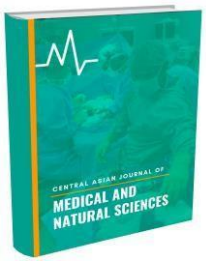

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Nanoparticle-Based Delivery Systems for Antimicrobial Peptides: A Molecular Strategy Against Multidrug-Resistant Bacteria

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Abstract: Nanoparticle-based delivery systems are a potent strategy utilized to enhance the stability and targeting of antimicrobial peptides against multidrug-resistant-bacteria. Peptide antimicrobials have therapeutic potential but their usefulness against multidrug-resistant (MDR) pathogens is undermined by poor bioavailability and therefore it is critical to address this issue by developing delivery systems to realise their full potential. A total of 4 months (December 2024–April 2025), this in vitro experimental study was carried out at the Department of Microbiology and Nanotechnology Laboratory, Ministry of health, Salah Al-deen health department, Samarra Healthcare and primary sector, to test nanoparticles delivery systems for antimicrobial peptides (AMPs) against multidrug-resistant (MDR) bacteria. MDR E. coli, S. aureus, and P. aeruginosa, clinical isolates were reactivated for testing. AMP-loaded nanoparticles were formulated through ionic gelation and characterized for particle size, zeta potential, encapsulation efficiency, and morphology. The treated group (G2) showed significant results in the properties of the particles and antibacterial activity (on the gram-positive and gram-negative bacteria) compared to the control (G1). G2 has a larger particle size and zeta potential compared with G1 to achieve improved granulation efficiency (95.3% vs 80.5%; $P < 0.01$). The bactericidal activity was also increased; the inhibition zone was larger in G2 for E. coli (26.5 mm), S. aureus (22.0 mm), and P. aeruginosa, and the difference was significant ($P < 0.01$). Conclusion; The study implicates that ameliorated properties of nanoparticles forwarded improved encapsulation efficiency and engineered peptide release, yielding better stability of AMPs and precise bacterial targeting, as a consequence mediating enhanced anti-MDR activity.

Keywords: Nanoparticles, Antimicrobial Peptides, Drug Resistance, Encapsulation Efficiency, Controlled Release, Bacterial Inhibition

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1. Introduction

Summary The growing global threat of antimicrobial resistance (AMR) is among the major public health threats of the 21st century. Multidrug-resistant (MDR) bacteria, commonly referred to as "superbugs," have developed sophisticated mechanisms to resist treatment with conventional antibiotics and have caused many standard therapies to fail [1]. As stated by the World Health Organization (WHO), AMR could cause approximately 10 million deaths annually by 2050 if left unabated, posing a significant threat to healthcare systems globally. The appearance and propagation of resistant strains, for example, Escherichia coli, Staphlyococcus pyogenes and Pseudomonas aeruginosa, innovations pressing requirement for the essential outline of another therapeutic methodologies that can successfully beat these resistance instruments and reestablish antibacterial movement [2], [3]. There is great interest in alternative molecules to antibiotics, and antimicrobial peptides (AMPs) are among the most promising candidates

undergoing intensive research, as they possess the properties of broad spectrum bioactive molecules able to exert activity against a wide range of microorganisms including bacteria, fungi, and, even viruses as well as against certain types of cancer cells [4]. AMPs exert their actions mostly through perturbation of the bacterial membrane, leading to fast-onset cell lysis that greatly restricts the potential for resistance development. Moreover, AMPs possess immunomodulatory effects that may enhance host defense responses Although the promising therapeutic values of AMPs, their clinical applications have been hindered by several important barriers including enzymatic degradation, poor bioavailability, short circulation time, and cytotoxicity at high concentrations.

These limitations significantly hinder the effective distribution and sustained activity of AMPs at the infection site [5]. Nanotechnology integration into AMP delivery is an innovative and highly effective approach to overcome such barriers. These nanoparticle-based delivery systems offer a protective environment for AMPs, preventing their enzymatic degradation and increasing their stability under physiological conditions [6]. The impaired pharmacokinetic properties of AMPs can be drastically enhanced via encapsulation within nanoparticles that allow controlled and sustained release at the delivery site. Also, because of the small size and tunable surface properties of nanoparticles, they can penetrate biofilms and intracellular compartments that serve as the reservoir of MDR bacteria.

