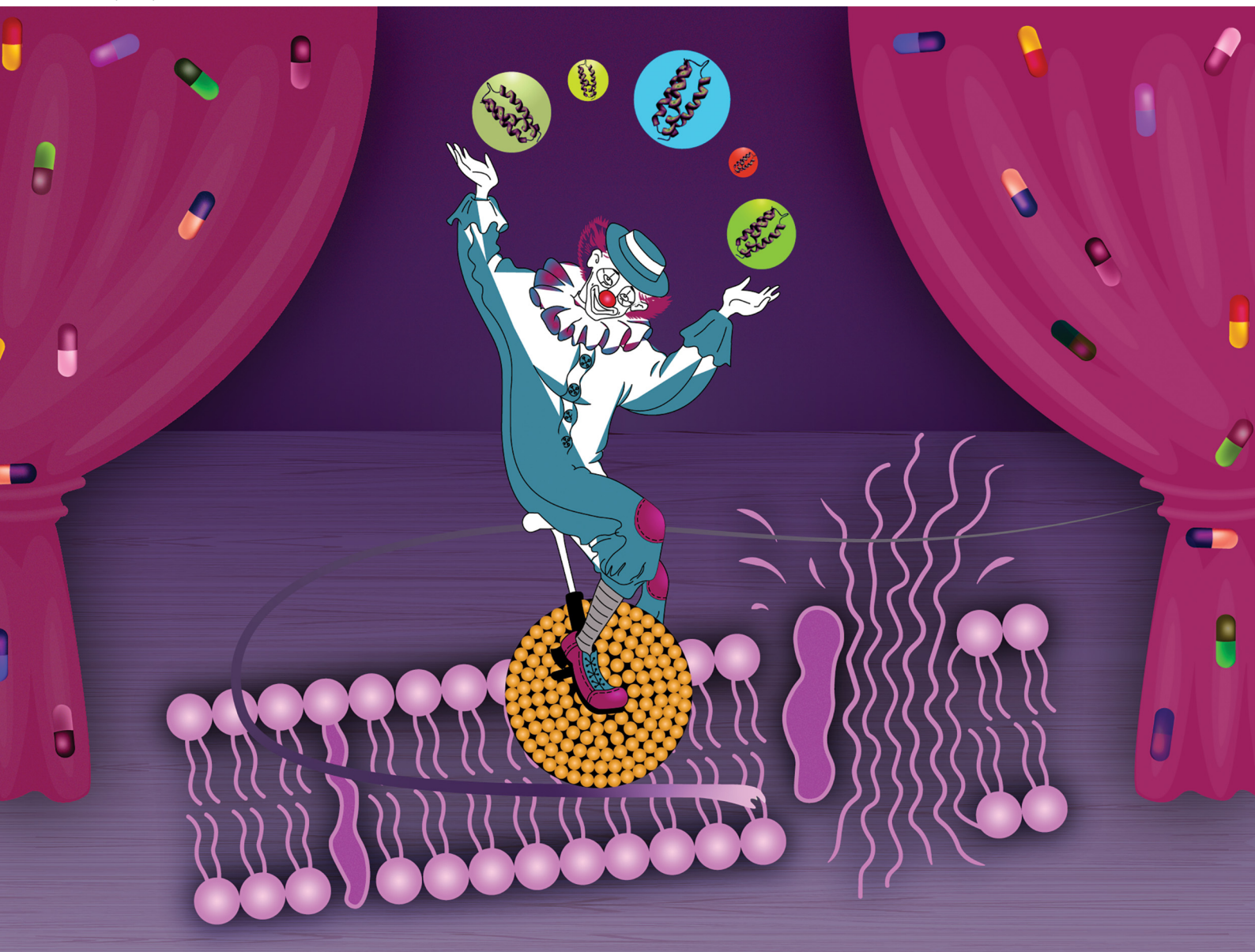


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**PERSPECTIVE**

Miroslava Nedyalkova *et al.*

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Cite this: *Phys. Chem. Chem. Phys.*, 2025, 27, 16284

# Harnessing antimicrobial peptide-functionalized nanoparticles: a perspective on experimental and computational strategies to combat antibiotic resistance

Miroslava Nedyalkova,<sup>†\*</sup><sup>abc</sup> Diana Potes Vecini,<sup>†\*ab</sup> Andrew S. Paluch<sup>ib</sup><sup>c</sup> and Marco Lattuada<sup>ib</sup><sup>a</sup>

Antimicrobial peptides (AMPs) and nanoparticles (NPs) are at the forefront of novel strategies against antimicrobial resistance (AMR). The focus of this perspective is a conjugated system: AMP–NPs, which can be used to enhance the stability and targeting of antimicrobial activity. This perspective highlights the emerging role of molecular dynamics (MD) simulations as a key tool for designing and optimizing these hybrid systems. By integrating experimental findings with MD-driven insights, researchers can accelerate the development of next-generation antimicrobial platforms that are both effective and scalable. This convergence of nanotechnology and computational modelling offers a promising path toward overcoming the AMR crisis.

Received 19th May 2025,  
 Accepted 24th June 2025

DOI: 10.1039/d5cp01880c

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## Introduction

Antimicrobial resistance (AMR) is a critical and escalating global health crisis, emerging from the adaptive capacity of microorganisms—bacteria, viruses, fungi, and parasites—to survive the effects of antimicrobial drugs. This adaptive evolution leads to increasingly challenging infections to treat, posing a threat to human, animal, and environmental health worldwide. If left unaddressed, AMR could cause up to 10 million deaths each year by 2050, potentially becoming a more common cause of death than cancer.<sup>1,2</sup> AMR is not a distant problem; it is an escalating crisis that requires immediate global attention and the implementation of more effective management strategies.<sup>3,4</sup> The slow process of new antibiotic development has exacerbated the AMR crisis, underscoring the urgent need for innovative approaches to circumvent resistance mechanisms and deliver effective treatments.

### Expanding arsenal against antimicrobial resistance

Among the most promising alternatives are bacteriophage therapy, antimicrobial peptides (AMPs), lipopeptides, and nanotechnology-based approaches. Each offers unique mechanisms of action that

precisely target resistant bacteria.<sup>5–8</sup> Bacteriophage therapy has gained renewed interest as a targeted, natural solution for bacterial infections, particularly those caused by multidrug-resistant (MDR) strains.

Our perspective focuses on how advanced materials can be utilized as carriers and boosters of the antimicrobial peptide activity. Materials such as hydrogels, liposomes, dendrimers, and polymeric nanoparticles can be used to optimize stability, bioavailability, and targeted delivery of AMPs. Such diversity in the delivery mode is not only crucial for protecting peptides from premature degradation caused by proteolytic enzymes, for example, but also for controlling their release and improving their penetration into pathogens. All of these are key challenges in treating infections that are resistant to treatment. Designing and modeling a fused system of AMPs – materials admit targeted activation and prolonged antimicrobial activity. This approach helps minimize and control the side effects, such as toxicity, and improves overall treatment outcomes.

When designing a new delivery system that is also sustainable, one key component should be considered: molecular-level insights should be integrated with the discovery, design, and optimization of advanced therapeutic systems. MD simulations serve as a nexus that enables researchers to explore atomic-scale interactions between antimicrobial agents, bacterial membranes, and advanced materials under dynamic, physiologically relevant conditions. This allows the rational design of peptides with enhanced stability and membrane-disruptive properties, as well as carriers with optimized drug-release kinetics and biocompatibility.

<sup>a</sup> Department of Chemistry, Fribourg University, Chemin Du Musée 9, 1700 Fribourg, Switzerland. E-mail: miroslava.nedyalkova@unifr.ch

<sup>b</sup> Swiss National Center for Competence in Research (NCCR) Bio-inspired Materials, University of Fribourg, Chemin des Verdiers 4, CH-1700 Fribourg, Switzerland

<sup>c</sup> Department of Pharmacy and Chemistry, Sofia University, Sofia, Bulgaria

<sup>†</sup> These authors have an equal contribution.



## Role of antimicrobial peptides

Antimicrobial peptides, both naturally occurring and synthetically designed, present a versatile and potent class of antimicrobial agents. AMPs target negatively charged bacterial membranes, utilizing their amphipathic structures to destabilize and permeabilize bacterial cells, resulting in rapid cell death. Despite challenges related to enzymatic degradation and cytotoxicity, ongoing research is focused on enhancing their stability, reducing toxicity, and optimizing their therapeutic profiles.

Nanotechnology-based approaches leverage the unique properties of nanoparticles (NPs), such as silver, gold, and other metallic NPs, which exhibit intrinsic antimicrobial properties. These NPs can directly disrupt bacterial membranes, generate reactive oxygen species (ROS), or serve as carriers for conventional antimicrobial agents, enhancing their efficacy.<sup>9–11</sup> Additionally, NPs' surface modification can further increase their targeting capabilities, offering a flexible platform for combating resistant pathogens.

