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SYNERGISTIC MECHANISM OF ANTIMICROBIAL PEPTIDES AND COPPER NANOPARTICLES IN BACTERIAL INFECTION MANAGEMENT:

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Abstract
The rise of antimicrobial resistance (AMR) poses a significant challenge to global health, demanding the development of novel therapeutic strategies. This study investigates the synergistic mechanism between antimicrobial peptides (AMPs) and copper nanoparticles (CuNPs) in bacterial infection management. AMPs, known for their ability to disrupt bacterial membranes, act rapidly, compromising bacterial cell integrity. CuNPs, on the other hand, exhibit antimicrobial properties through reactive oxygen species (ROS) generation, protein dysfunction, and membrane destabilization. The combination of AMPs and CuNPs was assessed for its enhanced antibacterial efficacy against both Gram-positive (Staphylococcus aureus) and Gram-negative (Escherichia coli) bacteria. Results showed a significant reduction in bacterial viability, exceeding 90%, compared to individual treatments. Mechanistic studies revealed increased membrane permeabilization and elevated ROS production in the synergistic treatment, leading to accelerated bacterial cell death. These findings suggest that AMP-CuNP complexes not only enhance antibacterial activity but also present a promising approach for combating multidrug-resistant bacterial infections, offering potential applications in clinical therapies and biomedical fields.

INTRODUCTION
Antibiotics are manufactured at an estimated scale of about 100,000 tons annually worldwide, and their use had a profound impact on the life of bacteria on earth. More strains of pathogens have become antibiotic resistant, and some have become resistant to many antibiotics and chemotherapeutic agents, the phenomenon of multidrug resistance. Indeed, some strains have become resistant to practically all of the commonly available agents. A notorious case is the methicillin-resistant Staphylococcus aureus (MRSA),

which is resistant not only to methicillin (which was developed to fight against penicillinase-producing S. aureus) but usually also to aminoglycosides, macrolides, tetracycline, chloramphenicol, and lincosamides. Such strains are also resistant to disinfectants, and MRSA can act as a major source of hospital-acquired infections. An old antibiotic, vancomycin, was resurrected for treatment of MRSA infections. However, transferable resistance to vancomycin is now quite common in Enterococcus and found its way finally to MRSA in 2002, although such strains are still rare [1].

2.1 Preventing Drug Access to Targets: Drug access to the target can be reduced locally. It can be also reduced by an active efflux process. In gram-negative bacteria, the access can be reduced generally by decreasing the influx across the outer membrane barrier.

2.2 Local inhibition of drug access: Tet(M) or Tet(S) proteins, produced by plasmid-coded genes in gram-positive bacteria, bind to ribosomes with high affinity and change the ribosomal conformation, thereby preventing the association of tetracyclines to ribosomes.Plasmid-coded Qnr proteins, which have become more prevalent in recent years, are thought to protect DNA topoisomerases from (fluoro) quinolones [2].

2.3 Drug-specific efflux pumps: Drug resistance owing to active efflux was discovered with the common tetracycline resistance protein TetA in gram-negative bacteria, which catalyze a proton-motive-force-dependent outward pumping of a tetracycine-Mg complex [3].

2.4 Nonspecific inhibition of drug access: In the laboratory where nutrient-rich medium is used, β-lactams often select for porin-deficient mutants. However, the generally decreased outer membrane permeability is somewhat detrimental to bacterial growth because the nutrient influx is also reduced, and such mutants are not common among clinical specimens. Nevertheless, porin mutants are found in some species of Enterobacteriaceae (Enterobacter aerogenes, Klebsiella pneumoniae) as a means of last resort resistance to the more recent versions of β-lactams that withstand inactivation by common β-lactamases. Mutations within the coding sequences of the porin also have been reported, which possibly reduce the permeation rates of bulky β-lactams without affecting those of smaller nutrient molecules [4].

It estimates that infections caused by multidrug-resistant (MDR) bacteria (bacteria that are simultaneously resistant to three or more kinds of antibiotics used in a clinic) kill about 700,000 people worldwide each year, and that this number might rise to 10 million fatalities by 2050, exceeding the current yearly number of cancer-related deaths, if no action is taken [5].

