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ANTIMICROBIAL EFFICACY OF COPPER NANOPARTICLES: A COMPREHENSIVE REVIEW

Comprehensive Review

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ABSTRACT

Background: Copper has long been recognized for its antimicrobial and anti-inflammatory properties. With the advancement of nanotechnology, copper nanoparticles (Cu NPs) have garnered significant attention for their broad-spectrum antibacterial and antiviral properties. Cu NPs demonstrate potential in various medical applications, including infection control, biofilm prevention, and viral inactivation.

Objective: This review aims to evaluate the medical applications of copper nanoparticles, focusing on their antimicrobial and antiviral properties, their mechanisms of action, and their potential therapeutic benefits in treating bacterial and viral infections. The paper also discusses the safety concerns and potential toxic effects associated with Cu NPs.

Methods: A comprehensive review of recent literature was conducted, focusing on the antimicrobial and antiviral activities of copper nanoparticles against a variety of pathogens. The antiviral effects of Cu NPs, particularly against viruses such as Hepatitis B, C, HIV, and COVID-19, are explored. The review also highlights the applications of copper nanoparticles in healthcare settings, particularly in medical devices and hospital environments.

Results: Copper nanoparticles have shown exceptional efficacy in eliminating pathogenic microorganisms, including antibiotic-resistant bacteria and various viruses. The mechanisms behind their antimicrobial action include contact-killing properties, the release of reactive oxygen species (ROS), and viral genome inactivation. Cu NPs also exhibit significant promise in reducing bacterial biofilm formation, enhancing the effectiveness of medical devices, and inactivation of respiratory viruses like SARS-CoV-2.

Conclusion: Copper nanoparticles are emerging as a promising tool for combating microbial infections. Their potential to inactivate a wide range of pathogens, including viruses and bacteria, makes them highly valuable in medical and healthcare settings. However, further research is necessary to address potential health risks and optimize the use of Cu NPs in clinical applications.

Keywords: Antimicrobial Agents, Antiviral Agents, Copper, Copper Nanoparticles, Medical Devices, Nanotechnology, Viral Infections.

INTRODUCTION

Antimicrobial agents are synthetic substances designed to eliminate or inhibit bacterial growth while minimizing harm to surrounding tissues in the host. The term "antimicrobials," coined by Selman Waksman in 1940, refers to compounds with antibacterial effects, and these agents have become integral in various fields, including food packaging, materials science, pharmaceuticals, and water treatment (1). However, the widespread use and overuse of antimicrobial drugs have led to the rise of antimicrobial resistance in numerous bacterial species, making the development of alternative solutions crucial (2). It is now well-established that at least one microorganism has developed resistance to nearly every known antimicrobial (2). Nanoparticles (NPs) are colloidal particles, ranging from 1 to 1000 nm in size, that have gained significant attention in recent years for their ability to enhance the delivery and effectiveness of antimicrobial agents (3). Due to their unique properties, such as the ability to target drugs to specific sites of action, nanoparticles help reduce side effects and enhance drug absorption. These particles can interact with mucosal surfaces, bypassing the endo-lysosomal pathway, and are increasingly being studied for their antibacterial and antifungal properties (4). As the field of nanotechnology advances, nanoscale metals like copper have emerged as promising candidates for antimicrobial applications (7). Copper, a metal known for its antimicrobial properties, has demonstrated potent antibacterial effects against a wide range of pathogens. Copper nanoparticles (Cu NPs), in particular, have been shown to exhibit enhanced antibacterial activity with lower required concentrations compared to traditional antimicrobial agents (8). Furthermore, copper NPs can induce the production of free radicals, which cause DNA damage in bacterial cells, leading to their death (11). The antibacterial properties of copper nanoparticles have been further explored in studies focusing on their interaction with microbial cell membranes, resulting in significant disruption and cell death (15).

