mild conditions, good size control	Oxidation-sensitive, requires alkaline medium
Hydrazine	Strong reduction causing very rapid nucleation	5–30 nm, uniform sizes with control	Fast production, very small sizes	Toxic and hazardous, nitrogenous residues
Sulfites	Moderate reduction via temporary Cu–sulfite complexes	20–100 nm, irregular shape	Low toxicity, inexpensive	Sulfur contamination, broader size distribution
Sodium hypophosphite	Reduction of Cu ²⁺ with a possible protective phosphate layer	10–70 nm, spherical	Good oxidation resistance, consistent production	Phosphorus residues may hinder some applications
Elemental copper	Displacement (cementation) or Cu ⁺ disproportionation	30–150 nm, mostly irregular	No major external reductant needed	Poor size control, prone to oxidation

2.2. Physical methods

Physical methods such as evaporation, condensation, and laser ablation also yield copper nanoparticles (CuNPs). Evaporation condensation utilizes a tube furnace where a copper source evaporates, diffuses, and condenses into nanoparticles in a controlled inert environment. Size is adjustable by changing reactor tube volume or inert gas pressure. Laser ablation employs concentrated infrared (IR) laser irradiation focused on a metallic target immersed in distilled water, creating nucleation sites and subsequently CuNPs at extended ablation times. While dispersion is better at a 2-mm laser spot size compared to 0.5 mm, the technique is reliable and does not generate harmful byproducts as it uses only water and a strong Nd: YAG laser [37], [38], [39], [40], as summarized in Table 2.

Table 2: Summary of section 2.2. Physical synthesis methods for CuNPs are devoid of chemicals and generally produce high-purity nanoparticles. Evaporation, condensation, and laser ablation offer superior control over particle purity; nonetheless, they exhibit limited scalability and significant energy requirements. Arc discharge facilitates quick production but compromises control over size distribution, whereas high-energy ball milling provides scalability at the cost of homogeneity and surface oxidation. Sputtering guarantees meticulous control and consistency, particularly for coatings or thin films; however, the technique is not ideal for extensive powder manufacturing. The selection is contingent upon the equilibrium among purity, size regulation, yield, and existing infrastructure.

Table 2. Comparison of prevalent physical techniques for synthesizing copper nanoparticles (CuNPs) and their principal characteristics.

Physical Method	Principle / Mechanism	Typical Size & Shape	Advantages	Disadvantages
Evaporation–Condensation	Copper is vaporized in a high-temperature furnace under inert gas, then condensed into nanoparticles	20–100 nm, spherical	High purity, adjustable size via gas pressure and tube volume, simple concept	High energy consumption, costly equipment, batch limitations
Laser Ablation (Nd: YAG)	High-energy IR laser pulses vaporize copper from a solid target in liquid, causing	10–80 nm, tunable by laser spot size/time	No chemical contamination, eco-friendly (water medium),	Low yield, expensive laser system, requires precise control for uniformity

	nanoparticle nucleation		high purity	
Arc Discharge	An electric arc between copper electrodes vaporizes material into plasma, followed by condensation	5–50 nm, various shapes depending on arc parameters	High production rate, crystalline particles	Requires high current, possible oxide formation, and less control over size distribution
High-Energy Ball Milling	Mechanical attrition reduces bulk copper into nanoscale particles via repeated collisions	20–200 nm, irregular	Scalable, no chemical waste, relatively low-cost equipment	Broad size distribution, possible contamination from milling media, oxidation risk
Sputtering (Physical Vapor Deposition)	Copper atoms ejected from a target by ion bombardment deposit on a substrate or in a collector medium	5–50 nm, uniform films or particles	High uniformity, controlled thickness/size, clean surfaces	Requires vacuum systems, limited yield for powders, and an expensive setup

2.3. Biological method

Copper nanoparticles (CuNPs) exhibit utility in areas such as catalysis, sensing, antimicrobial textiles, and inks for solar cells. Their excellent anticorrosion and electrical performance make them superior alternatives to gold and silver metal nanoparticles in electronics. A variety of physical, chemical, and biological methods have been established for the synthesis of CuNPs, with biological approaches frequently favored due to their low toxicity, cost-effectiveness, environmental sustainability, and accessibility [7], [20], [21], [41], [42].