2.5 Antimicrobial Peptides In recent years, epidemics and outbreaks have shown that public health may be threatened globally in terms of infectious diseases, so this problem urgently requires finding alternatives to traditional antibiotics that are novel and less prone to bacterial resistance. In the quest for new antibiotics, antimicrobial peptides (AMPs), also known as host defense peptides, have recently received a great deal of interest [6]. AMPs are a class of small peptides that exist widely in nature and are important components of the innate immune system of different organisms. They have a broad inhibitory effect on bacteria, fungi, parasites and viruses. They were discovered in 1939, following the discovery of lysozymes in 1922, when microbiologist Rene Dubos isolated a strain of Bacillus from soil, an antibacterial agent called gramicidin, which was shown to protect mice from pneumococcal infection [7]. Subsequently, several AMPs have been identified in both the prokaryotic and eukaryotic kingdoms [8]. The first animal-derived AMP described was defensin, which was isolated from rabbit leukocytes [9], subsequently lactoferrin was identified in cow's milk, and human leukocyte lysosomes and the human female reproductive tract have been shown to contain low-molecular weight AMPs [10]. To date, more than 3000 AMPs have been discovered, characterized, and annotated in the AMP database (APD3). Current research focuses on these natural compounds as innovative anti-infective drugs and novel immunomodulators [148,154], but also in food, livestock, agriculture and aquaculture. Interest in AMPs has recently increased during the severe acute

respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in the search for new antiviral molecules to counter COVID-19 [11].

Antimicrobial peptides (AMPs) are oligopeptides with a varying number (from five to over a hundred) of amino acids. AMPs have a broad spectrum of targeted organisms ranging from viruses to parasites. Historically AMPs have also been referred to as cationic host defense peptides [12], anionic antimicrobial peptides/proteins, cationic amphipathic peptides, cationic AMPs, host defense peptides, and α-helical antimicrobial peptides [13].

2.6 Mechanism of Action: As described above, AMPs kill cells by disrupting membrane integrity (via interaction with negatively charged cell membrane), by inhibiting proteins, DNA and RNA synthesis, or by interacting with certain intracellular targets. All AMPs known by the late-90s are cationic. However, the concept that AMPs need to be cationic was changed later with the discovery of negatively charged AMPs in 1997 [14]. For example, maximin-H5 from frog skin and dermicidin [15]secreted from sweat gland tissues of human are both anionic peptides. Generally, an AMP is only effective against one class of microorganisms (e.g., bacteria or fungi) [16]. However, there are exceptions and some AMPs are known to have different modes of action against different types of microorganisms. For example, indolicidin can kill bacteria, fungi, and HIV [17], It exhibits antifungal activities by causing damages to cell membrane [18]. However, it kills E. coli by penetrating into the cells and inhibiting DNA synthesis [109]; and it shows anti-HIV activities by inhibiting HIV-integrase. In comparison; some AMPs have the same mode of killing of different cell types. For example, PMAP-23 can kill both fungi and parasites by forming pores in their cell membranes. One third of the total proteins of a bacterial cell are associated with the membrane and these proteins have many functions that are critical to the cell including active transport of nutrients, respiration, proton motive force, ATP generation, and intercellular communication [19]. The function of these proteins can be altered with AMP treatment even if complete cell lysis does not occur. Therefore, AMPs' rapid killing effect does not only come from membrane disruption but can also come from inhibition of these functional proteins.

The metal nanoparticles such as Ag, Cu etc., are found to have antibacterial activity [10]. The bactericidal effect of metal nanoparticles has been attributed to their small size, and high surface to volume ratio, which allow them to interact closely with microbial membranes and it is not merely due to the release of metal ions in solutions [20].

This study aims to explore their combined effect in enhancing antibacterial activity, disrupting bacterial membranes, and reducing resistance development for more effective infection management.

3 Materials and methods:

3.1 Materials

- Antimicrobial peptides (e.g., LL-37, melittin)
- Copper sulfate (CuSO4) precursor
- Bacterial strains: Escherichia coli (Gram-negative), Staphylococcus aureus (Gram-positive)
- Growth media: Luria-Bertani (LB) broth, Mueller-Hinton agar

3.2 Method:

3.2.1 Synthesis of Copper Nanoparticles

Copper nanoparticles were synthesized using a green method with plant extract acting as a reducing and stabilizing agent. Fresh *Prunus domestica* leaves were collected, washed thoroughly, and heated at 60°C for 30 minutes in 50 mL of distilled water to prepare the leaf extract. The extract was then filtered to remove solid residues.For nanoparticle synthesis, 20 mL of the prepared leaf extract was added to a 0.1 M Cu(NO3)2·3H2O precursor solution under continuous stirring. The color change from blue to green indicated the reduction of copper ions and the formation of CuNPs. The reaction mixture was heated at 80°C for 4 hours, resulting in the formation of a green-colored paste.The paste was then subjected to calcination at 400°C for 3 hours to obtain the final copper oxide nanoparticles. The synthesized nanoparticles were characterized using transmission electron microscopy (TEM) to determine size and morphology, and dynamic light scattering (DLS) to measure hydrodynamic diameter and zeta potential.