Application and Availability of Copper

Copper is an essential element for all living organisms, and its versatile properties make it valuable in various sectors, including health care, environmental management, and materials science (16). Copper nanoparticles possess multifunctional properties that make them suitable for a wide range of applications, including gas sensors and antimicrobial treatments (17). Historically, copper has been used as an effective antimicrobial agent in various forms, including copper-based compounds like CuSO4 and Cu(OH)2 (18). In healthcare settings, copper is commonly used in the ionization of silver and copper to control legionella bacteria in hospital water systems (20). The antimicrobial effects of copper have been demonstrated against numerous bacterial species, such as *Listeria monocytogenes*, *Salmonella enterica*, *Campylobacter jejuni*, *Escherichia coli*, and *Staphylococcus aureus* (21). The U.S. Environmental Protection Agency (EPA) has even recognized copper as the only element with officially acknowledged antibacterial properties (22). In fact, copper is capable of eliminating 99.9% of disease-causing bacteria within two hours of exposure (23). When compared to silver nanoparticles, copper nanoparticles have been found to exhibit stronger antibacterial activity against *Bacillus subtilis* and *E. coli* (25). The ability of copper surfaces to kill microorganisms through direct contact—referred to as "contact killing"—makes it an effective material for combating a variety of pathogens, including bacteria, yeasts, and viruses (26). Studies have shown that copper nanoparticles can reduce microbial populations by 7-8 logs per hour, highlighting their rapid antimicrobial action (27). This self-ionizing property of copper nanoparticles contributes to their effectiveness by generating oxidative stress and damaging microbial cells (28). After treatment with copper nanoparticles, all microbial cells on the surface are killed, confirming the antimicrobial potential of copper for various applications (29).

Antimicrobial Resistance Against Copper

While copper has long been recognized as an effective antimicrobial agent, recent studies have highlighted the emergence of copper resistance in certain pathogens. Some bacteria, particularly those in human, animal, and plant environments, have developed mechanisms to resist the antimicrobial effects of copper (30). This resistance presents a challenge to the continued use of copper as an antimicrobial agent and underscores the need for further research to understand the underlying mechanisms of microbial adaptability (31). In *E. coli*, two chromosomally encoded genes, *Cus* and *Pco*, have been identified as key contributors to copper resistance (32). Additionally, other Gram-negative bacteria, such as *Yersinia enterocolitica, Yersinia pestis, Erwinia carotovora, Yersinia pseudotuberculosis,* and *Citrobacter koseri*, also contain *Cue P*-like proteins, which help maintain cellular homeostasis in environments with high copper ion concentrations, thereby contributing to their resistance (34).

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Bactericidal Mechanism of Copper

The bactericidal properties of metals, including copper, have been studied for more than a century. Copper nanoparticles, in particular, have demonstrated broad-spectrum antimicrobial activity against a wide range of pathogens, including parasites, fungi, bacteria, and viruses (36). Metals such as mercury, aluminum, zinc, copper, lead, and iron have long been known to possess antimicrobial properties, as evidenced by early research conducted at the Columbus laboratories (37-38).

Copper and Copper Composites as Antibacterial Materials

Research on copper as an antibacterial material dates back to the late 19th century, with over 312 references published between 1892 and 1997 highlighting the antimicrobial effects of copper (39). The antibacterial mechanism of copper nanoparticles involves electrostatic interactions with the cell wall of Gram-negative bacteria, leading to membrane disruption and subsequent bacterial cell death (40). Copper's proven effectiveness against a broad spectrum of pathogens, combined with its availability and low cost, positions it as a promising candidate for future antimicrobial applications, both in medical and environmental settings. However, the emergence of copper-resistant pathogens necessitates continued research to refine the use of copper-based antimicrobial materials and explore novel ways to combat resistance.

Copper Nanoparticles Toxicity in Nature

The increasing presence of synthetic copper nanoparticles (Cu NPs) in natural water bodies has raised concerns about their potential ecological impact. These nanoparticles have the ability to disrupt the functioning of beneficial microorganisms within aquatic ecosystems, which can, in turn, affect the broader environmental balance and pose a risk to human health (40). The long-lasting antibacterial effects of Cu NPs are attributed to their persistence and stability in the environment, which may interfere with vital biological processes of various living organisms (41). While these properties make Cu NPs ideal for use in healthcare environments, antimicrobial drug production, and medical device coatings to reduce infection risks, they also highlight the need for careful management to avoid unintended ecological consequences (42). Studies have indicated that Cu NPs exert antibacterial effects on antibiotic-resistant bacterial species associated with healthcare-related infections, suggesting both their potential benefits and risks (43). Moreover, Cu NPs have been shown to inhibit bacterial biofilm formation, making them valuable in preventing infections related to medical devices (44).

