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Recent Advances in Green Synthesis of Copper Nanoparticles and Their Therapeutic Delivery Applications

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Abstract

The environmentally sustainable approach of green synthesis for copper nanoparticles (CuNPs) has emerged as an effective and sustainable method within the field of nanotechnology, offering numerous advantages over traditional physical and chemical methodologies. This technique employs biological sources such as plant extracts, microorganisms, and natural biomolecules as reducing and stabilizing agents, thereby circumventing the use of toxic chemicals and excessive energy consumption. Recent advancements in green synthesis techniques have enabled the controlled production of CuNPs with specific size, shape, surface charge, and stability, which are essential for biomedical applications. CuNPs have demonstrated significant potential in drug delivery due to their unique properties, including high surface area, antimicrobial activity, and the ability to be functionalized for targeted delivery. Green-synthesized CuNPs not only enhance drug solubility but also improve bioavailability and facilitate controlled and sustained drug release. Furthermore, these nanoparticles can be engineered to recognize biological targets, thereby augmenting therapeutic efficacy and minimizing toxicity. Recent studies have also highlighted the application of CuNPs in treating various diseases, such as cancer, infections, and inflammatory conditions. Their antimicrobial and anticancer properties further complement their drug delivery capabilities. Nonetheless, challenges such as potential cytotoxicity, stability issues, and scalability must be addressed to facilitate clinical translation.

Introduction

Nanotechnology has emerged as a transformative force in contemporary science, offering innovative solutions across a wide range of biomedical applications, particularly in drug delivery. Among the various nanomaterials, metallic nanoparticles have garnered significant interest due to their unique physicochemical properties, such as a high surface-to-volume ratio, modifiable surface characteristics, and enhanced reactivity(1). These attributes facilitate effective interaction with biological systems, rendering nanoparticles particularly suitable for therapeutic applications. In recent years, copper nanoparticles (CuNPs) have attracted considerable attention owing to their cost-effectiveness, ease of synthesis, and remarkable biological activities, including antimicrobial, antioxidant, and anticancer properties. Traditional methods for synthesizing copper nanoparticles, such as physical and chemical approaches, are often associated with the use of hazardous chemicals, excessive energy consumption, and complex processing conditions. These methods can generate toxic by-products, posing risks to both the environment and human health, thereby limiting their applicability in biomedical contexts. In response to these challenges, green synthesis has emerged as a more sustainable and environmentally benign approach to nanoparticle production. This method utilizes natural resources, such as plant extracts, microorganisms, and biomolecules, as reducing and stabilizing agents, thereby circumventing the need for toxic reagents and harsh reaction conditions. This not only mitigates environmental impact but also enhances the biocompatibility of the synthesized nanoparticles. Plant-mediated green synthesis is particularly advantageous due to its simplicity, scalability, and cost-effectiveness. Plant extracts are rich in various phytochemicals, including flavonoids, phenolics, alkaloids, and proteins, which serve as natural reducing and capping agents in nanoparticle formation(2). These biomolecules play a crucial role in controlling the size, shape, and stability of copper nanoparticles, which are critical parameters in determining their biological efficacy. Furthermore, green-synthesized CuNPs tend to exhibit greater stability and reduced toxicity compared to those produced via conventional methods, making them more suitable for biomedical applications(3).

Copper nanoparticles (CuNPs) offer several advantages in drug delivery, enhancing therapeutic efficacy. Their diminutive size allows them to traverse biological barriers, facilitating the delivery of drugs to specific target sites within the body. Furthermore, the surface of CuNPs can be functionalized with various ligands, polymers, or biomolecules to achieve targeted drug delivery and controlled release. This capability is particularly pertinent in managing chronic and complex conditions, such as cancer, where precise delivery of therapeutic agents is essential to minimize side effects and improve treatment outcomes. Additionally, the intrinsic antimicrobial and anticancer properties of copper nanoparticles can augment the therapeutic potential of drug-loaded systems(4).

Recent advancements in green synthesis methods have enabled the production of copper nanoparticles with well-defined physicochemical characteristics suitable for in situ applications. Researchers have explored diverse plant and biological sources to optimize synthesis conditions and enhance nanoparticle properties. Consequently, CuNPs have been successfully employed in delivering various therapeutic agents, including small molecules, proteins, and nucleic acids. Green-synthesized CuNPs have also shown promise in targeted drug delivery, imaging, and theranostic applications, thereby broadening their utility in contemporary medicine.