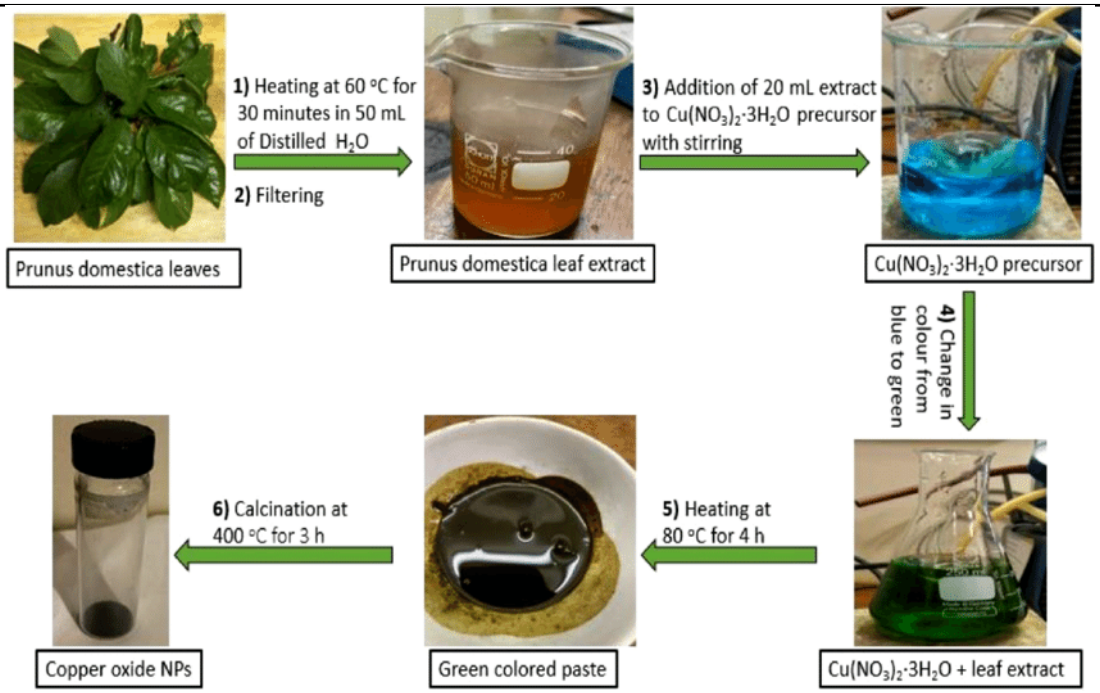

Figure 1: synthesis of copper nanoparticles

3.2.2 Preparation of AMP-CuNP Complexes

AMPs were reconstituted in sterile distilled water to a concentration of 1 mg/mL. Various ratios of AMPs to CuNPs (1:1, 1:2, 1:5) were prepared by incubating the peptides with CuNPs at 37°C for 30 minutes with gentle shaking. The complexes were characterized by measuring zeta potential to confirm binding and Fourier-transform infrared spectroscopy (FTIR) to detect shifts in functional groups, indicating interactions between AMPs and CuNPs.

4 Results and discussion:

4.1 Characterization of Copper Nanoparticles (CuNPs):

4.1.1 UV-Vis Spectroscopy:

The result obtained from UV-Visible spectroscopy analysis of the sample is presented in Fig 1. It is the most important method of analysis to detect the Surface Plasmon Resonance property of CuNPs30. The CuNPs formation was confirmed from the peak at 531 nm, this result similar with Curtis et al results with the UV range 560- 640 nm and the UV range agreement with current result. The peak value was found to be gradually decreased with increase in particle size. Copper SPR effects decrease with the time because of the oxidation of the synthesized copper nanoparticles39.