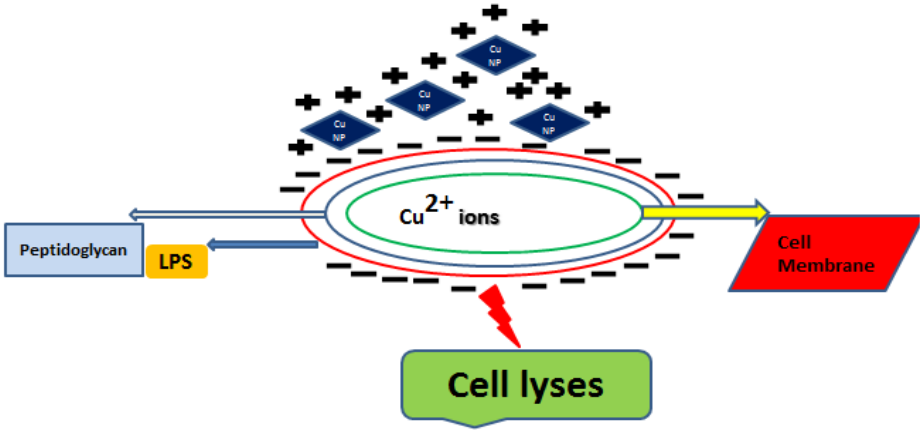

Figure 1: Mechanism of antibacterial action of Cu NPs causing lyses of the cell wall of gram negative cells.

Figure 1: The antibacterial mechanism of copper nanoparticles involves interacting with the cell wall of Gram-negative bacteria through electrostatic attraction (40).

Antimicrobial Potential of Copper Nanoparticles Against *E. coli* O157:H7

Escherichia coli O157:H7 is a pathogen classified as a group 3 biological agent due to its significant role in foodborne infections, particularly in the United Kingdom (45). This pathogen is capable of releasing highly toxic substances, leading to severe illnesses such as diarrhea in infected individuals. Research on the host response to these toxins has helped reveal the molecular mechanisms behind these dangerous infections (46). *E. coli* can cause a range of severe health issues, including hemolytic colitis, hemorrhagic diarrhea, and hemolytic uremic syndrome, with particular risk to immunocompromised individuals, children, and young adults under the age of 14 (47, 48). Given its clinical significance, it is crucial to explore effective antimicrobial agents, such as Cu NPs, to combat this pathogen.

Table 1: Copper Nanoparticle as Antimicrobial Agents

Bacteria	Copper Type/Method
Enterococci	Cu0 and Cu-alloy surfaces
S. cohnii	Cu0 and CuO/Cu2O
E. coli	Cu0 and CuO/Cu2O
S. aureus	CuO/Cu2O NPs
K. pneumonia	CuO/Cu2O NPs
E. coli	Inert gas condensation method (IGC)
E. coli; megaterium	Electrolysis method
Bacillus subtilis	Wet chemical synthesis
E. coli	N/A
Methicillin-resistant S. aureus (MRSA)	Thermal plasma technology
E. coli	Wet chemical synthesis
E. coli	Simple reduction method
Legionella pneumophila	Heating Cu2O NPs
Bacillus subtilis	Gel combustion route
E. coli (DH5)	Microwave irradiation
Salmonella typhi	Microwave irradiation
Pseudomonas aeruginosa	Through chemical means in chitosan polymer medium
Bacillus subtilis	Through chemical means in chitosan polymer medium
Staphylococcus aureus	Through chemical means in chitosan polymer medium
Salmonella choleraesuis	Through chemical means in chitosan polymer medium
Methicillin-resistant Staphylococcus epidermidis	Commercial CuO NPs
Vancomycin-resistant Enterococcus faecalis	Commercial CuO NPs
Pseudomonas spp.	Commercial CuO NPs
Proteus mirabilis	Commercial CuO NPs
Gram-negative: (Xanthomonas campestris)	Commercial CuO NPs
Pseudomonas fluorescens	Green synthesis method
Enterococcus faecalis	Based thermal decomposition
Shigella sonnei	Based thermal decomposition
Bacillus cereus	Hydrothermal synthesis method
S. mutans (PTCC1683)	Cu NPs MIC