These strategies represent a diversified approach to addressing AMR, offering targeted, adaptable, and innovative solutions.

Over the last three decades, considerable interest has been in the therapeutic potential and advancement of using AMPs.<sup>8,12–15</sup> Experimental and *in silico*-based approaches about the mechanism of action induced by AMPs have been presented in recent years.<sup>16–22</sup> The mechanisms underlying pore formation by AMPs have been thoroughly investigated. However, the mechanism remains incompletely resolved. MD simulations and experimental studies have provided significant insights, yet the complexity of membrane–peptide interactions leaves some aspects open to interpretation.<sup>23–25</sup>

On the other hand, NPs, when conjugated with AMPs, provide a powerful platform for combating antibiotic-resistant pathogens. These conjugates enhance stability by protecting AMPs from enzymatic degradation and harsh physiological conditions, prolonging their bioactivity. Among the systems that have undergone testing, noble metal NPs, particularly gold nanoparticles (AuNPs), stand out.<sup>26</sup> Due to their small size, they can interact with biomolecules both at the surface and within cells, yielding faster and more specific targeting for treatments. They possess excellent application spectra ranging from highly sensitive diagnostic assays<sup>27,28</sup> and radiotherapy enhancement<sup>29,30</sup> to applications in drug and gene delivery.<sup>31–33</sup> Iron oxide nanoparticles (IONPs) represent another versatile class of materials that can effectively disrupt bacterial cell membranes through various mechanisms, including thermal, magnetic, passive, and active targeting. Their diverse capabilities enable their application in numerous fields, particularly in medical imaging, biosensing, disease diagnosis, drug delivery, pollutant remediation, and antimicrobial therapies.<sup>34–40</sup> These examples of NPs' applications are fundamentally influenced by the interactions occurring at the nanoparticle–cell membrane interface—a complex environment where multiple biophysical interactions exist simultaneously. Specifically, steric hindrance, electrostatic attraction, hydrophobic interactions, solvent effects, and macromolecular interactions dictate how NPs engage with cellular surfaces. Understanding

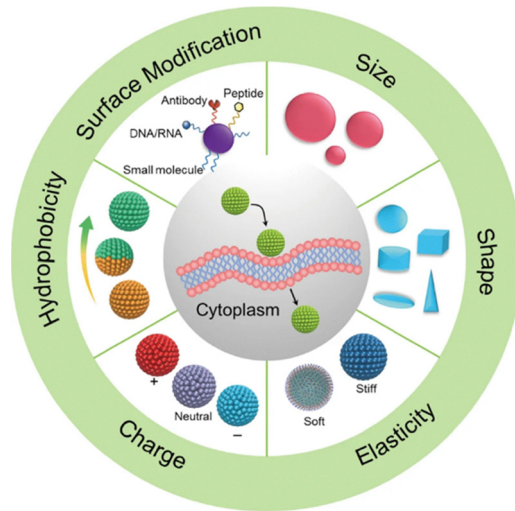


Fig. 1 Schematic diagram of the physicochemical properties of NPs.<sup>41</sup>

and optimizing these interactions are crucial for enhancing NP functionality in diverse applications, from precise antimicrobial targeting to efficient drug delivery. The main properties of NPs, such as size, shape, charge, and surface functionalization, play a pivotal role in their interactions with bacterial membranes (Fig. 1).<sup>41</sup> The permeability of NPs leads to greater disruption of membrane integrity, thereby enhancing the antimicrobial effectiveness of the NPs.<sup>42</sup>

The morphology and surface properties of NPs influence their interactions with bacterial membranes, either facilitating antimicrobial activity or, conversely, inhibiting it.<sup>43</sup> For example, rod-shaped NPs, with their larger surface area and aspect ratio, induce greater membrane disruption compared to spherical counterparts.<sup>44</sup> Furthermore, NPs bearing a positive surface charge are electrostatically attracted to negatively charged bacterial membranes, promoting adhesion and subsequent membrane destabilization. Surface modifications, such as conjugation with specific functional groups or AMPs, can further enhance selectivity and binding affinity.<sup>45</sup> The multivalent interactions achieved through such conjugation leverage the membrane-disrupting properties of both NPs and AMPs, resulting in synergistic antimicrobial effects.<sup>46</sup>

In addition to their well-known membrane-disruptive capabilities, many AMPs possess potent intracellular activities that contribute substantially to their antimicrobial efficacy.

Once internalized—either *via* direct translocation or endocytosis—AMPs can bind to nucleic acids, inhibiting DNA and RNA synthesis, or target ribosomal components to disrupt protein synthesis. For instance, buforin II penetrates bacterial membranes without causing lysis and binds directly to DNA and RNA, thereby impeding critical cellular processes such as transcription and replication.<sup>47</sup> Combining these intracellular actions with membrane-disruptive mechanisms, primarily when facilitated by appropriately designed NPs, enhances overall antimicrobial potency and weakens the probability of resistance development.<sup>16</sup> Recognizing and harnessing these dual mechanisms—membrane disruption and intracellular



targeting—are fundamental for the design of effective AMPs–nanoparticle conjugates. Achieving this optimization requires a deep understanding of AMP–NPs interactions, which can be obtained through molecular simulations. These simulations offer atomistic insights into binding mechanisms, stability, and adsorption dynamics, providing a precise, data-driven guide for the rational design and fine-tuning of AMPs–NPs systems, which have both advantages and limitations. These challenges also include limited targeting precision, stability issues in both *in vivo* and *in vitro* environments, difficulties in large-scale production, and concerns about toxicity. MD simulations can also be used to address these limitations.

MD simulations can be used to identify peptide sequences that preferentially disrupt bacterial membranes while sparing host cells. These simulations directly address the key limitations of peptide–NP systems, providing a foundation for precision targeting, enhanced stability, and scalable design. Moreover, we advocate for integrating quantum computing, which offers unparalleled precision in capturing electron-level interactions critical to NP–AMP systems, including charge transfer, electronic structure, and metal–peptide interactions. Quantum computing can uncover complex phenomena such as quantum tunnelling during AMP binding, which classical methods may overlook. This perspective envisions a transformative strategy for addressing AMR, where the convergence of MD simulations, quantum computing, and experimental validation bridges the current data gap, accelerates NP–AMP design, and redefines our approach to combating AMR.

### Enhancing AMPs' efficacy with nanoparticle carriers

The versatility of NP types—ranging from metal-based and metal oxide (e.g., zinc oxide, titanium dioxide) to polymer-based and composite formulations—further expands the potential of AMP–NP systems. Metal-based NPs provide intrinsic antimicrobial properties, while polymer-coated NPs enhance biocompatibility and enable controlled AMP release, optimizing therapeutic outcomes. Lipid-based carriers, such as liposomes and micelles, offer additional protection for AMPs, improving their stability in biological environments and enhancing their targeting capabilities.

This subsection highlights the crucial role of NPs-based carriers in overcoming the inherent limitations of AMPs, thereby transforming them into practical and versatile antimicrobial agents.

### Optimizing peptide–nanoparticle binding for enhanced antimicrobial ability

Before diving into the individual carriers' cases, we want to question the selection of peptide binding methods to NP surfaces. Such a summary is pivotal in determining the performance and versatility of NP-systems. This perspective highlights the importance of a rational, application-oriented approach to peptide attachment, where the choice among covalent, non-covalent, and hybrid strategies is informed by the desired therapeutic outcome. The optimal binding strategy must consider the physicochemical properties of the NPs' surface and the peptide, including charge, hydrophobicity, and

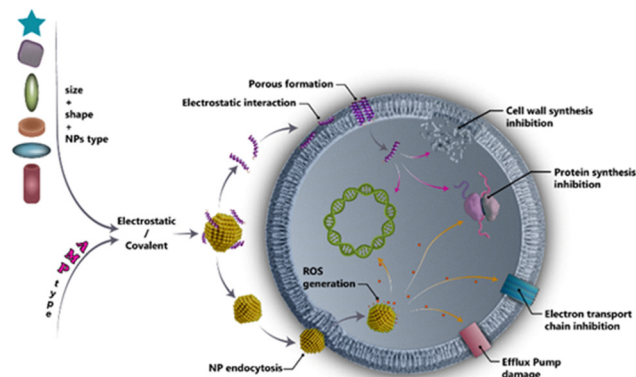


Fig. 2 Mechanisms of action and cellular interactions of AMP–nanoparticle conjugates against bacterial cells. The figure illustrates how AMPs and NPs, depending on their size, shape, and material type, interact with bacterial membranes *via* electrostatic or covalent conjugation strategies.

functional groups. Environmental factors, such as pH, ionic strength, and temperature, can significantly influence the strength and stability of peptide–NP interactions, necessitating context-specific optimization.<sup>48</sup>

The synergistic mechanism of action between nanoparticles and AMPs is illustrated in Fig. 2. This schematic representation highlights the interactions between AMP conjugates and nanomaterials, which function as delivery platforms that enhance antibacterial efficacy by combining the antimicrobial properties of AMPs with the distinct physicochemical characteristics of nanomaterials. A crucial aspect of this synergy lies in the surface interactions at the nano–bio interface, where the mode of AMP attachment—covalent or non-covalent—strongly influences stability, orientation, and biological function. AMPs primarily act by disrupting bacterial membranes through one of the existing mechanisms, which is pore formation or a carpet-like mechanism, and can further penetrate intracellular compartments to interfere with essential biological processes. Nanomaterials, on the other hand, protect AMPs from enzymatic degradation and contribute additional antimicrobial actions by disrupting membranes, generating ROS, and interfering with vital pathways such as efflux pumps and the electron transport chain.<sup>49</sup>

As we've represented and mentioned, and as shown in Fig. 2, conjugation strategies tailored to surface chemistry offer diverse and new advantages depending on the desired AMP release profile, bioactivity, and systemic stability.