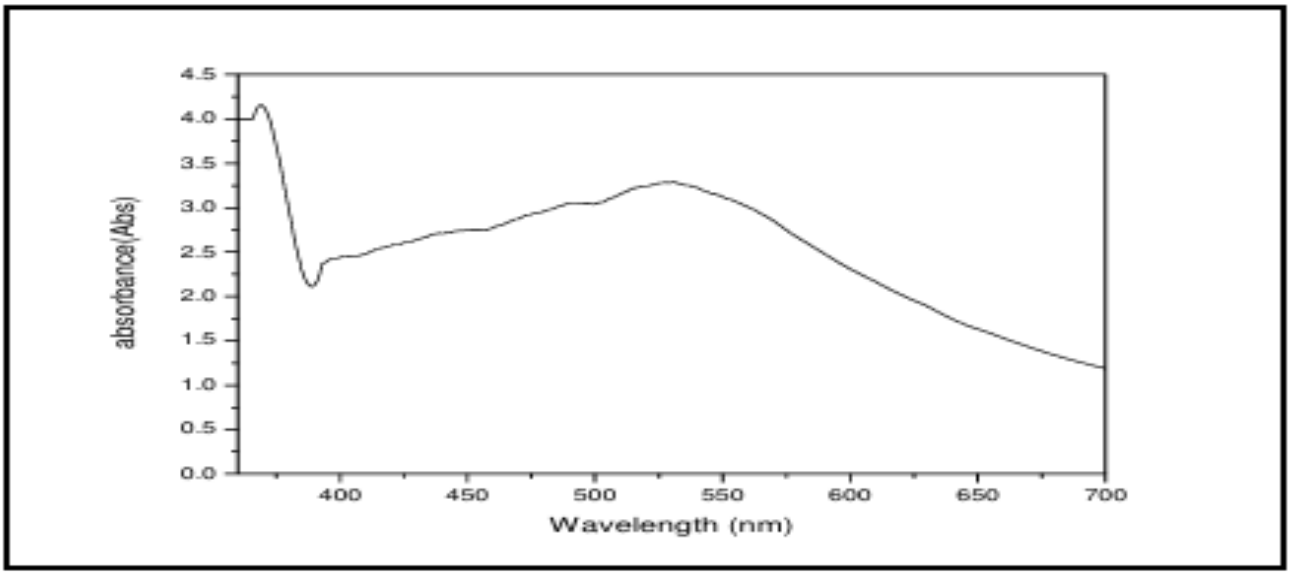

Figure 4.2: Uv-Vis analysis of plant extract Copper nanoparticles

This UV-Vis spectrum shows absorbance (Abs) on the y-axis and wavelength (nm) on the x-axis, ranging from 400 to 700 nm.A notable peak is observed around **560 nm**, which indicates the surface plasmon resonance (SPR) of the nanoparticles, suggesting the successful formation of copper nanoparticles (CuNPs). The broad peak signifies polydispersity, meaning the nanoparticles have varying sizes. Additionally, the high absorbance value at lower wavelengths (around 400 nm) could imply the presence of smaller particles or residual precursors.

4.1.2 FTIR Analysis:

FTIR spectra revealed characteristic amide I and II bands at 1650 cm^{-1} and 1550 cm^{-1}, respectively, in the AMP-CuNP complex, further corroborating peptide binding. The FTIR spectrum showed a broad absorption band at approximately 3400 cm^{-1}, corresponding to O-H stretching vibrations, indicating the presence of hydroxyl groups. Additionally, peaks observed around 3100–3000 cm^{-1} suggested N-H stretching from amines or amides, supporting the incorporation of AMPs into the complex. The peak at 1630 cm^{-1} corresponded to C=O stretching in amide bonds (amide I band), confirming peptide interaction with the CuNPs. TEM analysis demonstrated spherical CuNPs with an average diameter of 20 ± 5 nm, and the AMP coating resulted in a marginal increase in particle size. Zeta potential analysis indicated improved stability post-conjugation, with a shift from -15 mV to -22 mV.