Table 2: Antifungal Effects of Copper Nanoparticles

Fungi	References
Candida albicans	(49)
Candida species	(49)
Candida krusei (C.krusei)	(49)
Candida glabrata	(49)
Fusarium kuroshium	(50)
Fusarium solani	(50)
Neofusicoccum sp.	(50)
Fusarium oxysporum	(50)
Aspergillus niger	(51)
Aspergillus oryzae	(51)
Penicillium italicum	(52)
Penicillium digitatum	(52)
Fusarium solani	(53)
Curvularia	(53)
Botrytis cinerea	(54)
Sclerotinia sclerotiorum	(54)

Nano-sized Copper Particles as Antimicrobials

Copper nanoparticles have shown significant antimicrobial efficacy when compared to other nanoparticles, including silver. For example, when tested against *Bacillus species, S. aureus*, and *E. coli*, copper nanoparticles demonstrated greater effectiveness against *Bacillus subtilis* compared to silver nanoparticles. This enhanced effectiveness is attributed to the interaction between the carboxyl groups and surface amines of the bacterial cells and the copper nanoparticles, which disrupts bacterial membrane integrity (55). Copper oxide nanoparticles, in particular, are gaining attention for their ability to overcome microbial resistance by releasing copper ions that impair microbial cell function (56). In various studies, copper nanoparticles have been evaluated against a range of bacterial pathogens, including methicillin-resistant *S. aureus, S. epidermidis, E. coli*, and *Pseudomonas aeruginosa*, with minimum bactericidal concentrations (MBCs) ranging from 100 mg/ml to 5000 mg/ml. In one study, the antibacterial properties of copper nanoparticles against *E. coli* were investigated, and the results revealed significant antibacterial efficacy in both liquid and solid media (57, 58). Researchers found that Cu NPs disrupted bacterial cell walls, leading to irregular cell shapes and pore formation, which contributed to bacterial death (60).

Further studies on the cytotoxic effects of copper nanoparticles showed that their toxicity was influenced by several factors, including pH, temperature, air circulation rate, nanoparticle concentration, and microbial population (61). Additionally, copper nanoparticles in combination with carbon nanotubes have been shown to enhance antimicrobial properties, particularly in inhibiting the growth of *E. coli* (63). This combination of copper nanoparticles and multi-walled carbon nanotubes offers an improved killing rate, which is more effective than copper nanoparticles alone (64). Studies comparing copper nanoparticles synthesized through different methods, such as electrolysis and chemical reduction, have revealed that electrolysis-produced nanoparticles exhibit superior antibacterial effects, particularly against *E. coli* (65).

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Medical Applications of Copper

Copper has long been recognized for its antimicrobial and anti-inflammatory properties, making it an invaluable agent in various medical applications (70). Copper nanoparticles (Cu NPs), with their high surface area to volume ratio, exhibit broad-spectrum antibacterial and antiviral effects, making them particularly effective in combating a wide range of pathogens (71). In 2008, copper and its compounds were officially acknowledged as the primary metallic element with antibacterial properties. According to the U.S. Environmental Protection Agency (EPA), copper can eliminate 99.9% of bacterial infections within just two hours of contact, which has led to extensive research into its antibacterial properties, particularly on copper surfaces. These surfaces demonstrate a "contact-killing" mechanism, where pathogens are swiftly eradicated, achieving a killing rate of 7-8 logs per hour (72). This rapid action underscores the significant potential of copper in medical settings, particularly for infection control.

Antiviral Characteristics of Copper

The antiviral properties of copper have also garnered considerable attention in recent studies. Copper, in various forms such as copper oxide, copper oxide nanoparticles, and copper alloys, has been shown to effectively degrade and neutralize viral particles. These antiviral effects have been explored with a focus on diseases such as COVID-19, with copper surfaces found to inactivate the virus efficiently. Research has demonstrated that while SARS-CoV-2 can survive on non-copper surfaces like stainless steel and plastic for extended periods—up to 72 hours—no viable viral particles were detected on copper-impregnated surfaces (73, 74). This ability to inhibit viral survival, particularly in healthcare environments, positions copper as an effective and cost-efficient tool in preventing the spread of infectious diseases (75). Furthermore, copper nanoparticles have demonstrated efficacy against a wide range of viruses, including Hepatitis B, Hepatitis C, Herpes simplex, Human immunodeficiency virus (HIV), Respiratory Syncytial Virus (RSV), and many others (77). Studies have also highlighted the capacity of copper nanoparticles to target specific viral proteins, such as VPg (viral-genome-protein), which is associated with viral infectivity, reducing the viral genome's copy number (80). This specificity further supports copper's potential as a therapeutic agent in viral infections.