Despite the promising benefits of green-synthesized copper nanoparticles as a drug delivery system, several challenges persist in their development and application. Issues related to particle stability, reproducibility of synthesis procedures, and potential cytotoxicity require careful consideration. Variability in the biological sources used in green synthesis may lead to discrepancies in nanoparticle properties, affecting their performance and reliability. Moreover, the long-term safety and biocompatibility of CuNPs must be thoroughly investigated to facilitate their clinical application. Regulatory hurdles and challenges in large-scale production also represent significant obstacles that must be addressed(5).

The toxicity of copper nanoparticles at elevated concentrations is a critical concern, potentially attributable to the release of copper ions and the generation of reactive oxygen species. Consequently, it is imperative to optimize dosage and surface modification strategies to ensure both safety and efficacy. Advances in surface engineering, such as coating nanoparticles with biocompatible biomolecules or polymers, have shown promise in reducing toxicity and enhancing stability. These modifications can also improve the targeting efficiency and delivery duration of nanoparticles within the body. In summary, the sustainable development of advanced drug delivery systems is feasible through the green synthesis of copper nanoparticles. The integration of nanotechnology with environmentally friendly synthesis methods presents a unique opportunity to create biocompatible and effective therapeutic platforms. Despite significant

progress in this field, further research is necessary to address existing challenges and fully realize the clinical potential of copper nanoparticles. Continued advancements in the green synthesis, characterization, and functionalization of copper nanoparticles are likely to play a pivotal role in shaping the future of drug delivery and biomedical research(6).

Copper nanoparticles are synthesized using a green method.

The green synthesis of copper nanoparticles (CuNPs) has emerged as an environmentally friendly and sustainable alternative to traditional nanoparticle fabrication methods, addressing the limitations associated with conventional physical and chemical techniques. Traditional synthesis methods are often characterized by toxicity, high energy consumption, and the production of hazardous by-products, posing significant risks to human health and the environment. In contrast, green synthesis employs natural biological materials, such as plant extracts, microorganisms, and biomolecules, as reducing and stabilizing agents, thereby eliminating the need for harmful chemicals and harsh reaction conditions. This approach not only mitigates environmental impact but also enhances the biocompatibility and therapeutic potential of the synthesized nanoparticles(7).

The fundamental principle of green synthesis involves the reduction of metal ions to nanoparticles using naturally available phytochemicals or biological molecules. These biomolecules, including flavonoids, phenolic compounds, proteins, enzymes, and polysaccharides, serve dual roles as reducing and stabilizing (capping) agents. This process facilitates the reduction of copper ions (Cu^{2+}) to copper nanoparticles (Cu^{0}), with capping agents preventing aggregation and stabilizing the nanoparticles by forming a protective layer. This dual functionality is a significant advantage of green synthesis, as it simplifies the synthesis process and enhances nanoparticle stability(8).

Biological agents in green synthesis are crucial in determining the size, shape, surface charge, and overall physicochemical properties of copper nanoparticles. Factors such as the biological source, reaction conditions (pH, temperature, and concentration), and synthesis duration significantly influence nanoparticle characteristics. These parameters can be optimized to tailor nanoparticles for specific biomedical applications, particularly in drug delivery. Moreover, green synthesis offers several advantages over traditional methods, including cost-effectiveness, ease of use, scalability, and reduced toxicity. Green-synthesized CuNPs are particularly suitable for biomedical applications due to their lower toxicity, higher biocompatibility, and reduced side effects. Additionally, the use of renewable biological resources aligns with the principles of green chemistry and sustainable development(9).

Plant-Mediated Synthesis

Plant-mediated synthesis is a widely recognized and efficient approach for the green synthesis of copper nanoparticles (CuNPs) due to its simplicity, cost-effectiveness, and scalability. This method utilizes plant extracts derived from leaves, roots, stems, flowers, or fruits as both reducing and stabilizing agents. These extracts are rich in bioactive compounds, including flavonoids, phenolics, alkaloids, terpenoids, and proteins, which play a crucial role in the reduction of copper ions and the stabilization of the resulting nanoparticles(10).

The synthesis process typically involves the combination of an aqueous plant extract with a copper salt solution under controlled conditions. The phytochemicals present in the extract facilitate the reduction of (Cu^{2+}) nanoparticles, while simultaneously acting as capping agents to prevent nanoparticle agglomeration. A color change is often observed, indicating the formation of nanoparticles. A significant advantage of plant-mediated synthesis is the ability to tailor the properties of the nanoparticles by adjusting reaction parameters such as pH, temperature, extract concentration, and reaction time. Furthermore, this method does not require specialized equipment or sterile conditions, making it highly suitable for large-scale production.Plant-mediated CuNPs have demonstrated superior biological activities, including antimicrobial and antioxidant effects, which enhance their potential application in drug delivery systems. However, variability in plant composition can lead to challenges in reproducibility, presenting a limitation of this approach(11).