The covalent conjugation, such as carbodiimide chemistry, remains widely used due to its straightforward application to carboxyl- and amine-functionalized surfaces. However, this method often suffers from low efficiency, uncontrolled peptide orientation, and potential peptide crosslinking, which can impair biological activity.<sup>50</sup> Another popular covalent reaction protocol is the thiol–maleimide reaction, which allows more site-specific conjugation *via* cysteine residues but is prone to thiol-exchange reactions under physiological conditions, limiting long-term stability.<sup>51</sup> Pal *et al.* demonstrate that covalent attachment (*via* cysteine–Ag bond) improved serum stability and antimicrobial activity relative to non-covalent complexes.<sup>52</sup>



As was reported,<sup>53</sup> silver nanoparticles covalently functionalized with AMPs retain enhanced antimicrobial potency and specificity. The covalent attachment reduced peptide desorption and improved the targeting of bacterial cells, resulting in synergistic antibacterial effects. Compared to simple physical mixtures or electrostatically bound peptides, covalent conjugates maintained better activity over longer periods, supporting their therapeutic potential.

Site-selective disulfide re-bridging represents another innovative strategy, allowing precise control over AMP orientation and spacing, thereby improving accessibility and minimizing steric hindrance, which is crucial for maintaining bifunctionality.<sup>54</sup>

In contrast, electrostatic adsorption and hydrophobic interactions enable reversible and modular assembly of AMPs on NP carriers.<sup>55,56</sup> While attractive for dynamic delivery systems, these interactions often lack stability in physiological environments and may result in premature peptide release. Hydrophobic interactions, on the other hand, leverage the affinity between hydrophobic regions of AMPs and NP surfaces, promoting stable yet reversible attachment.<sup>57</sup>

Importantly, the chosen conjugation chemistry does not merely dictate attachment efficiency; it also significantly affects AMP activity, release profile, immune recognition, and *in vivo* biodistribution. Therefore, rigorous optimization and comparative evaluation of these conjugation strategies are essential for the rational design of AMP-NP systems tailored to combat AMR.

### Gold nanoparticles

AuNPs are biocompatible, chemically inert, and non-toxic, making them ideal for systemic treatments. Their surfaces can be easily modified, allowing for the attachment of AMPs and other functional ligands to enhance specificity and stability in biological environments.<sup>58</sup>

AuNPs disrupt bacterial membranes and enhance the effects of AMPs by delivering peptides directly to target sites while protecting them from enzymatic degradation, thus extending their half-life. The ability of AuNPs to generate ROS further amplifies their antimicrobial properties, leading to oxidative stress, membrane disruption, and bacterial death. Additionally, AuNPs can form strong bonds with thiol groups in bacterial proteins, disrupting the bacterial respiratory chain and further increasing oxidative damage.<sup>59</sup>

For instance, a recent study has shown enhanced AMP activity when five different amphiphilic  $\alpha$ -helical AMPs (PGLa, MSI-103, MAP, BP100, and TP10) were attached to AuNPs *via* their N-terminal cysteine.<sup>60</sup> This functionalization enhanced peptide stability against enzymes such as trypsin, thereby increasing antimicrobial activity against both Gram-negative and Gram-positive bacteria while maintaining the conformational flexibility of the AMPs.

Functionalized AuNPs have been utilized to combat MDR pathogenic bacteria. Tuning of the functional groups on the NPs' surface provided gold nanoparticles that were effective against both Gram-negative and Gram-positive pathogens, including MDR pathogens. These AuNPs exhibited low toxicity to mammalian cells, and bacterial resistance was not observed

after 20 generations. A strong structure–activity relationship was observed as a function of the AuNPs' functionality, guiding the prediction of activity and the rational design of effective antimicrobial nanoparticles.<sup>61</sup>

A recent review<sup>62</sup> highlights the AMP–AuNPs as a tool to combat MDR pathogens by summarizing advances in the design, functionalization, and antimicrobial evaluation of AMP–AuNPs, underlining their mechanisms of action, conjugation strategies, and effectiveness against resistant pathogens.

### Iron oxide nanoparticles

IONPs have garnered considerable attention in antimicrobial therapy due to their biodegradable nature and natural metabolic pathways, which significantly mitigate concerns about long-term toxicity.<sup>63,64</sup> The antimicrobial efficacy of IONPs is primarily attributed to their positive surface charge, which facilitates attraction to the negatively charged bacterial membranes, resulting in membrane disruption.<sup>65</sup> This mechanism is not unique to IONPs, as many other NPs with similar positive surface modifications exhibit comparable antimicrobial properties. However, IONPs are distinguished by additional characteristics, including magnetic properties that enable targeted delivery and overall biocompatibility. Moreover, IONPs can catalyze the Haber–Weiss reaction, a process involving Fenton chemistry, which leads to the generation of ROS that induce oxidative stress in bacteria. The use of ROS as an antibacterial agent is regarded as both safe and effective against a broad spectrum of pathogens, with the added benefit of not promoting antimicrobial resistance.<sup>66</sup> IONPs' catalytic capabilities can be synergistically coupled with AMPs to generate ROS or enhance membrane disruption, rendering these magnetic NPs versatile tools for advancing AMPs-based antibacterial strategies.

The catalytic activity of IONPs, influenced by their material composition, can be further modulated by their size and shape, significantly impacting their antimicrobial effectiveness. Smaller NPs, typically ranging from 5 to 10 nm, demonstrate enhanced antimicrobial activity due to their superior ability to diffuse through biological barriers and engage with cellular components.

Research has shown that atom doping can markedly enhance the catalytic activity of IONPs. For instance, studies conducted by Faisal *et al.*<sup>67</sup> revealed that the antimicrobial specificity and efficacy of IONPs could be significantly improved through surface functionalization with compounds such as *p*-amino benzoic acid and anthranilic acid. Typically, IONPs are spherical and range from 5 to 50 nm in size, and they have been successfully conjugated with AMPs such as nisin, indolicidin, temporin, and lasioglossin III. This conjugation exploits the high capacity of NPs for AMP adsorption and their magnetic and catalytic properties to enhance the stability and antibacterial efficacy of the AMPs. In contrast, larger particles (50–200 nm) may be more suitable for multifunctional therapeutic applications.

The magnetic properties of IONPs further enhance their antibacterial efficacy by enabling targeted delivery, controlled release of AMPs, effective biofilm penetration, and multifunctionality. External magnetic fields can guide these NPs to



infection sites, ensuring accurate and targeted delivery of AMPs, which minimizes side effects while maximizing therapeutic impact. The increased surface area associated with smaller magnetic NPs enhances the density of AMP conjugation, thereby improving antimicrobial efficiency. Finally, the application of a high-frequency alternating magnetic field in IONPs can generate hyperthermia, which can be used as an additional mechanism to eliminate pathogens.

### Mesoporous silica (MSNs)

Mesoporous silica nanoparticles have emerged as highly effective carriers for AMPs, offering several advantages that address key limitations in peptide-based therapies. One of the primary benefits of MSNs is their high surface area and tunable pore sizes, which enable efficient loading and controlled release of AMPs, thereby prolonging their antimicrobial activity and reducing the risk of early degradation.<sup>68</sup>

Recent advancements have further improved the efficacy of MSNs through organic modifications and virus-like structural designs. The incorporation of MSNs' surface functional moieties that enhance bacterial membrane interactions, facilitating targeted AMP delivery and controlled release, while also improving biofilm penetration and overcoming bacterial resistance mechanisms, was reported by Colila and Regi.<sup>69</sup> Additionally, virus-like MSNs, characterized by their spiky surface topology, mimic specific viral structures to enhance interactions with bacterial membranes. By designing in this manner, the topological features increase membrane permeability, thereby strengthening the antimicrobial efficacy of MSN-based delivery systems.<sup>70</sup>

Overall, the combination of MSNs and AMPs represents a promising strategy to overcome the challenges associated with peptide-based antimicrobial therapies. By offering enhanced stability, targeted delivery, controlled release, biocompatibility, and aggregation prevention, MSNs provide an advanced platform that can significantly improve AMP efficacy.