Biological approaches, also termed "green synthesis" or "biosynthesis," utilize reducing agents such as microorganisms, enzymes, and plant extracts. In comparison with microbial routes, photosynthesis offers advantages including widespread availability of reducing agents, absence of temperature or pressure controls, and faster production of nanoparticles. In hydrothermal synthesis, copper nitrate concentration affects particle morphology; lower concentrations facilitate rod formation, while higher concentrations result in clusters of rods [43], [44], [45], [46], as summarized in Table 3.

Table 3: Summary of section 2.3 Green synthesis of CuNPs uses natural reducing and stabilizing agents from plants, microbes, or enzymes to avoid toxic chemicals. Due to its speed, cost, and environmental sustainability, plant extract synthesis is popular, although raw material discrepancies limit it. Microbial and enzyme-mediated methods are slower and less scalable but more specific. Photosynthesis is fast and energy efficient, while hydrothermal green synthesis improves crystallinity and shape control. Method selection depends on environmental sustainability, reproducibility, scalability, and desired particle properties.

Table 3. Comparison of prevalent biological techniques for the creation of copper nanoparticles (CuNPs) and their principal characteristics.

Biological Method	Principle / Mechanism	Typical Size & Shape	Advantages	Disadvantages
Plant Extract-Mediated Synthesis	Phytochemicals (phenolics, flavonoids, sugars, proteins) reduce Cu^{2+} to Cu^0 and cap nanoparticles	5–100 nm, spherical, rods, irregular	Eco-friendly, low cost, fast production, no toxic chemicals	Variability in extract composition, batch-to-batch inconsistency
Microbial Synthesis	Bacteria, fungi, or yeast reduce Cu^{2+} via enzymatic/metabolic processes	10–80 nm, varied morphologies	Renewable source, mild conditions, possible intracellular stability	Slow production, requires sterile conditions, and downstream purification
Enzyme-Mediated Synthesis	Isolated enzymes (e.g., oxidoreductases) catalyze Cu^{2+} reduction in vitro	5–50 nm, controlled morphology	High specificity, fine control over size and shape	High cost of enzymes, stability issues, and limited scalability
Photosynthesis-Based Approach	Light-driven reactions in plant extracts or microbial systems promote Cu^{2+} reduction	10–60 nm, often spherical	No heating/pressure, renewable, fast	Dependent on light intensity and exposure, it may yield a broader size range.
Hydrothermal Green Synthesis	Aqueous plant extract with Cu salt processed under mild hydrothermal	20–100 nm, rods or clusters	Good crystallinity, possible shape control via	Requires a special reactor and, longer processing

	conditions		precursor concentration	time
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3. Characterization Techniques

Numerous techniques have been employed to study copper nanoparticles (CuNPs). UV-Vis spectroscopy provides a preliminary evaluation of CuNPs and allows monitoring of chemical state changes. Fourier Transform Infrared Spectroscopy (FTIR) delineates functional groups associated with the nanoparticles, elucidating features such as metal-carbon bonds.[12], [26], [47].

X-Ray Diffraction (XRD) has been widely utilized to ascertain nanoparticle dimensions and examine the synthesis of copper oxides. Scanning Electron Microscopy (SEM) analyzes surface appearance, whereas Transmission Electron Microscopy (TEM) directly assesses nanoparticle dimensions and form. [25], [48], [49].

Dynamic Light Scattering (DLS) is employed to evaluate particle size distribution. Atomic Absorption Spectroscopy (AAS) evaluates surface composition, while UV-Visible spectroscopy examines optical characteristics. [50].

Hot-stage optical microscopy determines particle morphology. Although Scanning Transmission Electron Microscopy (STEM) is ideal for analyzing particle size and distribution, sample preparation can be challenging; thus, XRD remains the preferred technique. SEM also facilitates examination of morphology and size distribution. These characterization methods, applied to samples originating from diverse synthesis approaches, establish correlations among preparation tailorability, structural and chemical properties, and consequences of exposure to various environments [51], [52], [53], as illustrated in Figure 2.