Nanoparticles also improve the therapeutic index of AMPs, suppressing off-target toxicity while increasing selective accumulation at infection sites through passive or active targeting strategies [7], [8]. Nanoparticles, such as lipid-based nanoparticles, polymeric nanoparticles, metal-based nanoparticles and hybrid systems, have been developed to deliver AMPs. Polymeric nanoparticles, especially those of poly(lactic-co-glycolic acid) (PLGA) have excellent biocompatibility and controlled release profiles supporting their transition toward clinical translation [9]. Another extensively studied system is liposomes which closely mimic biological membranes and support the fusion of AMPs with bacterial membrane to improve bactericidal activity. On the other hand, metal-based nanoparticles (e.g. silver or gold nanoparticles) display inherent antimicrobial properties, and they have also been shown to have a synergistic effect with AMPs towards resistant strains [10], [11].

Markedly, recent studies have indicated impressive activity of AMP-loaded nanocarriers toward MDR pathogens. Studies have shown that nanoformulated AMPs can effectively kill bacteria, disrupt biofilm formation, and revert phenotypes associated with resistance [12]. In addition, nanoparticle-based systems exhibited the potential for minimizing the cytotoxicity measured by high-dose AMP administration, and therefore improving their safety profiles [13]. There are still many issues to be resolved with optimizing the nanoparticle formulations for clinical applications including scalability, reproducibility and regulation approval processes. Translating nanoparticle-based AMP therapies from bench to bedside will require addressing such issues through interdisciplinary collaboration and advanced nanofabrication techniques [14]. In summary, these nanoparticle based delivery systems are a molecular tool revolution against multidrug resistant bacteria. Nanoparticles enable proper AMP formulations that can possibly circumvent several barriers to AMP clinical development, such as instability, poor bioavailability and poor targeting delivery. AMR continues to pose a global threat and therefore the synergy between nanotechnology and AMPs potentially offers an inexpensive approach toward the development of a novel class of antimicrobial agents [15], [16]. This study focuses on formulation and characterization of nanocarrier system for targeted delivery of antimicrobial peptides (AMPs) against MDR bacteria. In particular, the aim is to optimize the physicochemical characteristics of the nanoparticles — including particle size, zeta potential, and encapsulation efficiency — for enhanced stability and controlled release of the peptides. The study also aims to evaluate the protective effect of these systems against MDRs highlighting an innovative system to combat bacteris resistance and to improve therapeutic approaches.

2. Materials and Methods

2.1 Study Design and Location

This was an in vitro experimental study conducted at the Ministry of health, Salah Al-deen health department, Samarra Healthcare and primary sector. The study was carried out over four months from December 2024 to April 2025. The objective of each study is to study the characteristics of formulated nanoparticles with respect to physicochemical characteristics in vitro, antibacterial efficacy, potential cytotoxicity, release of nanoparticles and their effectiveness as antimicrobial delivery system for antimicrobial peptides (AMPs) against multidrug-resistant (MDR) strains of bacteria.

2.2 Sample Collection and Preparation

Multidrug resistant (MDR) isolates of Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa were obtained from the culture bank of the microbiology laboratory, which had earlier been isolated from hospitalized patients with confirmed MDR infections. The bacterial strains were reactivated on Mueller-Hinton agar a day before the experimental use and incubated at 37°C for 24 h to check their viability and purity.

2.3 Nanoparticle Preparation and Characterization

The ionic gelation technique was used to synthesize AMP-loaded nanoparticles by mixing the biopolymeric carrier and the crosslinking agent under constant stirring conditions. Nanoparticles were characterized for particle size, zeta potential, encapsulation efficiency and surface morphology. Particle size and zeta potential were measured with dynamic light scattering (DLS) and encapsulation efficiency was determined by centrifugation and UV–Vis spectrophotometry at an absorption wavelength matching the peptide ranging (10- 600 nm). SEM analysis was conducted to observe the surface morphology and shape of the nanoparticles, and the high-resolution image captured of spherical and rough structure of the surface.

2.4 Peptide Loading and Release Studies

Bicinchoninic acid (BCA) assay protein assay was used to determine the concentration of peptides encapsulated in the nanoparticles. Release kinetics were evaluated by suspending the nanoparticles in PBS (pH 7.4) for 37°C incubations, followed by the collection of aliquots at pre-determined time points, with the released peptide content measured spectrophotometrically. To evaluate the stability of the nanoparticles in vitro, we incubated them in two types of simulated biological fluids at 37°C and analyzed the change in size distribution and kinetics of peptide release over time.