Microbial Synthesis

The microbial synthesis of copper nanoparticles involves the utilization of microorganisms such as bacteria, fungi, algae, and yeast to generate nanoparticles. These microorganisms possess inherent metabolic activities and enzymatic processes capable of reducing metal ions into nanoparticles. The synthesis process can be categorized as either intracellular or extracellular, contingent upon the conditions and the organism employed. In intracellular synthesis, copper ions penetrate the microbial cell wall and are subsequently reduced within the cell by enzymes, culminating in nanoparticle formation. Conversely, during extracellular synthesis, enzymes secreted by the

microorganisms reduce copper ions in the surrounding medium, resulting in the formation of nanoparticles outside the cell. The ease of recovery and purification renders extracellular synthesis more favorable compared to intracellular synthesis(12).The advantages of microbial synthesis include enhanced stability, controlled particle size, and environmentally sustainable processing. Furthermore, due to their enzymatic mechanisms, microorganisms can produce nanoparticles with distinct shapes and sizes. Fungi, in particular, are extensively utilized due to their ability to synthesize substantial quantities of enzymes and nanoparticles. Despite these advantages, microbial synthesis presents certain challenges, such as the necessity for sterile conditions, a time-consuming synthesis process, and complex downstream processing. Nevertheless, it remains an effective method for sustainable nanoparticle production(13).

Biomolecule-Mediated Synthesis

The synthesis of copper nanoparticles through the utilization of isolated biological molecules, such as proteins, enzymes, amino acids, polysaccharides, and vitamins, is termed biomolecule-mediated synthesis. These biomolecules function to reduce and stabilize nanoparticles under mild conditions, facilitating the formation of controlled nanoparticles. Proteins and enzymes play a significant role in the reduction of copper ions via their functional groups, including amino, carboxyl, and thiol groups. Similarly, nanoparticles can be stabilized by polysaccharides and amino acids, which envelop them with a protective layer(14). This approach enables precise control over the size, shape, and surface characteristics of nanoparticles, which is essential for biomedical applications. The synthesis using biomolecules exhibits a high degree of reproducibility and uniformity compared to plant- or microbe-based methods. Furthermore, purified biomolecules minimize variability and enhance the predictability of nanoparticle properties. However, this method may incur higher costs due to the expenses associated with biomolecule isolation and purification. Overall, biomolecule-mediated synthesis represents a controlled and efficient method for producing high-quality copper nanoparticles suitable for drug delivery applications(15).

The green synthesis of copper nanoparticles (CuNPs) involves a series of processes including reduction, nucleation, growth, and stabilization. Initially, copper ions (Cu^{2+}) in the precursor solution are reduced to metallic copper (Cu) by biological reducing agents such as phytochemicals, enzymes, or biomolecules. This reduction is facilitated by electron-donating functional groups present in these biological agents. Following reduction, small clusters of copper atoms form, serving as nucleation centers(16). These nuclei subsequently expand into nanoparticles through mechanisms such as coalescence and aggregation. Factors influencing the growth phase include the concentration of reactants, temperature, and reaction time. Concurrently, stabilizing agents within the biological system adhere to the nanoparticle surfaces, preventing excessive aggregation and ensuring stabilization. This capping is crucial for maintaining the size, dispersion, and functionality of the nanoparticles(17).

Green Synthesized Copper Nanoparticles Properties.

Copper nanoparticles (CuNPs) synthesized through green methods exhibit remarkable and tunable characteristics, making them highly suitable for biomedical and drug delivery applications. The synthesis method, type of biological reducing agents, and reaction conditions are critical factors influencing these properties. Compared to traditionally synthesized nanoparticles, green-synthesized CuNPs demonstrate enhanced biocompatibility due to the presence of biologically-based natural capping agents. The physicochemical, optical, and surface properties of these nanoparticles are crucial in determining their interaction with biological systems, drug-loading capacity, and overall therapeutic efficacy. Furthermore, their physiological stability is essential for their functionality during storage and application. A comprehensive understanding of these properties is necessary to optimize nanoparticle design and ensure their successful implementation in drug delivery systems(18).