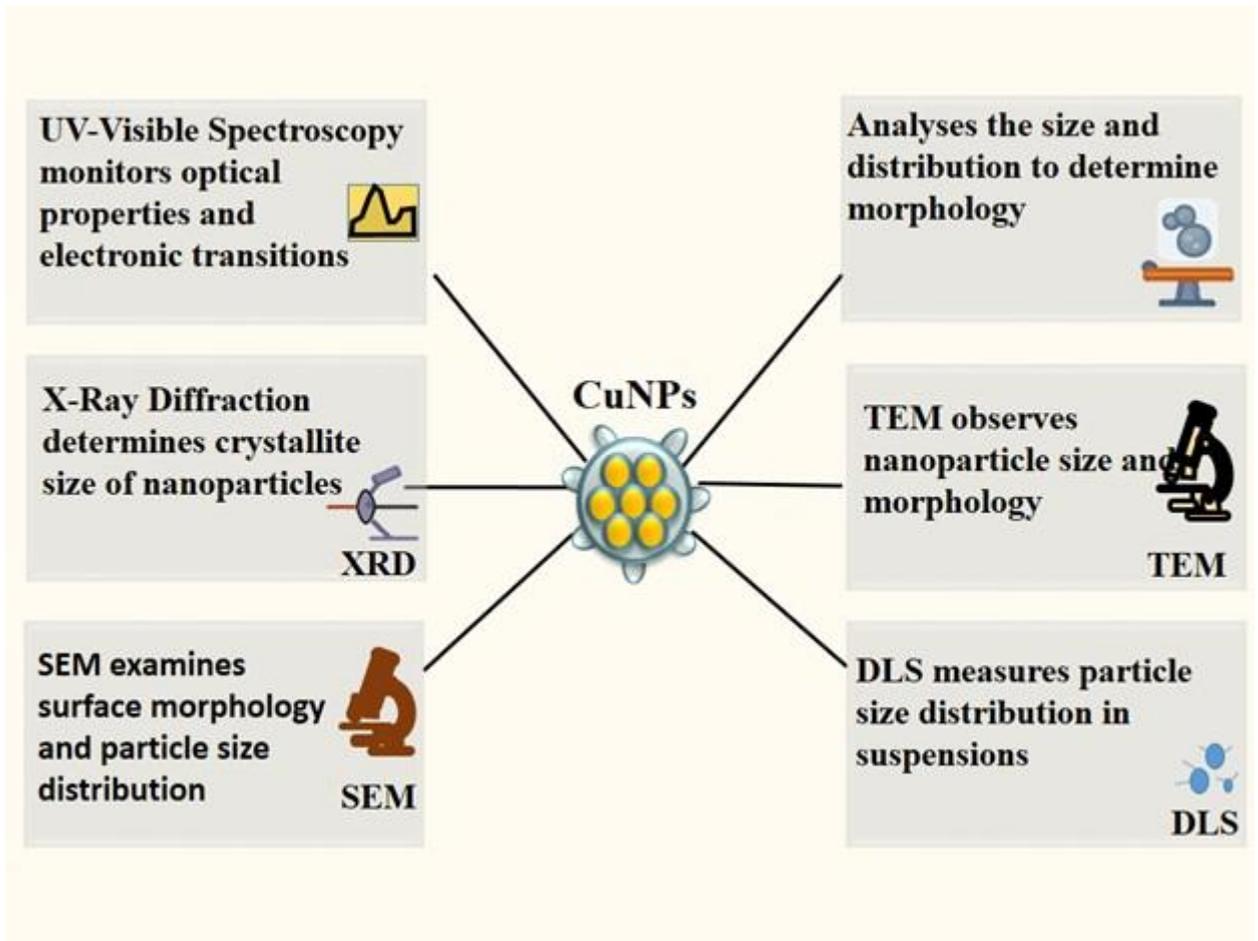


Fig 2. Characterization techniques for copper nanoparticles (CuNPs)

3.1. Spectroscopy techniques

Spectroscopy offers essential insights into copper nanoparticles (Cu-NPs), uncovering exploitable features and optical characteristics suitable for medicinal applications. UV-Vis, Surface-Enhanced Raman Scattering, and X-ray Spectroscopy are important techniques. Compact proportions guarantee a predominantly seamless fit. [11], [54], [55].