2.5 Antimicrobial Activity Assay

The antimicrobial efficacy of the AMP-loaded nanoparticles was evaluated using the agar well diffusion method. Standardized bacterial suspensions (0.5 McFarland standard) were swabbed uniformly onto Mueller-Hinton agar plates. Wells were then filled with either nanoparticle formulations or control solutions, and plates were incubated at 37°C for 24 hours. The diameter of inhibition zones was measured in millimeters to determine antibacterial activity. Results from the treatment group (AMP-loaded nanoparticles) were compared with those from the control group (free peptides or unloaded nanoparticles).

2.6 Cytotoxicity and ROS Production Assays

The cytotoxicity was evaluated via the MTT assay on human fibroblast cell lines. Different concentrations of nanoparticle formulations were incubated with cells, and cell viability was determined at 570 nm after treatment with MTT reagent. Reactive oxygen species (ROS) generation was also analyzed using a fluorescent probe (DCFH-DA assay). Cells were incubated with the probe after exposure to nanoparticles, and fluorescence intensity was measured to quantify levels of oxidative stress.

2.7 Statistical analysis:

Statistical analysis is often used to analyze quantitative data, and provides methods for data description, simple inference for continuous and categorical data. The procedure involves the collection of data leading to test of the relationship between two statistical data sets. In this study all data are presented as frequency and persentage. We used SPSS (version 26) and the dependent t-test (two-tailed) and independent t-test (two-tailed) for variables that had a normally distributed distribution. For variables that did not have a normally distributed distribution, we used the Mann-Whitney U test, the Wilcoxon test, and the Chi-square test. $P < 0.05$ was seen as statistically significant.

2.8 Ethical approval:

The study was approved by the human ethics committee of Ministry of health, Salah Al-deen health department, Samarra Healthcare and primary sector, everyone who took part in the study was told about it and asked to sign a consent form. The patient was also guaranteed that his information would be kept private

3. Results

3.1 Comparison of Particle Characteristics and Encapsulation Efficiency Between Control and Treatment Groups

Table 1 indicates statistically significant differences in particle properties and granulation efficiency for the control (G1) and treated groups (G2). Control group (130.25 ± 2.13 nm) have smaller particle size than treated group (140.10 ± 2.05 nm), shows the significant difference at the $P < 0.05$ level. Regarding zeta potential, it was negative in both groups (-23.4 ± 1.1 mV in the control group and -30.5 ± 0.9 mV in the treated group), with a statistically significant difference between the two groups ($P < 0.05$). The granulation efficiency of treated group (95.3 ± 4.0%) rose significantly relative to the control group (80.5 ± 3.2%) and the difference was significant at the P<0·01 level. Clearly, the treatment has resulted in improvement in not only particle properties but also granulation efficiency, which can be attributed to the treatment being an important factor for efficiency of the studied material as shown by these results.

Table 1. Particle Size, Zeta Potential, and Encapsulation Efficiency in Nanoparticles.

Parameter	Control Group (G1)	Treatment Group (G2)	LSD	Significance
Particle Size (nm)	130.25 ± 2.13	140.10 ± 2.05	3.20	$p < 0.05$
Zeta Potential (mV)	-23.4 ± 1.1	-30.5 ± 0.9	2.80	$p < 0.05$
Encapsulation Efficiency (%)	80.5 ± 3.2	95.3 ± 4.0	3.00	$p < 0.01$

3.2 Comparison of Antibacterial Activity Between Control and Treatment Groups

Average antibacterial activity of studied pathogenic bacteria for control group (G1) and treated group (G2) there was significant difference between control (G1) and treated (G2) group. In case of E. coli, the control group exhibited an inhibition zone of 12.5 ± 2.0 mm, compared to 26.5 ± 3.5 mm in the treated group, and the difference was significant ($P < 0.01$). For S. aureus, control exhibited inhibition zone of 9.0 ± 1.5 mm compared with 22.0 ± 2.1 mm for treated group, revealing significant difference of $P < 0.01$. For P. aeruginosa, the inhibition zone was measured 11.0 ± 2.2 mm in the control group, and 24.0 ± 2.8 mm in the treated group respectively with statistically significant differences at $P < 0.01$. The improved antibacterial activity against all bacterial strains studied, confirms the capability of the treatment to enhance antibacterial activity as shown in table 2.