Physicochemical Properties

The biological performance and drug delivery efficacy of green-synthesized copper nanoparticles (CuNPs) are significantly influenced by their physicochemical properties, including particle size, shape, surface charge, and crystallinity. Among these, particle size is a critical parameter, as it determines the nanoparticles' ability to traverse biological barriers and interact with target cells. Typically, the size of green-synthesized CuNPs ranges from 10 to 100 nm, which is considered optimal for enhancing cellular uptake and bioavailability. The shape of nanoparticles, such as spherical, rod-shaped, or cubic, also affects their interaction with biological membranes and drug release behavior. Spherical nanoparticles are generally preferred due to their uniform distribution and transport across biological boundaries(19). Zeta potential, or surface charge, is another crucial factor influencing nanoparticle

stability and interaction with biological systems. Positively charged nanoparticles tend to interact more effectively with negatively charged cell membranes, thereby enhancing cellular uptake and mucoadhesion. Crystallinity is a significant physicochemical characteristic that affects the stability and reactivity of nanoparticles, typically assessed using X-ray diffraction to determine structural integrity. Additionally, biological synthesis produces natural capping agents that improve nanoparticle dispersion and prevent aggregation(20).

Optical Properties

Surface plasmon resonance (SPR) represents the primary optical characteristic of green-synthesized copper nanoparticles (CuNPs), manifesting as a collective oscillation of electrons on the nanoparticle surface when exposed to light. This phenomenon is significantly influenced by the particle size, shape, and the surrounding medium. Typically, CuNPs exhibit characteristic absorption peaks within the UV-visible spectrum, which can be employed to confirm nanoparticle formation and assess their stability. UV-visible spectroscopy is frequently utilized to investigate the optical properties of CuNPs, with the position and intensity of the absorption peak providing insights into particle size distribution and aggregation. Variations in the absorption peak position may indicate changes in nanoparticle size or interactions with biological molecules. Additionally, the presence of phytochemicals or biomolecules on the nanoparticle surface can alter optical properties by modifying the local refractive index. These optical properties are not only instrumental in characterization but also have practical applications in biomedical imaging, sensing, and diagnostic methodologies. For instance, CuNPs can be employed in biosensors due to their responsiveness to environmental changes and their optical characteristics, which facilitate real-time monitoring of drug delivery processes(21).

Surface Chemistry

The surface chemistry of green-synthesized copper nanoparticles (CuNPs) plays a crucial role in determining their interactions with biological systems and their efficacy in drug delivery applications. Biomolecules generated during the green synthesis process, such as proteins, phenolics, flavonoids, and polysaccharides, are typically present on the surface of CuNPs. These biomolecules function as capping agents, providing stability and preventing aggregation. The presence of functional groups, including hydroxyl, carboxyl, and amino groups, on the nanoparticle surface facilitates the conjugation of drugs, targeting ligands, and other bioactive molecules(22). This functionalization enhances the specificity and efficacy of drug delivery by enabling targeted interactions with specific cells or tissues. Furthermore, the surface chemistry influences the hydrophilicity or hydrophobicity of the nanoparticles, affecting their solubility in biological fluids and cellular uptake. Surface-modified CuNPs may exhibit improved biocompatibility and reduced toxicity, as the capping agents act as a protective barrier between the nanoparticle core and the biological environment. Fourier-transform infrared spectroscopy (FTIR) is a widely employed technique to identify the presence of functional groups on the nanoparticle surface and to verify capping(23).

Stability

The stability of green-synthesized copper nanoparticles is a critical property that significantly influences their shelf life, functionality, and performance within biological systems. Stability is characterized by the nanoparticles' ability to maintain their size, shape, and dispersion without undergoing aggregation, oxidation, or degradation. The inherently reactive nature of copper nanoparticles, particularly their susceptibility to oxidation, can lead to the formation of copper oxide and a consequent loss of desired properties(24). Green synthesis enhances nanoparticle stability through the use of natural capping agents, which are biomolecules that coat the nanoparticles and prevent aggregation and oxidation. Factors such as pH, temperature, ionic strength, and storage conditions play a crucial role in determining nanoparticle stability. Zeta potential serves as an important measure of stability, with positive values indicating stronger repulsive electrostatic forces between particles, and negative values indicating weaker repulsive forces. Additionally, biomolecular steric stabilization contributes to stability by forming a physical protective layer around the nanoparticles. Stability studies are essential for understanding the behavior of copper nanoparticles under various environmental conditions, aiding in the establishment of optimal storage environments and ensuring consistent performance throughout their application. In conclusion, the stability of green-synthesized copper nanoparticles is vital for their successful application in drug delivery systems, as they represent one of the most reliable, safe, and effective therapeutic agents(25).