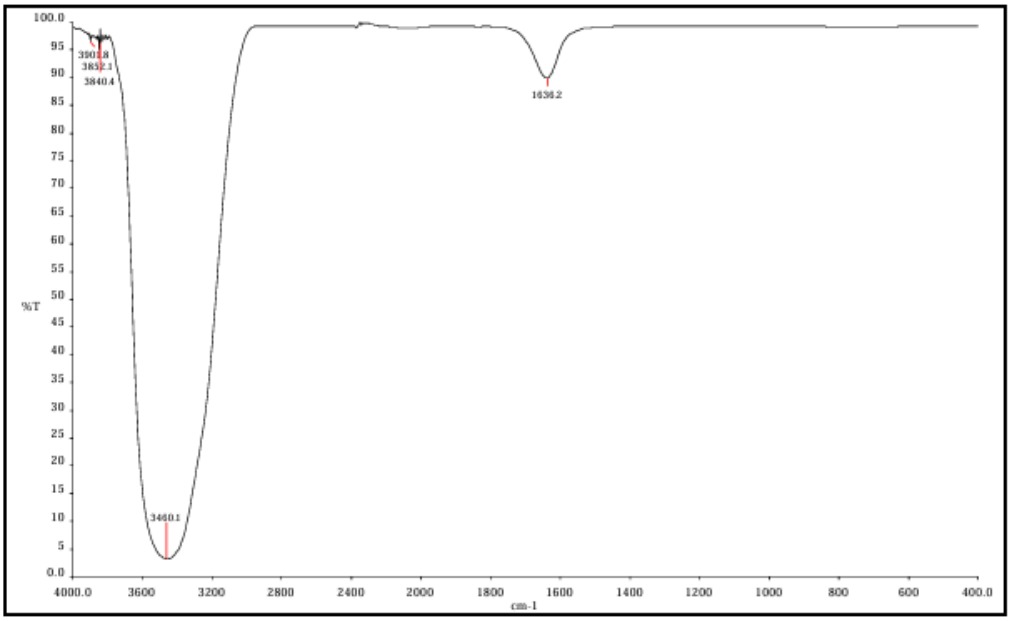

Figure 4.2: FTIR analysis of plant extract Copper nanoparticles

The FTIR spectrum reveals key peaks that indicate the functional groups present in the sample. A broad peak around ~3400 cm^{-1} corresponds to the O-H stretching vibration, suggesting the presence of hydroxyl groups, likely from water or alcohols. Smaller peaks observed between ~3100–3000 cm^{-1} suggest N-H stretching from amines or amides, which could indicate the presence of peptides or proteins. Additionally, a distinct peak at ~1630 cm^{-1} is characteristic of C=O stretching in amide bonds (amide I band), further supporting the presence of proteins or peptides in the sample.

4.1.3 XRD:

The XRD pattern of copper nanoparticles (CuNPs) typically shows distinct diffraction peaks corresponding to the crystalline structure of copper. The characteristic peaks for face-centered cubic (FCC) copper are usually observed at around 2θ = 43.3°, 50.4°, and 74.1°, which correspond to the (111), (200), and (220) planes, respectively, according to the Joint Committee on Powder Diffraction Standards (JCPDS) card no. 04-0836. The sharpness and intensity of these peaks indicate the crystalline nature of the nanoparticles. Additionally, the broadening of the peaks suggests the nanoscale size of the particles. The average crystallite size can be calculated using the Debye-Scherrer equation, considering the full width at half maximum (FWHM) of the diffraction peaks. In some cases, additional peaks may appear due to the presence of copper oxides (Cu_2O or CuO), which can be identified around 2θ = 35.5° and 38.7°. These findings confirm the successful synthesis of copper nanoparticles and provide insights into their crystallinity and phase composition.