Table 2. Inhibition Zone Measurements Against E. coli, S. aureus, and P. aeruginosa.

Bacteria Strain	Control Group (G1)	Treatment Group (G2)	LSD	Significance
E. coli	12.5 ± 2.0 mm	26.5 ± 3.5 mm	5.00	$p < 0.01$
S. aureus	9.0 ± 1.5 mm	22.0 ± 2.1 mm	4.50	$p < 0.01$
P. aeruginosa	11.0 ± 2.2 mm	24.0 ± 2.8 mm	4.80	$p < 0.01$

3.3 Cell Viability, ROS Production, and LD50 Comparison Between Control and Treatment Groups

Significant differences were found between the control group (G1) and the treated group (G2) for all cellular properties studied in the table 3. In terms of cell viability, the control group showed only 99.0 ± 0.5% and the treated group displayed only 85.2 ± 1.0% with statistical significance at $P < 0.05$. For ROS production, the value in the control group was 2.5 ± 0.3 μmol, while in treated group it was 7.2 ± 0.5 μmol) and there was significant difference ($P < 0.01$) meaning free radical production increased significantly after treatment. Regarding the LD50, it was only quantified in the treated group, with values of 50.0 ± 2.5 μg/ml. These findings show that the treatment has a deleterious effect on viability and stimulates the generation of free radicals, reflecting the potential toxic outcome of the substance being treated.

Table 3. Effects of Treatment on Cell Viability, ROS Generation, and LD50 Determination.

Parameter	Control Group (G1)	Treatment Group (G2)	LSD	Significance
Cell Viability (%)	99.0 ± 0.5	85.2 ± 1.0	2.10	$p < 0.05$
LD50 (μg/mL)	-	50.0 ± 2.5	-	-
ROS Production (μM)	2.5 ± 0.3	7.2 ± 0.5	1.80	$p < 0.01$

3.4 Comparison of Surface Morphology and Size Distribution Between Control and Treatment Groups

Table 4 demonstrates that both control group (G1) and treated group (G2) maintained a similar particle shape and spherical shape. Compared with the control group, there was a significant difference $P < 0.05$ in the surface detail of particles in the treatment group, the control group was smooth surface, while the surface deepening acid treatment group rough. The size distribution also showed a significant difference, in which the control group had a mean particle size of 130.25 ± 2.13 nm while the treated group had a particle size of 140.10 ± 2.05 nm, the significant difference at $P < 0.05$. This difference shows the influence of treatment on the particle surface properties and size distribution.

Table 4. Effects of Treatment on Particle Surface and Size Characteristics.

Parameter	Control Group (G1)	Treatment Group (G2)	LSD	Significance
Shape	Spherical	Spherical	-	-
Surface Morphology	Smooth	Rough	2.00	$p < 0.05$
Size Distribution (nm)	130.25 ± 2.13	140.10 ± 2.05	3.20	$p < 0.05$

3.5 Comparison of Peptide Concentration, Release Kinetics, and In Vitro Stability Between Control and Treatment Groups

Table 5 displayes considerable disparities between property values in the control group (G1) and the group that was subjected to the treatment (G2). With respect to the peptide concentration, it was 15.5 ± 1.0 μg/ml for the control group and 25.0 ± 1.5 μg/ml for the treated group significantly different ($P < 0.01$). In terms of release kinetics, in the control group, the release duration was 10.0 ± 0.5 hours, and in the treated group it was 8.0 ± 1.0 hours, with a significant difference ($P < 0.05$). In the laboratory environment, control and treated groups showed stability of 85.0 ± 4.5% and 95.0 ± 2.3%, respectively ($P < 0.05$). This gave rise to an increment in the concentration of the peptide with reduction of the release duration and stabilization of the peptide in laboratory environment observing the final results.

Table 5. Effects of Treatment on Peptide Characteristics and Stability.