Applications of Copper Nanoparticles (CuNPs) in Drug Delivery

The utilization of copper nanoparticles (CuNPs) as an innovative nanocarrier system in drug delivery has

garnered significant attention due to their unique physicochemical properties, high surface reactivity, and intrinsic biological activity. These nanoparticles are effectively loaded with and deliver a diverse array of therapeutic agents, attributed to their nanoscale dimensions and substantial surface area, as well as the ease with which their surfaces can be functionalized(26). Furthermore, green-synthesized CuNPs exhibit enhanced biocompatibility and reduced toxicity, rendering them suitable for biomedical applications. These nanoparticles possess the capability to enhance drug solubility, protect drugs from degradation, and facilitate targeted drug delivery to specific tissues or cells. Additionally, CuNPs can interact with biomembranes, thereby promoting more efficient cellular uptake and therapeutic delivery(27).

Mechanism of drug loading

The drug loading onto copper nanoparticles (CuNPs) primarily depends on the surface chemistry and the interaction between the therapeutic molecules and the nanoparticles. CuNPs can be loaded with drugs through various processes, including physical adsorption, electrostatic interactions, covalent bonding, and encapsulation(28). The presence of functional groups on the nanoparticle surface, such as hydroxyl, carboxyl, and amino groups, facilitates strong interactions between the nanoparticle surface and drug molecules, thereby enhancing loading efficiency(29). The release of drugs from CuNPs can occur through diffusion, desorption, or degradation of the nanoparticle matrix. Environmental factors, such as ionic strength, temperature, and pH, typically influence the release mechanism. For instance, pH-sensitive release systems can be developed to selectively release drugs in acidic environments, such as tumor tissues, to improve therapeutic specificity. The release of CuNPs is controlled to ensure a steady supply of the drug at the delivery site, thereby reducing the frequency of dosing and minimizing side effects on the human body. Additionally, surface coatings or polymer layers can be employed to further regulate the kinetics of drug release by providing a diffusion barrier. CuNPs can be modified to meet the specific requirements of various therapeutic applications due to their ability to control drug loading and release profiles(30).

Targeted Drug Delivery

The objective of targeted drug delivery using copper nanoparticles (CuNPs) is to selectively transport therapeutic agents to diseased tissues or cells while minimizing effects on healthy tissues. This is achieved by functionalizing the surface of CuNPs with targeting ligands, such as antibodies, peptides, or small molecules, which can recognize and bind to specific receptors on target cells. The small size of CuNPs facilitates their penetration through biological barriers and into target tissues, particularly tumors, via the enhanced permeability and retention (EPR) effect(31). Surface modification further enhances targeting capability by promoting receptor-mediated endocytosis, thereby increasing nanoparticle uptake by cells. Targeted delivery not only improves therapeutic efficacy but also reduces systemic toxicity and side effects, which is particularly advantageous in cancer treatment, where selective targeting of tumor cells is crucial. Additionally, the combination of targeting ligands with a controlled release system enhances the efficacy and precision of drug delivery systems(32).

Controlled Release Behavior

The behavior of controlled release is a critical characteristic of copper nanoparticle-based drug delivery systems, as it facilitates a sustained and predictable release of therapeutic agents over an extended duration. This property aids in maintaining optimal drug concentrations at the target site, thereby enhancing therapeutic efficacy and reducing the frequency of dosing. By modulating nanoparticle composition, surface coating, and environmental conditions, the release profile of drugs from CuNPs can be effectively controlled(33). For instance, polymer-coated CuNPs may provide a matrix that impedes drug diffusion, resulting in delayed release. Additionally, stimuli-responsive systems can be engineered to deliver drugs in response to specific triggers, such as pH, temperature, or enzymatic activity. Controlled release systems are particularly advantageous in the management of chronic diseases, where prolonged drug administration is necessary. They also contribute to reducing variability in drug concentration, thereby minimizing the risk of toxicity and adverse effects. Overall, controlled drug release significantly enhances the therapeutic efficacy and safety of CuNP-based delivery systems(34).

Interaction with Biological Systems

The interaction of copper nanoparticles (CuNPs) with biological systems is pivotal in determining their efficacy as drug carriers. Upon administration, CuNPs engage with biological fluids, proteins, and cell membranes, thereby influencing their distribution, cellular uptake, and therapeutic effects. A notable aspect of this interaction is the formation of a protein corona on the nanoparticle surface, which may affect their stability and cellular recognition. The interaction between CuNPs and cellular membranes, as well as their uptake mechanisms, is influenced by the surface

properties of the particles, such as charge and functional groups(35). Typically, cells internalize nanoparticles via endocytosis, facilitating efficient drug delivery. Additionally, CuNPs can generate reactive oxygen species, which may contribute to their therapeutic action, particularly in cancer treatment. However, excessive interaction can lead to toxicity, highlighting the necessity of designing nanoparticles optimally to ensure safe application. Overall, a comprehensive understanding of CuNPs' interactions with biological systems is essential to enhance their functionality and ensure their safe use in drug delivery(36).