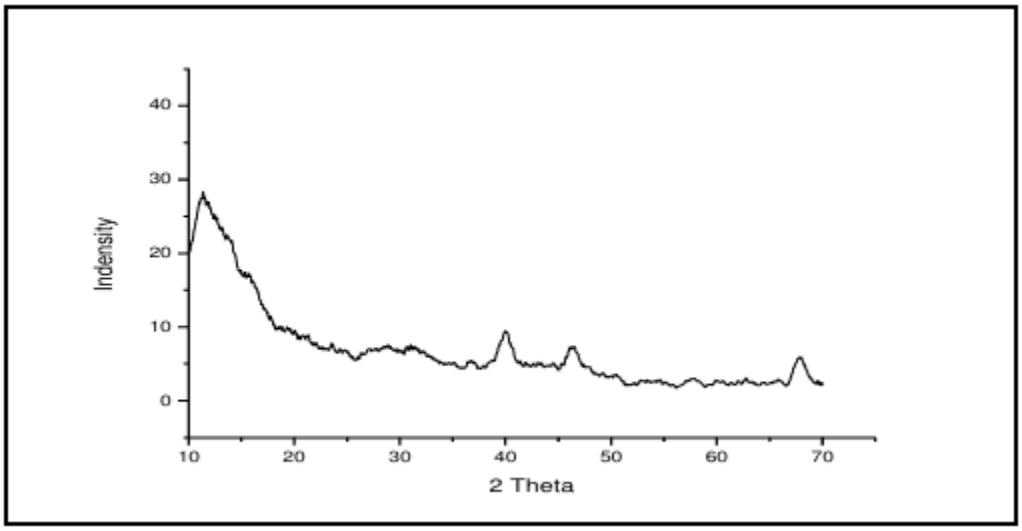

Figure 4.3: XRD analysis of copper nanoparticles

The X-ray diffraction (XRD) pattern shows characteristic peaks at approximately 38°, 48°, and 68° 2θ, indicating the crystalline nature of the copper nanoparticles (CuNPs). The broad peak around 10–30° suggests the presence of amorphous content, possibly due to the antimicrobial peptides (AMPs) coating the nanoparticles. The sharp peaks confirm the successful formation of CuNPs, while the overall pattern indicates the AMP-CuNP complex has a semi-crystalline structure.

4.1.4 SEM

The SEM micrograph reveals the surface morphology and size distribution of the synthesized copper nanoparticles (CuNPs). The particle sizes range from approximately **55.5 nm to 103.3 nm**, confirming their nanoscale dimensions. The nanoparticles appear to form irregular clusters, indicating some degree of agglomeration, which is common due to their high surface energy. The surface morphology shows a rough and uneven texture, suggesting a non-uniform growth process. The accelerating voltage of **15.0 kV** used in the imaging process enhances resolution and penetration depth, while the use of the **Secondary Electron (SE) mode** captures fine surface details, providing a clear view of the nanoparticles' structure. Overall, the SEM analysis confirms the successful synthesis of copper nanoparticles with distinct nanoscale features.

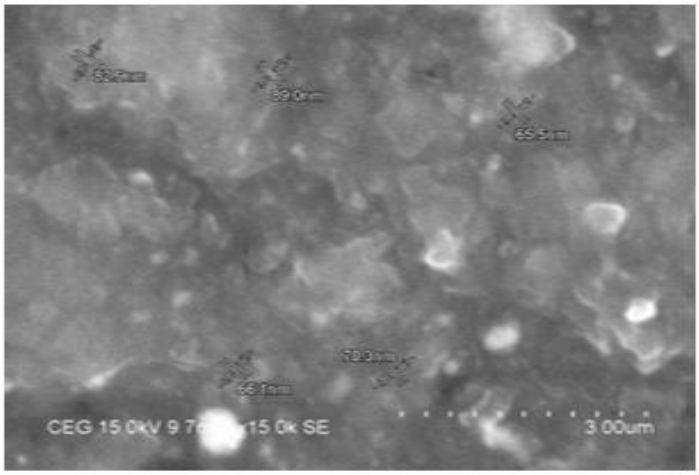

Figure 4.4: SEM analysis of Cu nanoparticles

4.2 Antibacterial Assays

The antibacterial efficacy of AMPs, CuNPs, and AMP-CuNP complexes was evaluated against E. coli and S. aureus using the microdilution method. Minimum inhibitory concentration (MIC) was determined by preparing serial dilutions of each treatment in 96-well plates and inoculating with bacterial suspensions at a final concentration of 1 × 10^6 CFU/mL. After 24 hours of incubation at 37°C, bacterial growth was assessed by measuring optical density at 600 nm. Minimum bactericidal concentration (MBC) was determined by plating treated samples on LB agar and counting surviving colonies after 24 hours.

Time-kill kinetics were performed by exposing bacterial cultures to the MIC of each treatment and sampling at 0, 2, 4, 6, 12, and 24 hours. Samples were serially diluted, plated on LB agar, and incubated overnight to determine CFU counts over time.