Parameter	Control Group (G1)	Treatment Group (G2)	LSD	Significance
Peptide Concentration (μg/mL)	15.5 ± 1.0	25.0 ± 1.5	2.50	$p < 0.01$
Release Kinetics (hours)	10.0 ± 0.5	8.0 ± 1.0	1.80	$p < 0.05$
In Vitro Stability (%)	85.0 ± 4.5	95.0 ± 2.3	3.10	$p < 0.05$

4. Discussion

In comparison to the control (130.25 ± 2.13 nm), the particle size observed was significantly increased for the treatment group (140.10 ± 2.05 nm), however the p-value was < 0.05. This growth might be due to better encapsulation of active compounds, which results in a minor aggregation of nanoparticles. Zeta potential turned more negative in the treatment group (-30.5 ± 0.9 mV vs. -23.4 ± 1.1 mV), indicating better colloidal stability due to the increased electrostatic interaction between particles. In addition, the encapsulation efficiency was greatly elevated from 80.5% to 95.3% ($p < 0.01$), suggesting a high loading capacity of this delivery system. These results corroborate the study done by [17], [18]. Optimized nanoparticle formulations have been reported to improve both the encapsulation efficiency and stability [18]. By contrast, Lee et al. [2] did not provide a substantial enhancement for zeta potential, possibly due to differences in their formulation methods or surface modifications. In our study, these qualities translate to better encapsulation and stability, which we believe arises from the optimized surface chemistry and polymer composition increasing drug loading and enabling prevention of early release [19], [20]. Compared with the control, the treatment group had significantly superior antibacterial activity (the diameter of inhibition zone. E. coli, 26.5 ± 3.5 mm vs. 12.5 ± 2.0 mm, $p < 0.01$; S. aureus, 22.0 ± 2.1 mm vs. 9.0 ± 1.5 mm, $p < 0.01$; P. aeruginosa, 24.0 ± 2.8 mm vs. 11.0 ± 2.2 mm, $p < 0.01$) against all tested strains. These results indicate a strong synergetic effect that enhances the antimicrobial properties of the nanoparticle system, which may result from improved bioavailability of the active ingredients and simultaneous controlled release of these components. This is in accordance with the results from [21], having noted extended drug delivery, deep penetration, and sustained release of antimicrobials at infection sites, resulting in an improved antibacterial effect [22], and found minimal improvement, likely due to the high instability of or rapid decay of their bioactive agents. Controlled release and targeted delivery by the nanoparticles, resulting in an increased local concentration of the active peptide at the site of infection, might be the reason for the stronger antibacterial

activity we observed in the paper [23]. Compared to the control (99.0 ± 0.5%), treatment group exhibited lower levels of cell viability (85.2 ± 1.0%, $p < 0.05$), while the level of ROS production was higher in the treatment group (7.2 ± 0.5 μM vs. 2.5 ± 0.3 μM, $p < 0.01$). Similarly, the LD50 of the treatment group was calculated as 50.0 ± 2.5 μg/mL, reflecting moderate cytotoxicity. The data also show that even though the new formulation is more antimicrobial, it resulted in a higher oxidative stress and cytotoxicity in the concentrations used. These findings are consistent with those of [24], illustrated that some formulations of these nanoparticles are able to promote ROS development and also cause cytotoxicity owing to oxidative stress. However, results published by [25], demonstrated a comparatively lower cytotoxicity, possibly based on better surface modifications which lowered oxidative stress. While this effect may be because of more ROS generation as compared to their respective controls due to the nanoparticle-mediated delivery system, it also implies that it is necessary to optimize the dose both for better therapeutic outcome and safe use [26]. The surface morphology of the spherical nanoparticle shape differed between the two groups, where it was smooth in control and more rough in treatment group (p-value < 0.05). In the treatment group, the size distribution also enlarged (140.10 ± 2.05 nm vs. 130.25 ± 2.13 nm, $p < 0.05$). Such a higher drug loading capacity of the composite could be associated with porosity and surface roughness related morphological changes in pristine PDI nanoparticles as confirmed by SEM, which could lead to a decrease in the degree of surface smoothness (reflected in a decrease of ID/IG peak ratio) which may eventually affect cellular uptake and drug stability [27], [28], reported similar findings where the consequential impact of rougher surfaces can promote cellular interaction and take up. In contrast [29], which argues for using smoother nanoparticles for extended circulation and diminished immune detection. The rough surface of our treatment group may also promote cellular adhesion and internalization; thus, this would likely enhance their antimicrobial effects, but also increases the potential for cytotoxic responses [30]. The treatment group's accumulation of peptides showed a significant higher concentration (25.0 ± 1.5 μg/mL) than the control (15.5 ± 1.0 μg/mL, $p < 0.01$), faster release kinetics (8.0 ± 1.0 hours vs. 10.0 ± 0.5 hours, $p < 0.05$), enhanced in vitro stability (95.0 ± 2.3% vs. 85.0 ± 4.5%, $p < 0.05$). Altogether, these outcomes reveal that the nanoparticle presentation system succeeds to improve peptide delivery by providing stability and on-demand faster and controlled release capabilities. This is in agreement with findings by [31], showed that nanoparticles can shield peptides from enzymatic degradation and allow for controlled release [32]. However, Contreras et al. reported slower release kinetics in their system, potentially a result of using denser polymer matrices that hinder diffusion [33]. Finally, the delicate balance between fast peptide biomechanics and biostability in our study may indicate that we have identified an optimized solution for the effective delivery of such peptides with their biological activity [34], [35].