Medical Uses of Copper Nanoparticles

The utilization of copper nanoparticles in biological therapies has demonstrated significant potential across various therapeutic applications. This potential is largely attributable to the unique biological properties of copper nanoparticles and their capacity to function as drug carriers. Their multifunctionality enables them to facilitate drug delivery while also providing intrinsic therapeutic effects, thereby enhancing their efficacy in the treatment of diverse diseases(37).

Anticancer Activity

Copper nanoparticles have been demonstrated to have a promising anticancer effect because of their capability in producing oxidative stress, reactive oxygen species, and interfering with the cellular processes in cancer cells. These nanoparticles have the ability to localize into tumor tissues selectively and increase delivery of chemotherapeutic agents. Also, CuNPs have the ability to induce apoptosis and prevent tumor growth; hence, they can be used to treat cancer(38).

Antimicrobial Activity

Copper nanoparticles (CuNPs) exhibit significant antimicrobial potential against a broad spectrum of microorganisms, including Gram-positive and Gram-negative bacteria, fungi, and certain viruses. This antimicrobial activity is primarily attributed to various synergistic mechanisms that disrupt essential cellular processes in microbial systems(39). A prominent mechanism involves the interaction of CuNPs with microbial cell membranes, resulting in structural damage, increased membrane permeability, and cell lysis. Due to their small size and large surface area, CuNPs can efficiently penetrate microbial cells, thereby enhancing their antimicrobial efficacy. Another critical mechanism is the generation of reactive oxygen species (ROS), such as hydroxyl radicals and superoxide anions, which induce oxidative stress in microbial cells. This oxidative stress damages cellular components, including lipids, proteins, and nucleic acids, ultimately leading to cell death(40). Additionally, copper ions released from CuNPs can interact with intracellular proteins and enzymes, disrupting metabolic pathways and inhibiting microbial growth. CuNPs also interfere with DNA replication and protein synthesis in microbes, further contributing to their antimicrobial effect. These properties are particularly significant as biofilms often exhibit resistance to conventional antibiotics. Consequently, CuNPs have been widely applied in antimicrobial coatings, wound dressings, and drug delivery systems for the treatment of infectious diseases. Furthermore, green-synthesized CuNPs demonstrate enhanced biocompatibility and reduced toxicity, making them suitable for biomedical applications. Overall, CuNPs represent a promising next-generation antimicrobial agent due to their potent antimicrobial activity and ability to overcome drug resistance(41).

Anti-inflammatory Activity

Copper nanoparticles (CuNPs) have demonstrated significant anti-inflammatory properties, making them potentially beneficial in the treatment of various inflammatory diseases. Inflammation is a complex biological process involving the mobilization of immune cells and the release of pro-inflammatory mediators, such as cytokines, chemokines, and reactive oxygen species. CuNPs have been shown to modulate these inflammatory pathways by regulating the expression of key inflammatory mediators. One of the primary mechanisms by which CuNPs mitigate inflammation is through the suppression of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β). By inhibiting these cytokines, CuNPs help control excessive inflammatory responses and prevent tissue damage. Additionally, CuNPs can inhibit the activation of nuclear factor kappa B (NF-κB), a crucial transcription factor in the regulation of inflammation. The antioxidant properties of CuNPs, which include scavenging free radicals and reducing oxidative stress, further contribute to their anti-inflammatory effects(42). This dual action enhances their therapeutic potential. Furthermore, green-synthesized CuNPs, which are coated with natural biomolecules, offer increased biocompatibility and reduced cytotoxicity, making them safer for therapeutic use. These attributes render CuNPs applicable in treating inflammatory conditions such as arthritis, skin disorders, and chronic inflammatory diseases. Moreover, CuNPs can enhance the efficacy and reduce the side effects of anti-inflammatory drugs by

being incorporated into drug delivery systems for targeted delivery. Overall, copper nanoparticles present a promising avenue for the development of innovative anti-inflammatory therapies(43).