3.2. Microscopy techniques

Microscopy techniques are essential for assessing the morphology, size, and surface characteristics of copper nanoparticles (CuNPs), which subsequently affect their physical and chemical properties [56], [57].

Transmission electron microscopy (TEM) is widely employed because it relies on the transmission of an electron beam through the sample to generate images at the nanometer scale. High-resolution TEM provides atomic-scale images, facilitating direct measurement of crystal structures and surface morphology [14].

Scanning electron microscopy (SEM), which scans the sample surface with an electron probe, offers three-dimensional images and enables analysis of topography, morphology, and its chemical composition when combined

with energy dispersive spectroscopy (EDS) [58].

Atomic force microscopy (AFM) utilizes various tip–sample interactions (van der Waals, electrostatic, magnetic, and chemical forces) to produce three-dimensional topography images of nanoparticle surfaces. CuNPs' size, a critical factor influencing their properties and applications, can be determined by measuring diameters and projected areas from TEM, SEM, or AFM images [59].

3.3. X-ray diffraction

X-ray diffractometry (XRD) is essential for determining the crystalline and phase properties of copper nanoparticles synthesized using various methods. XRD examination utilizes $\text{CuK}\alpha$ radiation with a wavelength of 1.5406 \AA , covering a 2θ range of 30° to 70° to investigate the crystalline structure essential to the nanoparticles' biological properties. [60], [61], [62].

Moreover, microwave-assisted copper-oxide nanorods demonstrate significant antioxidant, antimicrobial, and anticancer activities applicable to both normal skin and breast cancer cellular models [63].

3.4. Dynamic light scattering

Dynamic light scattering (DLS) is a technique for measuring size that relies on the analysis of fluctuations in particle number within the intensity of laser-scattered light. It can be used to collect statistically significant data for a suspension of particles of about 1 nm to $3 \text{ }\mu\text{m}$ in size. DLS is extensively employed to characterize the dimensions of polymers, tiny particles, and big molecules in suspension. DLS measures the time-dependent fluctuations in the scattering intensity due to the Brownian motion of the particles in the suspension or molecules in solution, over a wide angular range (typically $90\text{--}173^\circ$); the scattering angle depends mainly on the sample cell design [64], [65].

4. Properties of Copper Nanoparticles

Copper nanoparticles possess unique optical, electrical, and thermal characteristics that make them especially valuable for various medical applications, such as cancer, drug delivery, and antimicrobial therapies. Their efficient synthesis and characterization are essential to enhance their performance for these applications [57], [66].

Metal nanoparticles manifest unique properties once their dimensions approach the few-nanometer range. By reducing particle sizes, strain, and defects such as dislocations and grain boundaries can be incorporated. Additionally, their lattice constants often differ from those of form bulk samples, thereby exerting a direct influence on intrinsic properties [67], [68].

Nanoparticles are a subset of nanomaterials characterized by sizes ranging between 1 and 100 nm . Within this class, copper nanoparticles are generally defined as copper particles confined to these dimensions. A variety of chemical, physical, and biological methods have been established for their synthesis. Common methodologies encompass chemical reduction, sonochemical techniques, electrochemical methods, laser ablation, microwave-assisted processes, and biological synthesis utilizing microbial or plant extracts.[69], [70].

4.1. Optical properties

Copper nanoparticles have optical, electrical, and magnetic properties distinct from bulk copper, influenced by their dimensions and morphology. The optical features stem from the surface plasmon resonance (SPR) effect, which is caused by the collective oscillations of free electrons interacting with the electromagnetic field of incident visible light. The SPR energy scales with the conduction electron density, which is highest in copper among metals like copper, silver, and gold, leading to distinctive optical behavior [57], [71].

A sudden change is observed in the refractive index on the surface of noble metals due to long-range intermolecular

forces. This peculiar optical property has generated widespread interest in metal nanoparticles. Exposure of nanoparticles to visible light in the ultraviolet region produces scattered light of specific wavelengths, owing to the SPR effect [72].

The UV-Visible absorption of copper nanoparticles displays a distinctive surface plasmon resonance peak that fluctuates with particle size ranging from 200 to 800 nm, as ascertained using UV-Visible Spectroscopy, Fourier Transform Infrared Microscopy, X-ray Diffraction Analysis, and Scanning Electron Microscopy [73], [74].