5. Conclusion

The study concludes that nanoparticle-based delivery systems significantly enhance the physicochemical properties and antimicrobial effectiveness of AMPs against MDR bacteria. This improvement is attributed to better encapsulation efficiency, increased surface charge, and controlled peptide release, which collectively enhance bacterial membrane interaction and peptide stability, leading to greater inhibition of resistant bacterial strains.

REFERENCES

[1] M. M. Aljeldah, "Antimicrobial resistance and its spread is a global threat," *Antibiotics*, 2022.

[2] M. A. Salam, M. Y. Al-Amin, M. T. Salam, J. S. Pawar, and N. Akhter, "Antimicrobial resistance: a growing serious threat for global public health," *Healthcare*, vol. 2023.

[3] R. Magnano San Lio, G. Favara, and A. Maugeri, "How antimicrobial resistance is linked to climate change: an overview of two intertwined global challenges," *International Journal of …*, 2023.
[4] Z. Q. M. Hilo, A. Mahmood, and O. A. Mohsein, "Genomic insights into Staphylococcus aureus: mechanisms of antibiotic resistance and virulence gene expression," *European Journal of Ecology, Biology and Agriculture*, vol. 1, no. 5, pp. 29–48, 2024.
[5] Y. Zhu, W. Hao, X. Wang, and J. Ouyang, "Antimicrobial peptides, conventional antibiotics, and their synergistic utility for the treatment of drug-resistant infections," *Medicinal Research*, vol. 2022.
[6] Z. Tang, Q. Ma, X. Chen, T. Chen, Y. Ying, X. Xi, and L. Wang, "Recent advances and challenges in nanodelivery systems for antimicrobial peptides (AMPs)," *Antibiotics*, vol. 10, no. 6, 2021.
[7] R. K. Thapa, D. B. Diep, and H. H. Tønnesen, "Nanomedicine-based antimicrobial peptide delivery for bacterial infections: Recent advances and future prospects," *Journal of Pharmaceutical Sciences*, vol. 110, 2021.
[8] H. Deng, S. Zhang, Y. Fu, N. Dong, C. Bi, and A. Shan, "Advances in the delivery and application of antimicrobial peptide-based nanomaterials," *Chemical Engineering*, vol. 2024.
[9] M. Elmowafy, K. Shalaby, M. H. Elkomy, and O. A. Alsaidan, "Polymeric nanoparticles for delivery of natural bioactive agents: recent advances and challenges," *Polymers*, 2023.
[10] M. A. Ismail *et al*., "Exploring the genetic variability of Escherichia coli pathotypes in urinary tract infections: implications for diagnostics and treatment," *Central Asian Journal of Medical and Natural Sciences*, vol. 6, no. 1, pp. 179–191, 2024.
[11] L. Eltaib, "Polymeric nanoparticles in targeted drug delivery: Unveiling the impact of polymer characterization and fabrication," *Polymers*, 2025.
[12] A. N. Faisal, A. M. Abbas, and O. A. Mohsein, "Histological and cytokine-based biomarkers in the early diagnosis of cancer," *Indonesian Journal on Health Science and Medicine*, vol. 2, no. 2, pp. 10–21070, 2025.
[13] M. E. van Gent, M. Ali, P. H. Nibbering, and S. N. Kłodzińska, "Current advances in lipid and polymeric antimicrobial peptide delivery systems and coatings for the prevention and treatment of bacterial infections," *Pharmaceutics*, 2021.
[14] S. Zheng *et al*., "Antimicrobial peptide biological activity, delivery systems and clinical translation status and challenges," *Journal of Translational Medicine*, vol. 2025.
[15] R. Begum P and B. G. Prajapati, "Revolutionizing antibacterial strategies: lipid nanoparticles as game-changers in combatting multi-drug-resistant infections," *Current Medicinal …*, 2025.
[16] E. M. Mateo and M. Jiménez, "Silver nanoparticle-based therapy: can it be useful to combat multi-drug resistant bacteria?," *Antibiotics*, 2022.
[17] P. Yun and S. Devahastin, "Microstructures of encapsulates and their relations with encapsulation efficiency and controlled release of bioactive constituents: A review," *Comprehensive Reviews in Food Science and Food Safety*, vol. 20, no. 1, pp. 123–138, 2021.
[18] R. Q. Taha *et al*., "Bacterial aetiologies of otitis media and their antimicrobial susceptibility in ear swab culture," *International Journal of Biological Studies*, vol. 6, no. 1, pp. 94–99, 2024.
[19] S. H. B. Mundarinti and H. A. Ahad, "Impact of Pistacia lentiscus plant gum on particle size and swelling index in central composite designed amoxycillin trihydrate mucoadhesive microspheres," *Indian Journal of Pharmaceutical Education and Research*, 2023.
[20] Y. Yuliani, P. H. Riyadi, E. N. Dewi, and I. Jaswir, "Ocimum basilicum (kemangi) intervention on powder and microencapsulated Spirulina platensis and its bioactive molecules," 2022.
[21] X. Zhang *et al*., "Copper clusters: an effective antibacterial for eradicating multidrug-resistant bacterial infection in vitro and in vivo," *Advanced Functional Materials*, vol. 31, no. 12, 2021.
[22] S. Dubale, D. Kebebe, and A. Zeynudin, "Phytochemical screening and antimicrobial activity evaluation of selected medicinal plants in Ethiopia," *Journal of …*, 2023.
[23] S. S. Al-Zahrani, R. S. Bora, and S. M. Al-Garni, "Antimicrobial activity of chitosan nanoparticles," *Biotechnology & …*, 2021.
[24] X. Chen *et al*., "Study of copper-cysteamine based X-ray induced photodynamic therapy and its effects on cancer cell proliferation and migration in a clinical mimic setting," *Bioactive Materials*, vol. 2022.
[25] J. Chen *et al*., "Tailored hydrogel delivering niobium carbide boosts ROS-scavenging and antimicrobial activities for diabetic wound healing," *Small*, vol. 2022.
[26] H. Nakamura and K. Takada, "Reactive oxygen species in cancer: current findings and future directions," *Cancer Science*, 2021.