Wound Healing

Copper nanoparticles (CuNPs) are instrumental in wound healing by stimulating various biological activities essential for tissue repair and regeneration. CuNPs have been demonstrated to positively influence the intricate process of wound healing, which includes the phases of hemostasis, inflammation, proliferation, and remodeling(44). A primary mechanism of CuNPs in wound healing is the stimulation of angiogenesis, or the formation of new blood vessels. CuNPs release copper ions that activate angiogenic factors, such as vascular endothelial growth factor (VEGF), thereby enhancing blood flow to the injured tissue and expediting the healing process. In addition to promoting angiogenesis, CuNPs also enhance collagen synthesis, which is crucial for the integrity and strength of newly formed tissue. They facilitate the proliferation and migration of fibroblasts, further aiding tissue regeneration. The antimicrobial properties of CuNPs are vital in preventing wound infections, which can otherwise prolong the healing process. By inhibiting the growth of pathogenic microorganisms, CuNPs create a conducive environment for tissue repair(45).

Other Biomedical Applications

In addition to their established roles in drug delivery, antimicrobial activity, and wound healing, copper nanoparticles (CuNPs) have found diverse applications in various biomedical fields due to their unique physicochemical and biological properties. A key application of CuNPs is in biosensing, where their excellent electrical conductivity and surface reactivity enable the detection of biomolecules with high sensitivity and specificity. CuNP-based sensors have been developed for the detection of glucose, proteins, DNA, and other clinically relevant biomarkers. Another significant application is in biomedical imaging, where CuNPs serve as contrast agents due to their optical and electronic properties(46). These nanoparticles facilitate enhanced imaging of tissues and organs, aiding in early diagnosis and monitoring of diseases. Furthermore, CuNPs are extensively explored in theranostics, which combines therapeutic and diagnostic functions in a single platform. This approach allows for simultaneous disease detection and treatment, thereby improving clinical outcomes. Copper nanoparticles also exhibit catalytic properties that can be utilized in enzyme-mimicking systems and oxidative stress modulation. Additionally, their role in tissue engineering is gaining attention, as they are used to enhance scaffold properties and promote cell growth and differentiation. Green-synthesized CuNPs offer added advantages of biocompatibility and reduced environmental impact, making them suitable for advanced biomedical applications. Overall, the multifunctional nature of CuNPs continues to expand their potential in modern medicine, paving the way for innovative therapeutic and diagnostic solutions(47).

New Developments and Research Directions.

Hybrid Nanoparticles

Hybrid nanoparticles constitute an advanced class of nanocarriers that amalgamate the advantageous properties of diverse materials, including metals, polymers, and lipids, to optimize drug delivery performance. Specifically, in the context of copper nanoparticles, hybrid systems are frequently engineered by integrating CuNPs into polymeric scaffolds, lipid-based carriers, or other metallic nanoparticles to enhance stability, biocompatibility, and targeting capabilities(48). These systems address the limitations of unifunctional nanoparticles, which are composed of single components, by offering multifunctionality, such as improved drug loading, controlled release, and enhanced interaction with biological systems.For instance, polymer-copper hybrid nanoparticles can provide a protective layer that mitigates oxidation and toxicity without compromising the therapeutic efficacy of copper. Similarly, lipid-copper hybrid systems improve membrane compatibility and facilitate efficient cellular uptake. These hybrid nanocarriers can also be designed to deliver multiple therapeutic agents concurrently, enabling combination therapy for complex diseases such as cancer. Furthermore, the physicochemical properties of hybrid nanoparticles, including particle size, surface charge, and release kinetics, can be more readily controlled. Their multifunctionality renders them suitable for theranostic applications, where both diagnosis and therapy are integrated on a single platform. Despite these promising advantages, challenges related to formulation complexity, scalability, and cost persist. Nonetheless, ongoing research and technological advancements are anticipated to address these challenges and enhance the utility of hybrid nanoparticles in medical applications(49).

Functionalization Strategies

Functionalization of copper nanoparticles (CuNPs) is a critical strategy aimed at enhancing their efficacy in drug delivery systems. This process involves the surface modification of CuNPs with various

molecules, including polymers, ligands, peptides, antibodies, or small targeting moieties, to augment their stability, specificity, and biocompatibility. Surface functionalization ensures improved interaction between the nanoparticles and biological systems, thereby increasing the likelihood of successful drug delivery to specific body regions. A primary objective of functionalization is to achieve effective targeted drug delivery through receptor-mediated mechanisms. Nanoparticles can selectively target and penetrate specific cells by conjugating ligands that bind to particular cell receptors, resulting in enhanced therapeutic efficacy and reduced off-target effects(50). Additionally, functionalization may enhance the solubility and dispersion of nanoparticles in biological fluids, preventing aggregation and extending circulation time. Polymer coatings, such as polyethylene glycol (PEG), are frequently employed to provide steric stabilization and reduce immune system recognition. This process, known as PEGylation, enhances the stability of nanoparticles and prolongs their systemic circulation. Furthermore, functionalization can impart stimuli-responsive behavior, enabling nanoparticles to release drugs in response to specific environmental conditions, such as pH or temperature(51).