4.2. Electrical properties

Electrical conductivity is a fundamental property of metallic elements that determines the ability of materials to conduct an electric current. Among the first metals identified as electrical conductors, copper has received particular attention in material science and engineering [75], [76].

Copper is widely distributed throughout the human body in the bloodstream, skeletal muscles, and brain. Copper-based materials demonstrate superior biocompatibility, fulfilling criteria for biological applications like wound healing, hemostasis regulation, and antibacterial efficacy [77], [78].

4.3. Thermal properties

The thermal behavior of CuNPs is dependent on particle size and is usually measured by differential scanning calorimetry (DSC) [79], [80].

DSC analysis typically shows endothermic and exothermic peaks attributable to water evaporation, Copper phase changes, melting, and oxidation [81].

Differential Scanning Calorimetry (DSC) analyses of copper nanoparticles frequently display characteristic endothermic and exothermic transitions at temperatures significantly lower than that of bulk copper (1085 °C). For instance, CuNPs of approximately 50 nm in diameter have demonstrated exothermic and endothermic peaks near 473 °C and 563 °C, respectively, values consistent with the melting point depression phenomenon observed in metallic nanoparticles. The decrease in melting temperature is due to the elevated surface-to-volume ratio and augmented surface energy linked to nanoscale dimensions, which together diminish the thermal energy necessary for phase transitions [81], [82].

5. Applications in Medicine

Copper nanoparticles occupy a unique niche in the biomedical sector. Their extensive antimicrobial activity extends the options available for antibacterial therapy [14].

Copper nanoparticles have been explored as versatile nanovehicles due to their modifiable surfaces and capacity for drug conjugation. They present a promising platform for targeted delivery, including potential encapsulation or surface conjugation of anticancer agents such as doxorubicin, methotrexate, gefitinib, and folic acid, although direct implementations with these agents require further investigation [83], [84], [85], [86].

Copper and its derivatives have been utilized in chemotherapy, as copper is crucial in various biochemical pathways, including glucose, cholesterol, and iron metabolism, which are essential for cardiovascular health, lung elasticity, bone formation, and erythropoiesis [87], [88], [89].

Copper shortage and excess are perilous, resulting in hepatic damage, impairment of gastrointestinal and renal functions, pleural effusions, anemia, tissue injury, fragility, and skeletal anomalies [3], [90].

The antibacterial properties of copper have been widely used in agriculture, water treatment, in the preservation of wood and textiles, solar energy conversion, and batteries and sensors [91], [92], [93].

Copper nanoparticles exhibit an extraordinary antibacterial activity against Gram-positive bacteria (*S. aureus*) and Gram-negative bacteria (*E. coli*) that is, in many cases, superior to silver nanoparticles [8], [94].

Synergistic antibacterial activities have also been observed between copper and silver nanoparticles. Copper nanoparticles nowadays constitute low-cost, biocompatible substrates for biosensing and colorimetric analysis, while offering new perspectives in the development of smart textiles. Their integration within polymeric materials can provide composite materials with increased functionality, such as protection against radiation or electromagnetic interference [10], [95], [96], [97].

Copper nanoparticles are furthermore exploited in wound healing dressings, personal equipment, and the treatment of inflammatory diseases by enhancing the effects of anticancer drugs and antibiotics. They are used in anticancer therapy to inhibit the growth of tumour cells, while their optical and electrical properties enable their exploitation in imaging and diagnostics [78], [88], [98], [99].

5.1. Antimicrobial applications

Copper-based nanomaterials demonstrate significant antibacterial efficacy against a wide range of Gram-positive and Gram-negative bacteria, including resistant strains such as methicillin-resistant *Staphylococcus aureus*, *Bacillus subtilis*, *Proteus vulgaris*, and *Escherichia coli*, surpassing the capabilities of silver-based alternatives [7], [100], [101], [102].

5.2. Drug delivery systems

The pharmaceutical sector faces ongoing challenges related to the solubility, degradation, and bioavailability of drugs. Incorporating active ingredients into polymer matrices constitutes a crucial tactic to alleviate these shortcomings [103], [104], [105].