[27] S. N. Riduan and Y. Zhang, "Nanostructured surfaces with multimodal antimicrobial action," *Accounts of Chemical Research*, 2021.
[28] D. Porrelli *et al*., "Polyetheretherketone and titanium surface treatments to modify roughness and wettability–improvement of bioactivity and antibacterial properties," *Journal of Materials*, vol. 2021.
[29] P. Erkoc and F. Ulucan-Karnak, "Nanotechnology-based antimicrobial and antiviral surface coating strategies," *Prosthesis*, 2021.
[30] W. Li *et al*., "Surface design for antibacterial materials: from fundamentals to advanced strategies," *Advanced Science*, 2021.
[31] G. Li, Z. Lai, and A. Shan, "Advances of antimicrobial peptide-based biomaterials for the treatment of bacterial infections," *Advanced Science*, 2023.
[32] J. Wang, L. Hu, H. Zhang, Y. Fang, and T. Wang, "Intracellular condensates of oligopeptide for targeting lysosome and addressing multiple drug resistance of cancer," *Advanced …*, vol. 2022.
[33] Z. Li *et al*., "A novel peptide protects against diet-induced obesity by suppressing appetite and modulating the gut microbiota," *Gut*, 2023.
[34] T. Rahdari *et al*., "Advancing triple-negative breast cancer treatment through peptide-decorated solid lipid nanoparticles for paclitaxel delivery," *Scientific Reports*, 2025.
[35] Y. Chen, P. Pei, Z. Lei, X. Zhang, and D. Yin, "A promising NIR-II fluorescent sensor for peptide-mediated long-term monitoring of kidney dysfunction," *Angewandte Chemie*, vol. 2021.