Despite their potential in combating bacterial infections, these nanosystems have yet to be clinically applied. Further research is required to address challenges related to the complex composition, optimization of nanoformulations, reproducibility in production, large-scale manufacturing, and cost-effective development of organically modified MSNs to meet regulatory approval.

### Copper nanoparticles (CuNPs)

While MSNs offer controlled AMP release and excellent biocompatibility, their lack of intrinsic antimicrobial activity limits their efficacy in acute infections. To overcome this challenge, copper nanoparticles have garnered attention due to their strong antibacterial properties, which enable direct disruption of the bacterial membrane and oxidative stress-mediated killing. CuNPs can directly kill bacteria through the release of copper ions and oxidative stress, making them effective carriers and active antimicrobial agents. This makes CuNPs a promising alternative to MSNs or even a complementary system when

combined, offering sustained AMP delivery and immediate bactericidal action.

Several studies have investigated the synergistic effects of combining CuNPs with AMPs to enhance antibacterial efficacy. The results demonstrated a synergistic bactericidal effect, highlighting the potential of integrating CuNPs with AMPs for enhanced antibacterial strategies.<sup>71</sup> A review from 2021<sup>72</sup> focuses on a subclass of AMPs with a metal-binding motif called the amino-terminal copper and nickel (ATCUN) motif. The study explores how incorporating copper(II) ions can enhance the antimicrobial properties of these peptides, providing novel therapeutic opportunities.

Ultimately, the future of CuNPs in antimicrobial applications lies in developing safer, more targeted, and sustainable formulations that maximize antibacterial potential while minimizing adverse effects. By integrating CuNPs with responsive drug delivery platforms, such as pH-sensitive hydrogels or stimuli-responsive nanocarriers, researchers can enable site-specific release of copper ions and AMPs, improving therapeutic outcomes while reducing systemic toxicity.

Additionally, incorporating biodegradable coatings and smart nanocomposites, such as CuNPs embedded in mesoporous silica or chitosan scaffolds, could enhance biocompatibility, mitigate environmental concerns, and extend antimicrobial efficacy. By leveraging these advancements, CuNPs can pave the way for next-generation antimicrobial solutions addressing the urgent need for novel, resistance-proof antibacterial strategies.

### Polymeric nanoparticles

Polymeric nanoparticles demonstrate enhanced robustness and stability due to their structural integrity maintained by covalent bonds. Various types of polymeric NPs have been utilized as vehicles for a range of AMPs across numerous applications.<sup>73-75</sup>

Studies have shown that polymeric nanoparticles facilitate the delivery of antimicrobial peptides (AMPs), significantly improving their bioavailability, safeguarding them against degradation, and enhancing cellular penetration through membrane binding.<sup>76</sup> For example, Almaaytah *et al.*<sup>77</sup> reported that encapsulating AMPs within chitosan NPs reduced toxicity and enhanced antimicrobial efficacy compared to free AMPs. Furthermore, a study from Primo *et al.*<sup>78</sup> demonstrated that rifampicin encapsulated in NPs derived from *N*-acetylcysteine-conjugated chitosan, further linked to the AMP Ctx(Ile21)-Ha, produced a synergistic effect with improved stability against multi- and extensively drug-resistant *Mycobacterium tuberculosis*.

Moreover, novel star-shaped peptide polymers have gained attention in biomedical applications, particularly for synthesizing NPs that encapsulate AMPs. These star-shaped polymers exhibit antimicrobial activity through multiple mechanisms, potentially mitigating host toxicity and making them more advantageous than conventional nanocarriers.<sup>79</sup>

The versatility of polymeric NPs enables the incorporation of various functional groups, allowing for the conjugation of AMPs through different strategies, such as covalent bonding or electrostatic interactions. This adaptability is crucial for



tailoring the delivery system to meet specific clinical needs, including the treatment of MDR bacterial infections.

In summary, utilizing polymeric NPs as carriers for AMPs presents a promising approach to enhance the stability, bio-availability, and targeted delivery of these therapeutic agents, thereby addressing some of the key challenges in antimicrobial therapy.

Additional representative examples of AMPs–NPs systems are summarized in Table 1, illustrating the diversity of nanoparticle platforms employed, as well as the variety of AMPs conjugated using different strategies, such as covalent bonding, electrostatic interactions, and encapsulation. Notably, many of these nanoformulations offer enhanced stability, prolonged antimicrobial activity, and reduced cytotoxicity compared to free peptides.

### Hydrogels

Hydrogels have emerged as a promising alternative to NPs. These materials possess unique characteristics that enable the encapsulation of various molecules for various applications.

In 2014, Liskamp *et al.*<sup>80</sup> were among the first to use cross-linked polyethylene glycol diacrylate (PEGDA) hydrogels to deliver AMPs through thiolene photoclick chemistry. Their study revealed strong antimicrobial activity against Gram-positive bacteria, such as *Staphylococcus aureus* and *Staphylococcus*

*epidermidis*, as well as the Gram-negative bacterium *Escherichia coli*, *in vitro*.

Following this, another study explored the immobilization of Cecropin A onto PEGDA hydrogel cores with thiol-containing molecular linkers.<sup>81</sup> Their findings demonstrated that the antimicrobial efficacy of the hydrogel–AMP conjugate was subject to both the length of the linker utilized and the peptide loading within the system. Additionally, Nordström *et al.*<sup>82</sup> explored how the charge density in poly(ethyl acrylate-co-methacrylic acid) microgels influenced the release of three different peptides effective against *Pseudomonas aeruginosa* and *Escherichia coli*. They also evaluated hemolysis rates, the proteolytic stability of the hydrogels, and their interactions with biological membranes to assess their biocompatibility.

Overall, current research highlights the flexibility of hydrogel formulations in optimizing the delivery of AMPs to combat various bacterial strains. Numerous studies have demonstrated that these hydrogels enhance antimicrobial efficacy and offer stability and controlled release, making them a promising platform for effective AMPs delivery.

### Liposomes

Liposomes have demonstrated significant potential in enhancing the antimicrobial efficacy of AMPs while simultaneously reducing their toxicity. Research has explored the encapsulation

Table 1 Representative AMPs–NPs conjugate systems and their key findings

NPs type	AMP type	Size and shape	Mechanism of action	Main findings <i>in vitro/in vivo</i>	Ref.
Au	CSA-131	45–250 nm, rod-, peanut-, and star-shaped	ROS generation, membrane disruption, and protein leakage	Superior bactericidal activity against MDR bacterial strains compared to CSA-131 alone. Strong <i>in vitro</i> effectiveness with minimal toxicity to human red blood cells.	93
Au	Short peptides with an amidated C terminus	3 nm, spherical	Membrane disruption, biofilm inhibition	Specific antibacterial activity against <i>S. Aureus</i> , rapid <i>in vitro</i> bactericidal effects. <i>In vivo</i> studies: in mice; reduced bacterial load, enhanced survival rates, and alleviation of infection, all with good safety and excellent therapeutic outcomes.	94
IO (Fe <sub>3</sub> O <sub>4</sub> )	Ceragenin CSA-13	15 nm, spherical	Membrane disruption and inhibition of biofilm formation	Enhanced antimicrobial efficacy and biofilm disruption against <i>P. Aeruginosa</i> while significantly reducing hemolytic toxicity to red blood cells <i>in vitro</i> .	95
IO (Fe <sub>3</sub> O <sub>4</sub> ) with metronidazole	Amphotericin B	220 nm, spherical	Isolate amoebae	Promising for treatment for <i>A. Castellanii</i> infections, with potential for future <i>in vivo</i> studies. It is biocompatible with human and rat cell lines and exhibits no hemolytic activity <i>in vitro</i> , indicating safety for further development.	96
Mesoporous silica with gentamicin	Ovotransferrin	100 nm, spherical	Growth inhibition	Targeted antibiotic delivery to bacterial infection sites, to inhibit the growth of <i>E. coli</i> both <i>in vitro</i> and <i>in vivo</i> .	97
Mesoporous silica	$\alpha$ -defensin: T7E21R-HD5	60 nm, spherical	Aggregation, membrane disruption	Enhance the effectiveness of antibiotic therapy by directing treatment to infection areas, potentially reducing side effects and improving outcomes.	98
CuS-ZIF8	$\alpha$ -helical: At10	50–200 nm, framework	Membrane disruption	A promising oral antibacterial formulation has been developed that effectively inactivates <i>E. coli</i> and <i>S. aureus in vitro</i> . Non-toxic and proven to eradicate MDR <i>E. coli in vivo</i> , indicating its potential as a safe and effective treatment option.	99
Polymeric NPs (chitosan)	RBRBR (Arginine (R), L-4-phenyl-phenylalanine (B))	120 nm, spherical	Membrane disruption, inhibition	Synergistic effects against MDR bacteria such as <i>E. coli</i> and <i>S. aureus in vitro</i> , indicating potential for improved clinical treatment of resistant infections.	71
Polymeric NPs (chitosan)	Poly(Z-Lys11-stat-Phe10) lysine + phenylalanine	160–230 nm, capsule	Membrane disruption	Potent, selective, and long-lasting inhibition of biofilm formation <i>in vitro</i> , effectively targeting various Gram-positive bacteria, including resistant <i>S. aureus</i> strains. The drug delivery system demonstrates effective <i>in vitro</i> activity, showing significant antibacterial effects against both <i>E. coli</i> and <i>S. aureus</i> , highlighting its potential for targeted antimicrobial therapy.	77



of various AMPs within liposomes, highlighting their potential applicability in biomedicine, among other fields.<sup>83</sup>