Exploiting the antibacterial, anticancer, and antifungal capacities of copper nanoparticles has facilitated the design of efficient drug delivery systems [25].

Utilizing copper nanoparticles as nanovehicles represents an emerging avenue to enhance current delivery methodologies, mitigating the deleterious effects of drug degradation and surmounting multidrug resistance [18], [106].

5.3. Cancer treatment

Copper nanoparticles (CuNPs) represent a highly attractive tool for cancer therapy, as they meet the criteria of excellent biocompatibility, easy functionalization, and low cost [107].

These attractive attributes, combined with established knowledge about their synthesis and characterization, open multiple medical applications, including drug delivery systems, antimicrobial uses, imaging, diagnosis, and cancer treatment. The latter, increasingly investigated, benefits from copper's recognized role during angiogenesis and tumor development [88], [108], [109].

In this context, metallic and oxide CuNPs have been synthesized through several physicochemical routes, characterized by spectroscopic and microscopic methods, and employed to develop implantable drug delivery systems in which the nanoparticles are hosted in various polymeric matrices [93], [110], [111].

Alternatively, CuNPs of curcumin have been evaluated for their intrinsic antitumor activity. Metallic copper (Cu NPs) also acts as an effective photothermal agent in several cancer therapy approaches. The discussed synthesis procedures are straightforward and scalable, offering CuNPs suitable for different diagnostic and therapeutic applications [112], [113].

5.4. Imaging and diagnostics

Copper nanoparticles complement conventional imaging sources by overcoming limitations associated with their

inability to cross biological barriers [18].

Molecular imaging (MI) is a non-invasive technology employed to observe biological processes at cellular and subcellular levels through the use of tailored imaging agents that bind to specific targets with great specificity [114], [115].

Metal nanoclusters, including copper nanoclusters, are noteworthy for bioimaging owing to their diminutive size, robust fluorescence, stability, low toxicity, and biocompatibility, rendering them potential probes for biosensing and bioimaging applications [116], [117], [118].

The most widely studied radio nuclides for positron emission tomography (PET) imaging of nanoparticles are ^{18}F , ^{64}Cu , and ^{124}I . Several different ^{64}Cu -chelators, such as NOTA, DOTAGA, and DOTA, have been conjugated to various nanoparticles to allow imaging of their in vivo distribution. Chelators, such as (1,4,7-triazacyclononane 1,4,7-triyl) triacetic acid (NOTA) and 1,4,7,10-tetraazacyclododecane 1,4,7,10-tetraacetic acid (DOTA), have been used for ^{64}Cu -labelling of metal-based and organic nanoparticles [119], [120].

6. Toxicity and Safety Considerations

Copper nanoparticles (CuNPs) have garnered significant interest in biomedical applications owing to their antibacterial characteristics, economic viability, and similarity to noble metal nanoparticles [101], [121]. Nevertheless, their potential toxicity warrants careful evaluation. CuNPs can accumulate in the pericellular environment, dissolve, and subsequently adhere to cell membranes through electrostatic interactions [122], [123], [124].

This adhesion, accompanied by the release of copper ions, disrupts membrane integrity, enabling the entry of nanoparticles and ions into the cytoplasm. Once internalized, elevated reactive oxygen species (ROS) levels may induce protein oxidation, reduce adenosine triphosphate (ATP) synthesis, and cause DNA damage [122], [125], [126].

The greatest solubility and liberation of copper ions occur in the stomach and intestinal fluids. Human exposure to nanoparticles occurs via four primary pathways: inhalation, ingestion, dermal contact, and ocular exposure. Copper nanoparticles may infiltrate the gastrointestinal tract via ingestion from food or water, or through inhalation followed by the swallowing of particles from the respiratory tract [127], [128].

The aggregation of nanoparticles in tissues and organs can lead to severe diseases, including neurological disorders such as Alzheimer's and Parkinson's [129], [130].

6.1. Cellular toxicity

Copper is an essential trace dietary element that plays a fundamental role in the proper functioning of organisms due to its involvement in many biological processes [131].

Copper nanoparticles have remarkable properties like those observed for silver and gold nanoparticles. They are biologically active, biocompatible, and low-cost materials [10], [13], [14].

The synthesis and characterization of copper-based nanoparticles can therefore be a crucial issue in developing novel therapies and drugs [132].