Copper's antiviral action is not limited to bacterial or respiratory viruses; it also has demonstrated inactivation effects against other viruses, such as Hepatitis B and C, Herpes simplex, and the common cold (77). Copper alloys, composed of 65% to 99.9% copper, have been particularly effective in inactivating murine norovirus (MNV-1), a common surrogate for human norovirus. The antiviral mechanism is primarily driven by the release of reactive oxygen species (ROS) and the subsequent degradation of the viral genome (78, 79). Moreover, research has shown that copper nanoparticles, when integrated into surfaces like masks and medical devices, can help prevent the transmission of viral infections, including monkeypox and vaccinia viruses (81).

Table 3: Antiviral Effects of Cu NPs and Mechanism of Degradation Modified from (84)

Virus	Method
Human coronavirus	Capsid damage, loss of surface spikes, and viral genome inactivation
Human norovirus	RNA degradation and capsid damage
Junin Virus	Inactivation by ROS
Cytomegalovirus (CMV)	Viral neutralization
Human Immunodeficiency Virus (HIV)	Protease inactivation, nucleic acid degradation
Hepatitis B Virus (HBV)	Cu NPs
Hepatitis C Virus (HCV)	Blockage of attachment and entry stages
Influenza A	RNA damage
Herpes Simplex Virus (HSV-1)	Degradation of viral genome
Bacteriophage Qß	ROS, leached copper ions

Virus	Method
Bacteriophage R17	Degradation of phage genome
Poliovirus	Inactivation of viral RNA
Adenovirus Type I (HAdV)	Viral neutralization
Rhinovirus 2 (HRV-2)	Viral neutralization

Adverse Effects of Copper Nanoparticles on Human Health

While copper nanoparticles offer considerable medical benefits, their potential toxicity on human health, particularly at the cellular level, cannot be overlooked. Research has demonstrated that copper nanoparticles can have cytotoxic effects on human cardiovascular microvascular endothelial cells (HCMECs). When exposed to Cu NPs at concentrations ranging from 1.001 to 100 µg/mL for 12 to 24 hours, both copper and zinc nanoparticles exhibited cytotoxic effects, as evidenced by reduced cell proliferation rates measured using the tetrazolium salt (MTT) test. Additionally, studies using Capitella teleta models further revealed that the harmful effects of copper nanoparticles are influenced by their form, whether they are spherical, platelet, or rod-shaped CuO NPs (85). These findings emphasize the need for further research to assess the safety of copper nanoparticles in clinical applications and to develop strategies to mitigate potential risks associated with their use.

CONCLUSION

Copper, particularly in the form of nanoparticles, has emerged as a highly effective antimicrobial and antiviral agent. The nanoscale properties of copper nanoparticles significantly enhance their ability to eliminate pathogenic microorganisms, making them a promising tool for combating infections caused by bacteria, viruses, and fungi. Copper nanoparticles have demonstrated efficacy in treating a variety of viral infections, including influenza, HIV, Hepatitis B and C, and COVID-19, while also inhibiting the formation of bacterial biofilms, a common challenge in medical device-related infections. Despite their significant potential, the potential toxic effects of copper nanoparticles on human cells necessitate further investigation to ensure their safe use in medical applications. Overall, copper nanoparticles represent a promising future in the development of therapeutic agents for a range of microbial infections, both bacterial and viral, while offering a valuable tool in infection prevention, particularly in healthcare environments.

Author	Contribution
Author 1	Conceptualization, Methodology, Formal Analysis, Writing - Original Draft, Validation, Supervision
Author 2	Methodology, Investigation, Data Curation, Writing - Review & Editing
Author 3	Investigation, Data Curation, Formal Analysis, Software
Author 4	Software, Validation, Writing - Original Draft
Author 5	Formal Analysis, Writing - Review & Editing
Author 6	Writing - Review & Editing, Assistance with Data Curation

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