The unique architecture of liposomes, composed of lipid bilayers derived from phospholipids and cholesterol, allows for the encapsulation of both hydrophobic and hydrophilic compounds.<sup>84</sup>

Furthermore, the composition and size of liposomes can be tailored to optimize the delivery of specific molecules, minimize degradation, regulate release rates, and improve targeting affinity.

Recent studies have increasingly focused on the encapsulation of AMPs in liposomes, resulting in enhanced stability and bioactivity of these peptides. For instance, Ron-Doitch *et al.*<sup>85</sup> developed liposomes containing LL-37 coated with PEG, which showed reduced toxicity and improved antiviral activity against herpes simplex virus 1 (HSV-1). Furthermore, Cantor *et al.*<sup>86</sup> demonstrated significant improvements in the antibacterial properties of the AMP Alyteserin-1c when delivered *via* Eudragit E-100<sup>®</sup>-coated liposomes, which showed marked efficacy against *Listeria monocytogenes* and *Escherichia coli*.

Encapsulating AMPs within liposomes represents a promising strategy to address the challenges associated with direct AMP applications, including cytotoxicity and instability. This innovative approach enhances the therapeutic potential of AMPs but also opens new avenues for developing effective antimicrobial therapies.

### Metal complexes

Metal ions play a crucial role in numerous biological processes and significantly impact the functionality of AMPs. These peptides can interact with metal ions, restricting microbial access to vital nutrients through nutritional immunity.<sup>87</sup> Moreover, specific metal ions can enhance the antimicrobial efficacy of AMPs by altering their charge and structural properties.<sup>88,89</sup>

The relationship between metal ions and peptides is influenced by several principles, primarily shaped by the unique characteristics of the metal ions and the peptide sequence. Peptides are particularly adept at binding metal ions, mainly due to the involvement of the amino group at their N-terminal and the action of deprotonated nitrogen atoms along the peptide chain.<sup>90</sup> This binding activity leads to robust complexes between peptides and metal ions.

AMPs combat microorganisms through multiple strategies, including sequestering essential metal ions. Important metal ions, such as Zn(II) and Cu(II), serve a dual function in AMP activity: they can be captured by AMPs, thereby depriving pathogens of critical metals vital for their survival and pathogenicity, or they can boost the antimicrobial efficacy of AMPs by affecting the peptides' charge and conformation.<sup>91,92</sup>

Although the development of effective metal-AMP complexes may provide foundational models for creating new potent AMP-based therapeutic agents, there is a notable deficiency in data that clarifies the intricate relationships between metal-AMP coordination modes, thermodynamic parameters, structural attributes, and their resultant biological activities, encompassing mechanisms of action and host specificity.<sup>91</sup>

As demonstrated in the previous examples, recent advances in nano-formulations have been promising, showcasing the successful development of diverse AMP-carrier hybrid systems. However, *in vitro* results often fail to translate to *in vivo* efficacy, and issues like the stability of AMPs coatings on, for instance, NPs persist.<sup>49,100</sup> Addressing these challenges requires careful study design and a focus on the physicochemical properties of AMPs to select suitable materials for functionalization. A comprehensive analysis of formulation characteristics, carrier composition, and release kinetics is necessary to enhance the clinical applicability of AMP therapies.

### Addressing the challenges and optimizing AMP-carrier systems

AMP-carrier systems offer a promising approach to combat MDR infections by enhancing the stability, delivery, and efficacy of AMPs. However, their clinical translation faces significant challenges. Ensuring stability and concentration dependence of AMPs on NP surfaces is a constant issue, as peptides can desorb or degrade over time, reducing their antimicrobial effectiveness.

Another aspect to be addressed is selective targeting and specificity. AMP-NP systems can exhibit non-specific interactions with host cells, triggering cytotoxicity. Cationic AMPs may bind negatively charged host cell membranes, leading to off-target effects.

Bioavailability is also a concern. Although polymeric nanoparticles and liposomes enhance the AMPs' stability and delivery, they are still prone to rapid clearance or limited penetration into biofilms. Additionally, achieving consistent and sustained AMP release is challenging, as environmental factors such as pH and temperature often influence the release profiles. These limitations necessitate a deeper understanding of the factors governing the adsorption, stability, and release of AMPs from NP surfaces.

## Role of MD simulations in understanding AMP-metal systems

MD simulations are required to understand the complex interactions between AMPs and metal nanoparticles. They provide atomistic insights that complement and are challenging to obtain by the existing experimental approaches.

How AMPs bind, orient, and interact with metal surfaces can be revealed only through an atomistic approach to treating the systems, and this understanding can be critical for factors such as stability and controlled release, for instance. Applications of MD simulations in the design and evaluation of AMP-nanoparticle conjugates are illustrated in Fig. 3.

### Elucidating binding mechanisms and peptide orientation

One of MD's most significant contributions is its ability to elucidate the binding mechanisms of AMPs on metal surfaces. Such insights are crucial for designing AMP-metal systems with improved binding efficiency and stability. For instance, Roccatano *et al.*<sup>101</sup> highlighted methods for studying peptide interactions with uncoated gold surfaces, demonstrating how peptide sequences adapt their conformations to maximize



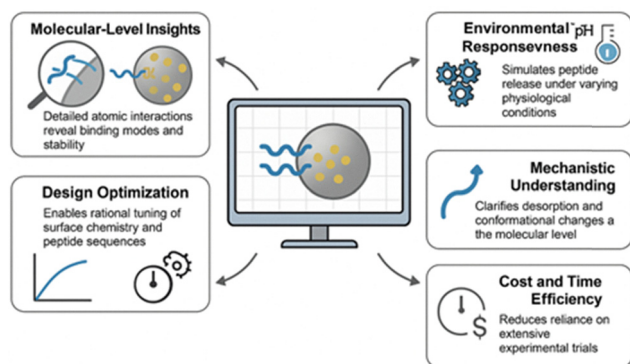


Fig. 3 Schematic workflow for MD simulations for AMPs–NPs conjugations.

contact with the metal. These simulations have shown that AMPs can adopt various orientations on gold surfaces, from parallel to perpendicular configurations, depending on their sequence and surface properties.

In the case of hybrid AMPs such as cecropin-melittin, Simões *et al.*<sup>102</sup> demonstrated that these peptides bind to AuNPs through electrostatic and hydrophobic interactions, significantly enhancing their antimicrobial activity. Their MD simulations revealed that gold alters peptide orientation, promoting conformations that favor membrane disruption when the conjugates approach bacterial cells. This interaction mechanism is driven by the amphipathic nature of the peptide, where hydrophobic regions interact with the NP surface, while cationic regions remain exposed for bacterial targeting.

MD simulations have also highlighted the importance of specific amino acids in promoting stable peptide binding. For instance, Monti *et al.*<sup>103</sup> focused on the behavior of cysteine-based peptides on gold surfaces, using classical MD simulations with a reactive force field to provide atomic-level insights. Their findings demonstrated that cysteine acts as a preferential anchoring point, leading to rapid peptide stabilization during the adsorption process. The study also revealed that cysteine's thiol group not only promotes stable binding but also influences the overall orientation of the peptide, enhancing its antimicrobial efficacy by maintaining an active conformation.

### Exploring the effect of surface modifications on AMP adsorption

MD simulations have also helped explore how surface modifications, such as ligand coating or the attachment of functional groups, affect the adsorption of AMP. For example, a citrate coating on AuNPs can alter the electrostatic landscape, promoting the adsorption of cationic AMPs through charge attraction. Simulations have shown that by adjusting the density and type of surface ligands, it is possible to fine-tune the balance between peptide stability and release.<sup>104,105</sup>

In the study by Monti *et al.*,<sup>103</sup> the authors demonstrated that the surface chemistry of AuNPs directly affects peptide adsorption and desorption kinetics. Reactive force field MD simulations revealed that modifying the NP surface with

specific ligands can enhance peptide retention, reduce desorption, and provide a controlled release mechanism under specific conditions, such as pH changes or enzymatic activity.