Limited knowledge exists regarding the direct impact of copper nanoparticles on human cells and the potential dangers associated with various particle sizes, despite the recognized size dependency in other particles, such as silver nanoparticles [128], [133].

Recent studies highlight the urgent need to investigate how copper nanoparticles (CuNPs) transform within biological matrices and whether specific nanoforms pose heightened cytotoxic risks. Experimental evidence from comparative assays on three distinct CuNPs sizes against human cell lines demonstrates that particle size significantly influences cytotoxicity, with medium-sized particles (40–60 nm) showing higher cellular uptake and toxicity. Optimization studies further reveal that the presence of serum in cell culture media improves nanoparticle dispersibility, whereas different sonication methods have no substantial effect. Moreover, the stability of CuNPs

dispersions declines over time, making the age of suspensions a critical factor in reliable cytotoxicity assessment [134], [135].

7. Future Perspectives of Copper Nanoparticles in Biomedicine.

Copper nanoparticles (CuNPs) have emerged as highly promising agents in biomedicine due to their multifunctional properties, spanning antimicrobial action, drug delivery, cancer therapy, and bioimaging. Their unique optical, electrical, and thermal characteristics, combined with selective cytotoxicity toward pathogens and demonstrated biocompatibility, position them at the forefront of next-generation nanomedicine. These capabilities, however, impose new demands on synthesis control, surface engineering, and precise physicochemical characterization to optimize their therapeutic performance while ensuring safety.

Recent advances in synthesis, particularly biologically mediated routes, offer safer, scalable, and more eco-friendly alternatives to traditional chemical and physical methods, enabling better control over particle size, morphology, and stability. Parallel progress in advanced characterization techniques, such as XPS, FTIR, TGA, BET, zeta potential analysis, and ICP-MS, is essential for elucidating structure-property-function relationships and tailoring nanoparticles for specific biomedical tasks.

In clinical contexts, CuNPs hold potential for integrated theranostic systems, combining targeted diagnostics and therapy, particularly in oncology, infectious disease management, and organ-specific interventions. Their versatility extends to serving as imaging contrast agents (MRI, PET) and enabling personalized medicine strategies through tunable targeting and release profiles. Moreover, copper's role as an essential trace element in metabolic pathways provides a unique physiological relevance, though precise dose control is critical to prevent toxicity while avoiding deficiency-related disorders.

The path forward lies in converging three pillars: innovative synthesis, precision characterization, and rigorous toxicological profiling. Addressing these simultaneously will accelerate the safe translation of CuNP-based systems from experimental platforms to commercial biomedical applications, enabling more efficient, targeted, and multifunctional treatments in modern healthcare.

8. Conclusion

Copper nanoparticles (CuNPs) exhibit a wide range of beneficial properties, including optical, electrical, and catalytic characteristics, which render them suitable for various biomedical applications. Their notable antibacterial, antifungal, and anticancer activities have sparked intense research interest regarding their biological properties and production methods. The numerous synthesis approaches permit tailoring of physical, chemical, and structural characteristics of CuNPs, influencing their biological efficacy in a direct relationship to their size, morphology, and composition. The inherent instability of copper poses a challenge addressed by employing surface-stabilizing agents, enabling the production of uniform, well-defined, and stable nanoparticles for biomedical purposes. This compilation systematically outlines the common synthesis routes encompassed within chemical, physical, and biological methods. Subsequent sections delineate characterization techniques vital for assessing particle size, morphology, and composition. Elucidation of the chemical, optical, electrical, and thermal properties of copper is followed by an overview of major biomedical applications, including antimicrobial agents, targeted drug delivery systems, cancer therapeutics, and imaging-guided diagnostics. Toxicity related to both CuNPs and copper ions is discussed by examining cellular impacts. Concluding perspectives suggest potential directions for advancing the synthesis, characterization, and application of CuNPs in medicine.

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Türkiye, they are proud to be citizens of this country.

Author Contributions

Farah Mutlag, Hussein Elaibi; Conceptualization, Methodology, Visualization, Writing – original draft, Ebru Halvacı; Writing – review & editing, Visualization, Fatih Sen; Supervision, Project Administration, Writing – Review&Editing

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