Smart Nanocarriers

Smart nanocarriers represent an advanced class of drug delivery systems engineered to respond to specific internal or external stimuli, thereby enabling the precise and controlled delivery of therapeutic agents. In the context of copper nanoparticles, these intelligent systems are designed to react to variations in pH, temperature, enzymatic activity, or redox conditions, which are often altered in pathological tissues. This capability facilitates site-specific drug delivery, thereby minimizing systemic exposure and enhancing therapeutic efficacy(52). For instance, pH-sensitive copper nanoparticles can be employed to release drugs in acidic environments, such as tumor tissues or inflamed areas, ensuring targeted therapeutic action. Similarly, enzyme-responsive nanoparticles can be utilized to deliver drugs in the presence of specific enzymes that are overexpressed in certain diseases. These sophisticated systems offer superior control over drug delivery compared to traditional carriers. Beyond controlled release, smart nanocarriers can be integrated with imaging agents, allowing for real-time monitoring of drug delivery and therapeutic response(53). This versatility is particularly advantageous in theranostic applications, where therapeutic and diagnostic processes are combined. Despite their promise, the design and development of smart nanocarriers necessitate rigorous optimization to achieve stability, reproducibility, and safety. Nonetheless, they hold significant potential in the field of nanomedicine and are anticipated to play a crucial role in the future of targeted drug delivery(54).

Clinical Research

Clinical investigations into copper nanoparticle (CuNP)-based drug delivery systems remain in their nascent stages; however, significant progress has been achieved in preclinical trials, demonstrating their therapeutic potential. The majority of existing studies focus on the safety, efficacy, and pharmacokinetics of CuNPs in animal models(55). These investigations have yielded promising results in areas such as cancer treatment, antimicrobial therapy, and wound healing. Nonetheless, the transition from laboratory research to clinical application necessitates extensive evaluation in terms of toxicity, biodistribution, and long-term safety. Copper nanoparticles exhibit dose-dependent toxicity due to the release of copper ions and the generation of reactive oxygen species, necessitating the optimization of dosages and surface modification techniques(56). Although there is a gradual increase in clinical trials of nanoparticle-based drug delivery systems, including those containing metals, specific CuNP-based formulations remain limited. The regulatory landscape for nanomedicines is evolving, and standardized procedures should be more widely adopted to ensure consistent evaluation and acceptance(57).

Challenges and Limitations

Stability Issues

One significant challenge in the application of copper nanoparticles is their stability, primarily due to their pronounced tendency to oxidize and aggregate. Upon exposure to air or moisture, copper nanoparticles readily oxidize, forming copper oxide, which can alter their physicochemical properties and diminish their efficacy in drug delivery applications. Additionally, inadequate surface stabilization can lead to nanoparticle aggregation, resulting in increased particle size and decreased bioavailability. To mitigate these issues, green synthesis techniques employ natural capping agents to enhance stability to a certain extent(58). However, the long-term stability during storage and use remains problematic. Factors such as temperature, pH, and ionic strength of the medium can significantly impact nanoparticle stability. To address these limitations, surface modification and the use of stabilizing agents, often polymers, are commonly employed. Nonetheless, achieving sustained and stable performance continues to be a major concern that necessitates further investigation(59).

Reproducibility
Reproducibility presents a significant challenge in the green synthesis of copper nanoparticles, particularly when utilizing biological sources such as plant extracts. These biological materials may exhibit variability due to factors such as geographical location, climate, and extraction conditions, leading to differences in the properties of nanoparticles, including size, shape, and surface chemistry. Such variability can impact the performance and reliability of copper nanoparticle-based drug delivery systems, complicating the achievement of consistent results across different batches. Therefore, it is imperative to standardize synthesis protocols and characterization methods to address this issue(60).

Scale-Up Problems
Scaling up the production of copper nanoparticles from laboratory to industrial scale presents several challenges, including maintaining product consistency, regulating reaction conditions, and ensuring cost-effectiveness. Although green synthesis methods are simple and environmentally friendly, they are not necessarily easily scalable due to the variability in biological materials and reaction conditions(61).

Regulatory Challenges
The regulatory approval of nanoparticle-based drug delivery systems presents a considerable challenge due to the absence of standardized guidelines and comprehensive long-term safety data. It is imperative that copper nanoparticles undergo rigorous evaluation of their toxicity, biocompatibility, and environmental impact prior to their clinical application(62).

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