### Investigating controlled release and desorption mechanisms

MD simulations are also valuable for understanding the conditions under which AMPs desorb from NPs' surfaces, which is essential for designing controlled-release systems. These simulations can model how environmental factors, such as pH, temperature, or ionic strength, influence peptide release. This understanding is crucial for designing smart, stimulus-responsive AMP–NP systems. By fine-tuning surface chemistry and leveraging specific environmental triggers, researchers can develop AMP–NP systems that release peptides only under conditions that mimic infection sites, maximizing their therapeutic impact while minimizing off-target effects.

### Predicting AMP aggregation and self-assembly on NP surfaces

MD simulations offer insights into the behavior of AMP molecules at high surface densities, revealing potential aggregation or self-assembly behaviors. Such insights are crucial for metal-based NP systems, where peptide aggregation can also affect NPs' stability, leading to particle aggregation or sintering.

By integrating MD simulations with experimental studies, researchers can develop more rational design strategies for AMP–metal systems that exhibit enhanced stability, selectivity, and antimicrobial efficacy. These computational insights bridge the gap between theoretical understanding and practical application, accelerating the development of next-generation AMPs–NPs therapies.

## Outlook

From this perspective, we draw the reader's attention to the experimental design and illustrate how MD simulations play a crucial role in creating a unified platform for AMP–metal nanoparticle formulations.

MD simulations can guide the design of AMP–nanoparticle systems, from initial concept to formulation. At the pre-synthesis stage, MD simulations can help screen peptide sequences, optimize nanoparticle surface chemistry, and predict peptide stability under physiological conditions, providing valuable insights before commencing experimental work. As the design progresses to the formulation stage, simulations continue to support surface functionalization strategies, including the exploration of ligand environments and interaction modeling, which enables the rational development of stable, responsive systems that enhance antimicrobial efficacy and controlled release. By embedding MD throughout the design pipeline, this strategy ensures a more optimal, faster, and transferable approach through the mechanism-driven development process.

Furthermore, as a future direction, the MD simulations should be combined with machine learning techniques to accelerate the optimization process of the new AMPs. By training ML models on MD-generated data as a surrogate mode, researchers can rapidly identify peptide and NP designs that



maximize antimicrobial activity while minimizing cytotoxicity. Such an approach transforms MD simulations from a theoretical tool into a predictive framework for the rational design of AMP–metal systems.

Moreover, there is a critical need for more accurate simulations, improved force fields, and reliable pipelines for experimental validation. Overcoming these challenges will require interdisciplinary collaboration, leveraging advancements in computational power, algorithmic efficiency, and experimental techniques to achieve practical solutions. Enhanced force fields that accurately capture the unique properties of peptides and NP surfaces, combined with hybrid quantum mechanics/molecular mechanics (QM/MM) methods, could further enhance the predictive power of simulations.

One future perspective is the implementation and use of quantum computing as a transformative approach to modeling peptide–NP interactions, thereby overcoming the limitations of classical computations. Variational Quantum Eigensolvers (VQE) and Quantum Monte Carlo (QMC) methods can provide accurate energy profiles for peptide–surface interactions at the atomic level, even for complex systems. These quantum approaches enable the exploration of quantum effects, such as electron delocalization and tunneling, which are crucial for accurately describing the dynamics of peptide adsorption and desorption.

For instance, applying quantum computing (QC) to model peptide–gold interactions can reveal the nature of electron transfer processes and the role of electronic structure in stabilizing peptide conformations. Unlike classical simulations, which approximate molecular interactions using force fields, QC directly calculates the behavior of electrons, enabling an accurate description of peptide–NP interactions. This capability is crucial for designing stable, efficient, and targeted AMP–NP systems.

Addressing the challenges of peptide–NP interaction studies will require a synergistic approach that combines MD simulations, quantum computing, and experimental validation. Such a comprehensive framework will pave the way for the rational design of peptide-functionalized nanomaterials with enhanced stability, selectivity, and functionality.

## Author contributions

The authors' contributions have been defined following the CRediT system. Conceptualization: M. N. and M. L.; investigation: M. N., A. S. P., D. P. V., M. L.; writing – original draft: M. N., D. P. V., A. S. P., M. L.; writing – review & editing: M. N., A. S. P., M. L.; visualization: M. N.; project administration: M. N.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

As this is a Perspective article, no primary research results, data, software or code have been included.

## Acknowledgements

NCCR Bioinspired Materials financially supported the authors (MN and DPV). MN, DPV, and ML are also grateful for the financial support of the University of Fribourg. MN supported by the program “Research, Innovation and Digitalization for Smart Transformation,” co-financed by the European Regional Development fund no. BG16RFPR002-1.014-0014-C01, “Development and Sustainability Program with a Business Plan for a Laboratory Complex at Sofia Tech Park”. MN acknowledges the European Union Next Generation EU through the National Recovery and Resilience Plan of the Republic of Bulgaria, project no. BG-RRP-2.004-0008-C01. M. N. wish to acknowledge particularly to Dr G. G. for the discussions that significantly influenced the structure and thematic organization of the graphical representation of the work.

## References

- 1 World Health Organization, Global antimicrobial resistance and use surveillance system (GLASS) report: 2022. Geneva, Switzerland.
- 2 J. O'Neill, chair. 2016. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. Review on Antimicrobial Resistance., 2016.
- 3 C. Llor and L. Bjerrum, *Ther. Adv. Drug Saf.*, 2014, 5, 229–241.
- 4 R. C. Founou, A. J. Blocker, M. Noubom, C. Tsayem, S. P. Choukem, M. Van Dongen and L. L. Founou, *Future Sci. OA*, 2021, 7, 8.
- 5 R. Y. Pelgrift and A. J. Friedman, *Adv. Drug Delivery Rev.*, 2013, 65, 1803–1815.
- 6 G. P. C. Salmond and P. C. Fineran, *Nat. Rev. Microbiol.*, 2015, 13, 777–786.
- 7 M. Mahlapuu, J. Håkansson, L. Ringstad and C. Björn, *Front. Cell. Infect. Microbiol.*, 2016, 6, 194.
- 8 N. Mookherjee, M. A. Anderson, H. P. Haagsman and D. J. Davidson, *Nat. Rev. Drug Discovery*, 2020, 19, 311–332.
- 9 M. Guerrero Correa, F. B. Martínez, C. P. Vidal, C. Streitt, J. Escrig and C. L. de Dicastillo, *Beilstein J. Nanotechnol.*, 2020, 11, 1450–1469.
- 10 A. S. Rodrigues, J. G. S. Batista, M. Á. V. Rodrigues, V. C. Thipe, L. A. R. Minarini, P. S. Lopes and A. B. Lugão, *Front. Microbiol.*, 2024, 15, 1440065.
- 11 M. Hancharova, K. Halicka-Stępień, A. Dupla, A. Lesiak, J. Sołoducho and J. Cabaj, *Biomaterials*, 2024, 37, 773–801.
- 12 U. Rajchakit, S. Lamba, K. Wang, N. Lyons, J. Lu, S. Swift, D. Pletzer and V. Sarojini, *Mol Pharm*, 2024, 21, 596–608.
- 13 L. Wang, N. Wang, W. Zhang, X. Cheng, Z. Yan, G. Shao, X. Wang, R. Wang and C. Fu, *Signal Transduct Target Ther*, 2022, 7, 48.
- 14 M. Muttenthaler, G. F. King, D. J. Adams and P. F. Alewood, *Nat Rev Drug Discov*, 2021, 20, 309–325.
- 15 A. Henninot, J. C. Collins and J. M. Nuss, *J. Med. Chem.*, 2018, 61, 1382–1414.
- 16 K. A. Brogden, *Nat. Rev. Microbiol.*, 2005, 3, 238–250.