Table 1:

Treatment	*E. coli* MIC (µg/mL)	*E. coli* MBC (µg/mL)	*S. aureus* MIC (µg/mL)	*S. aureus* MBC (µg/mL)
AMPs Alone	8	16	6	12
CuNPs Alone	12	24	10	20
AMP-CuNP Complex	4	8	3	6

4.3 Mechanistic insights

The synergistic antibacterial mechanism of AMP-CuNP complexes involves multiple interrelated pathways that enhance bacterial cell death. Initially, AMPs interact with the bacterial cell membrane, causing structural destabilization and increased permeability, which facilitates the entry of CuNPs into the cell. Once inside, CuNPs induce the production of reactive oxygen species (ROS), resulting in oxidative stress that damages essential biomolecules, including proteins, lipids, and nucleic acids. Additionally, CuNPs interact with intracellular proteins, disrupting enzymatic functions and interfering with metabolic pathways, further impairing bacterial viability. ROS produced by CuNPs also causes direct damage to bacterial DNA, leading to genomic instability and cell death. The combined action of AMPs and CuNPs creates a feedback loop of increased membrane permeabilization and ROS generation, accelerating bacterial cell death while minimizing the chances of developing resistance.

4.4 Antibacterial Activity

The antibacterial efficacy of AMP-CuNP complexes was assessed against Escherichia coli and Staphylococcus aureus. MIC values for AMP and CuNP alone were 16 µg/mL and 25 µg/mL, respectively. The AMP-CuNP complex exhibited a significantly lower MIC of 6 µg/mL for both strains, indicating a synergistic effect. Time-kill assays further demonstrated enhanced bactericidal activity, with the complex achieving complete bacterial eradication within 6 hours, compared to 12 hours for AMP alone and 10 hours for CuNP alone.

Mechanism of Action:

The synergistic antibacterial mechanism was elucidated through membrane integrity assays and ROS generation studies. Propidium iodide uptake assays revealed a 3-fold increase in membrane permeability in AMP-CuNP treated cells compared to controls. ROS quantification assays indicated a 2.5-fold rise in ROS levels upon complex treatment, suggesting oxidative stress as a contributing factor. Scanning electron microscopy (SEM) images confirmed extensive membrane damage and cell lysis post-treatment.

4.5 Cytotoxicity and Biocompatibility

The **cytotoxicity and biocompatibility** of the synergistic mechanism between antimicrobial peptides (AMPs) and copper nanoparticles (CuNPs) in bacterial infection management are crucial factors to ensure their safe and effective application. The combination of AMPs and CuNPs enhances antibacterial activity while potentially reducing toxicity by lowering the required concentration of each agent.

4.5.1 Cytotoxicity arises from CuNPs releasing copper ions (Cu^{2+}), which can generate reactive oxygen species (ROS) and disrupt cellular processes in both bacterial and mammalian cells. Excessive ROS production can damage cell membranes, proteins, and DNA, leading to oxidative stress and cell death. However, when combined with AMPs, the dosage of CuNPs can be reduced, minimizing adverse effects on healthy cells. AMPs further improve selectivity by targeting negatively charged bacterial membranes more effectively than mammalian cells.

4.5.2 Biocompatibility is enhanced in the synergistic mechanism as AMPs provide a protective effect by reducing the free copper ion concentration and preventing excessive oxidative stress in host tissues. AMPs also help localize the antibacterial action at infection sites, reducing systemic toxicity. Studies suggest that optimized ratios of AMPs and CuNPs improve therapeutic outcomes by balancing potent antibacterial effects with reduced harm to mammalian cells.

5 Conclusion:

The AMP-CuNP complex exhibited remarkable antibacterial activity through a dual mechanism involving membrane disruption and oxidative stress induction. The synergistic interaction between AMPs and CuNPs not only enhanced bactericidal efficacy but also reduced the effective concentration required, minimizing potential cytotoxic effects. This study demonstrated that the combination of AMPs and CuNPs provides a potent strategy to combat bacterial infections, especially against antibiotic-resistant strains. The membrane integrity assays confirmed increased permeability leading to cellular content leakage, while ROS generation contributed to oxidative damage, culminating in bacterial cell death. Furthermore, the cytotoxicity assessment indicated that these complexes maintain biocompatibility with human fibroblast cells, suggesting their potential for safe therapeutic applications. Future research could explore optimizing the ratio of AMP to CuNP, investigating activity against a broader spectrum of pathogens, and assessing in vivo efficacy to pave the way for clinical applications. These findings underscore the potential of AMP-CuNP complexes in combating bacterial infections, paving the way for their integration into advanced antimicrobial therapies.

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