- 17 C. H. Chen, C. G. Starr, E. Troendle, G. Wiedman, W. C. Wimley, J. P. Ulmschneider and M. B. Ulmschneider, *J. Am. Chem. Soc.*, 2019, **141**, 4839–4848.
- 18 Y. Wang, C. H. Chen, D. Hu, M. B. Ulmschneider and J. P. Ulmschneider, *Nat. Commun.*, 2016, **7**, 13535.
- 19 P. G. A. Aronica, L. M. Reid, N. Desai, J. Li, S. J. Fox, S. Yadahalli, J. W. Essex and C. S. Verma, *J. Chem. Inf. Model.*, 2021, **61**, 3172–3196.
- 20 M.-A. Sani, A. P. Le Brun, S. Rajput, T. Attard and F. Separovic, *Biophys. J.*, 2023, **122**, 1058–1067.
- 21 H. Leontiadou, A. E. Mark and S. J. Marrink, *Biophys. J.*, 2004, **86**, 2156–2164.
- 22 C. H. Chen, M. C. Melo, N. Berglund, A. Khan, C. de la Fuente-Nunez, J. P. Ulmschneider and M. B. Ulmschneider, *Curr. Opin. Struct. Biol.*, 2020, **61**, 160–166.
- 23 B. Ding, L. Soblosky, K. Nguyen, J. Geng, X. Yu, A. Ramamoorthy and Z. Chen, *Sci. Rep.*, 2013, **3**, 1854.
- 24 J. Steinkühler, R. Lipowsky and M. S. Miettinen, *J. Phys. Chem. B*, 2024, **128**, 8782–8787.
- 25 M. Aguilar, K. Al Nahas, F. Barrera, P. Bassereau, M. Bastos, P. Beales, B. Bechinger, B. Bonev, I. Brand, A. Chattopadhyay, R. J. Clarke, W. DeGrado, E. Deplazes, A. J. Garcia Saez, B. Hoogenboom, R. Lund, P. Milán Rodríguez, P. O'Shea, G. Pabst, S. Pal, A. Roux, J. Sanderson, E. F. Semeraro, D. Sengupta, D. P. Siegel, L. van't Hag, A. Vijayakumar and L. Zoranić, *Faraday Discuss.*, 2021, **232**, 256–281.
- 26 J. Conde, G. Doria and P. Baptista, *J. Drug Delivery*, 2012, **2012**, 1–12.
- 27 S. T. Selvan, T. T. Y. Tan, D. K. Yi and N. R. Jana, *Langmuir*, 2010, **26**, 11631–11641.
- 28 P. Baptista, E. Pereira, P. Eaton, G. Doria, A. Miranda, I. Gomes, P. Quaresma and R. Franco, *Anal. Bioanal. Chem.*, 2008, **391**, 943–950.
- 29 X. Huang, P. K. Jain, I. H. El-Sayed and M. A. El-Sayed, *Nanomedicine*, 2007, **2**, 681–693.
- 30 X. Huang and M. A. El-Sayed, *J. Adv. Res.*, 2010, **1**, 13–28.
- 31 P. Ghosh, G. Han, M. De, C. Kim and V. Rotello, *Adv. Drug Delivery Rev.*, 2008, **60**, 1307–1315.
- 32 S. Bhattacharyya, R. A. Kudgus, R. Bhattacharya and P. Mukherjee, *Pharm. Res.*, 2011, **28**, 237–259.
- 33 M. S. Yavuz, Y. Cheng, J. Chen, C. M. Cobley, Q. Zhang, M. Rycenga, J. Xie, C. Kim, K. H. Song, A. G. Schwartz, L. V. Wang and Y. Xia, *Nat. Mater.*, 2009, **8**, 935–939.
- 34 A. M. Negrescu, M. S. Killian, S. N. V. Raghu, P. Schmuki, A. Mazare and A. Cimpan, *J. Funct. Biomater.*, 2022, **13**, 274.
- 35 L. Fernández, M. D. Cima-Cabal, A. C. Duarte, A. Rodriguez, P. García, M. del and M. García-Suárez, *Antibiotics*, 2020, **9**, 916.
- 36 S. M. Dadfar, K. Roemhild, N. I. Drude, S. von Stillfried, R. Knüchel, F. Kiessling and T. Lammers, *Adv. Drug Delivery Rev.*, 2019, **138**, 302–325.
- 37 E. Łojewska and T. Sakowicz, *Curr. Microbiol.*, 2021, **78**, 4037–4049.
- 38 E. Sánchez-López, D. Gomes, G. Esteruelas, L. Bonilla, A. L. Lopez-Machado, R. Galindo, A. Cano, M. Espina, M. Ettcheto, A. Camins, A. M. Silva, A. Durazzo, A. Santini, M. L. Garcia and E. B. Souto, *Nanomaterials*, 2020, **10**, 292.
- 39 M. S. Shakil, M. S. Bhuiya, M. R. Morshed, G. Babu, M. S. Niloy, M. S. Hossen and M. A. Islam, *Curr. Med. Chem.*, 2023, **30**, 1756–1775.
- 40 S. Mahaparale and A. Patil, *Int. J. Pharm. Sci. Drug Res.*, 2024, 736–745.
- 41 X. Zhang, G. Ma and W. Wei, *NPG Asia Mater.*, 2021, **13**, 52.
- 42 S. K. Modi, S. Gaur, M. Sengupta and M. S. Singh, *Front. Microbiol.*, 2023, **14**, 1135579.
- 43 A. E. Nel, L. Mädler, D. Velegol, T. Xia, E. M. V. Hoek, P. Somasundaran, F. Klaessig, V. Castranova and M. Thompson, *Nat. Mater.*, 2009, **8**, 543–557.
- 44 G. Nirmala Devi, R. N. Viswanath, C. Lakshmanan, G. Suresh and R. Rajaraman, arXiv, 2020, preprint, DOI: 10.48550/arXiv.2011.10003.
- 45 M. Kumari, S. N. Klodzinska and M. C. Chifiriuc, *Front. Microbiol.*, 2023, **14**, 1273364.
- 46 S. Malekhhaiat Häffner, L. Nyström, R. Nordström, Z. P. Xu, M. Davoudi, A. Schmidtchen and M. Malmsten, *Phys. Chem. Chem. Phys.*, 2017, **19**, 23832–23842.
- 47 C.-F. Le, C.-M. Fang and S. D. Sekaran, *Antimicrob. Agents Chemother.*, 2017, **61**, 4.
- 48 G. Li, C. Yuan and X. Yan, *Soft Matter*, 2025, **21**, 1781–1812.
- 49 K. B. S. de Oliveira, M. L. Leite, N. T. M. Melo, L. F. Lima, T. C. Q. Barbosa, N. L. Carmo, D. A. B. Melo, H. C. Paes and O. L. Franco, *Antibiotics*, 2024, **13**, 1042.
- 50 K. Werengowska-Ciećwierz, M. Wiśniewski, A. P. Terzyk and S. Furmaniak, *Adv. Condens. Matter Phys.*, 2015, **2015**, 1–27.
- 51 M. H. Zaleski, L. S. Chase, E. D. Hood, Z. Wang, J. Nong, C. L. Espy, M. E. Zamora, J. Wu, L. J. Morrell, V. R. Muzykantov, J. W. Myerson and J. S. Brenner, *Adv. Mater.*, 2025, **37**, 5.
- 52 I. Pal, V. P. Brahmkhatri, S. Bera, D. Bhattacharyya, Y. Quirishi, A. Bhunia and H. S. Atreya, *J. Colloid Interface Sci.*, 2016, **483**, 385–393.
- 53 M. S. Zharkova, O. Yu Golubeva, D. S. Orlov, E. V. Vladimirova, A. V. Dmitriev, A. Tossi and O. V. Shamova, *Front. Microbiol.*, 2021, **12**, 750556.
- 54 L. Lu, V. T. Duong, A. O. Shalash, M. Skwarczynski and I. Toth, *Vaccines*, 2021, **9**, 563.
- 55 J. Yang, R. Yang, J. Sun, G. Peng, M. Li, W. Li, L. Zhu, W. Zhang, F. Ge, J. Wang and P. Song, *ACS Appl. Nano Mater.*, 2025, **8**(20), 10742–10753.
- 56 W. Li, Y. Li, P. Sun, N. Zhang, Y. Zhao, S. Qin and Y. Zhao, *RSC Adv.*, 2020, **10**, 38746–38754.
- 57 M. Zaslhoff, *Nature*, 2002, **415**, 389–395.
- 58 E. de Alteriis, V. Maselli, A. Falanga, S. Galdiero, F. M. Di Lella, R. Gesuele, M. Guida and E. Galdiero, *Infect. Drug Resist.*, 2018, **11**, 915–925.
- 59 X. Li, S. M. Robinson, A. Gupta, K. Saha, Z. Jiang, D. F. Moyano, A. Sahar, M. A. Riley and V. M. Rotello, *ACS Nano*, 2014, **8**, 10682–10686.
- 60 P. Wadhvani, N. Heidenreich, B. Podyeyn, J. Bürck and A. S. Ulrich, *Biomater. Sci.*, 2017, **5**, 817–827.



- 61 X. Li, S. M. Robinson, A. Gupta, K. Saha, Z. Jiang, D. F. Moyano, A. Sahar, M. A. Riley and V. M. Rotello, *ACS Nano*, 2014, **8**, 10682–10686.
- 62 U. Rajchakit and V. Sarojini, *Bioconjugate Chem.*, 2017, **28**, 2673–2686.
- 63 M. G. Montiel Schneider, M. J. Martín, J. Otarola, E. Vakarelska, V. Simeonov, V. Lassalle and M. Nedyalkova, *Pharmaceutics*, 2022, **14**, 204.
- 64 M. Nedyalkova, J. Medinger, G. Mirabello and M. Lattuada, *Adv. Colloid Interface Sci.*, 2024, **323**, 103056.
- 65 S. Ashrafi-Saiedlou, M. Rasouli-Sadaghiani, M. Fattahi and Y. Ghosta, *Sci. Rep.*, 2025, **15**, 1018.
- 66 L. Leena Panigrahi, S. Shekhar, B. Sahoo and M. Arakha, *RSC Adv.*, 2023, **13**, 25497–25507.
- 67 S. Faisal, S. Sadiq, M. Mustafa, M. H. Khan, M. Sadiq, Z. Iqbal and M. Khan, *RSC Sustainability*, 2023, **1**, 139–146.
- 68 N. Namdar, B. Nayeri Fasaee, P. Shariati, S. M. Joghataei and A. Arpanaei, *Sci. Rep.*, 2024, **14**, 29242.
- 69 M. Colilla and M. Vallet-Regí, *Chem. Mater.*, 2023, **35**, 8788–8805.
- 70 S. M. Häffner, E. Parra-Ortiz, K. L. Browning, E. Jørgensen, M. W. A. Skoda, C. Montis, X. Li, D. Berti, D. Zhao and M. Malmsten, *ACS Nano*, 2021, **15**, 6787–6800.
- 71 D. Zhang, S. Bie, M. Anas Tomeh, X. Zhang and X. Zhao, *Eur. J. Pharm. Biopharm.*, 2024, **204**, 114516.
- 72 J. Portelinha, S. S. Duay, S. I. Yu, K. Heilemann, M. D. J. Libardo, S. A. Juliano, J. L. Klassen and A. M. Angeles-Boza, *Chem. Rev.*, 2021, **121**, 2648–2712.
- 73 N. M. Hamelmann and J. M. J. Paulusse, *J. Controlled Release*, 2023, **356**, 26–42.
- 74 R. Nordström, L. Nyström, H. Ilyas, H. S. Atreya, B. C. Borro, A. Bhunia and M. Malmsten, *Colloids Surf., A*, 2019, **565**, 8–15.
- 75 H. Zhao, J. Sun, Y. Cheng, S. Nie and W. Li, *J. Mater. Chem. B*, 2025, **13**, 1518–1530.
- 76 S. Maleki Dizaj, S. Salatin, K. Khezri, J.-Y. Lee and F. Lotfipour, *Front. Microbiol.*, 2022, **13**, 831655.
- 77 A. Almaaytah, G. Mohammed, A. Abualhajja and Q. Al-Balas, *Drug Des., Dev. Ther.*, 2017, **11**, 3159–3170.
- 78 L. M. D. G. Primo, C. A. Roque-Borda, C. S. Carnero Canales, I. P. Caruso, I. O. de Lourenço, V. M. M. Colturato, R. M. Sábio, F. A. de Melo, E. F. Vicente, M. Chorilli, H. da Silva Barud, P. A. Barbugli, H. Franzky, P. R. Hansen and F. R. Pavan, *Carbohydr. Polym.*, 2024, **323**, 121449.
- 79 W. Wu, W. Wang and J. Li, *Prog. Polym. Sci.*, 2015, **46**, 55–85.
- 80 R. T. C. Cleophas, M. Riool, H. (Linda), C. Quarles van Ufford, S. A. J. Zaat, J. A. W. Kruijtzter and R. M. J. Liskamp, *ACS Macro Lett.*, 2014, **3**, 477–480.
- 81 M. A. Cole, T. F. Scott and C. M. Mello, *ACS Biomater. Sci. Eng.*, 2016, **2**, 1894–1904.
- 82 R. Nordström, L. Nyström, O. C. J. Andrén, M. Malkoch, A. Umerska, M. Davoudi, A. Schmidtchen and M. Malmsten, *J. Colloid Interface Sci.*, 2018, **513**, 141–150.
- 83 M. Faya, R. S. Kalhapure, H. M. Kumalo, A. Y. Waddad, C. Omolo and T. Govender, *J. Drug Delivery Sci. Technol.*, 2018, **44**, 153–171.
- 84 M. Alavi, N. Karimi and M. Safaei, *Adv. Pharm. Bull.*, 2017, **7**, 3–9.
- 85 S. Ron-Doitch, B. Sawodny, A. Kühbacher, M. M. N. David, A. Samanta, J. Phopase, A. Burger-Kentischer, M. Griffith, G. Golomb and S. Rupp, *J. Controlled Release*, 2016, **229**, 163–171.
- 86 S. Cantor, L. Vargas, O. E. Rojas A, C. J. Yarce, C. H. Salamanca and J. Oñate-Garzón, *Int. J. Mol. Sci.*, 2019, **20**, 680.
- 87 J. Wątyły, S. Potocki and M. Rowińska-Żyrek, *Chem. – Eur. J.*, 2016, **22**, 15992–16010.
- 88 L. Yang, V. D. Gordon, A. Mishra, A. Som, K. R. Purdy, M. A. Davis, G. N. Tew and G. C. L. Wong, *J. Am. Chem. Soc.*, 2007, **129**, 12141–12147.
- 89 M. Malkoski, S. G. Dashper, N. M. O'Brien-Simpson, G. H. Talbo, M. Macris, K. J. Cross and E. C. Reynolds, *Antimicrob. Agents Chemother.*, 2001, **45**, 2309–2315.
- 90 L. Falcigno, S. Braccia, R. Bellavita, G. D'Auria, A. Falanga and S. Galdiero, *Front. Drug Discovery*, 2024, **4**, 1440378.
- 91 D. Łoboda, H. Kozłowski and M. Rowińska-Żyrek, *New J. Chem.*, 2018, **42**, 7560–7568.
- 92 W. F. Walkenhorst, J. N. Sundrud and J. M. Laviolette, *Biochim. Biophys. Acta, Biomembr.*, 2014, **1838**, 2234–2242.
- 93 S. Chmielewska, K. Skłodowski, J. Depciuch, P. Deptuła, E. Piktel, K. Fiedoruk, P. Kot, P. Paprocka, K. Fortunka, T. Wollny, P. Wolak, M. Parlinska-Wojtan, P. Savage and R. Bucki, *Pharmaceutics*, 2021, **13**, 425.
- 94 Z. Zhang, Y. Chen, J. Gao, M. Yang, D. Zhang, L. Wang, T. Zhang, Q. Cao, J. Mwangi, C. He, Y. Li, X. Liu, X. Jiang, P. M. Kamau and R. Lai, *Nano Lett.*, 2023, **23**, 11874–11883.
- 95 K. Niemirowicz, U. Surel, A. Z. Wilczewska, J. Mystkowska, E. Piktel, X. Gu, Z. Namiot, A. Kułakowska, P. B. Savage and R. Bucki, *J. Nanobiotechnol.*, 2015, **13**, 32.
- 96 S. Abdelnasir, A. Anwar, M. Kawish, A. Anwar, M. R. Shah, R. Siddiqui and N. A. Khan, *AMB Express*, 2020, **10**, 127.
- 97 B. Ma, Y. Chen, G. Hu, Q. Zeng, X. Lv, D. H. Oh, X. Fu and Y. Jin, *ACS Biomater. Sci. Eng.*, 2022, **8**, 109–118.
- 98 G. Zhao, Y. Chen, Y. He, F. Chen, Y. Gong, S. Chen, Y. Xu, Y. Su, C. Wang and J. Wang, *Biomater. Sci.*, 2019, **7**, 2440–2451.
- 99 C. Zhou, M. Wang, K. Zou, J. Chen, Y. Zhu and J. Du, *ACS Macro Lett.*, 2013, **2**, 1021–1025.
- 100 L. S. Biswaro, M. G. da Costa Sousa, T. M. B. Rezende, S. C. Dias and O. L. Franco, *Front. Microbiol.*, 2018, **9**, 855.
- 101 D. Roccatano, *Nanoparticles in Biology and Medicine*, 2020, vol. 2118, pp. 177–197.
- 102 A. F. Ferreira, A. Rai, L. Ferreira and P. N. Simões, *Eur. Biophys. J.*, 2017, **46**, 247–256.
- 103 S. Monti, G. Barcaro, L. Sementa, V. Carravetta and H. Ågren, *Nano Res.*, 2018, **11**, 1757–1767.
- 104 F. Tavanti, A. Pedone and M. C. Menziani, *Int. J. Mol. Sci.*, 2020, **22**, 26.
- 105 K. Kubiak-Ossowska, G. Burley, S. V. Patwardhan and P. A. Mulheran, *J. Phys. Chem. B*, 2013, **117**, 14666–14675.

