pISSN 1229-1153 / eISSN 2465-9223 *J. Food Hyg. Saf.*
Vol. 40, No. 3, pp. 169~182 (2025)
https://doi.org/10.13103/JFHS.2025.40.3.169

Journal of Food Hygiene and Safety
Available online at http://www.foodhygiene.or.kr

Review

Mechanistic Insights and Application Strategies of Electrostatic Interaction-Based Cationic Antimicrobials: A Review

Jaeyoung Ma, Yoonjee Chang*
Department of Food & Nutrition, Kookmin University, Seoul, Korea

(Received April 23, 2025/Revised June 13, 2025/Accepted June 16, 2025)

ABSTRACT - In this comprehensive review, we explore the types, mechanisms, and recent advances in cationic antimicrobial agents that interact with negatively charged bacterial membranes and disrupt their structure and function. With growing concerns regarding food safety, the demand for alternative antimicrobial strategies beyond conventional antibiotics is increasing. Cationic antimicrobials, including quaternary ammonium compounds, polyethyleneimine, antimicrobial peptides, and chitosan, exhibit potent bactericidal properties by rapidly adhering to bacterial surfaces and compromising membrane integrity, thereby inhibiting early bacterial proliferation. These systems, designed using diverse formulation strategies, show significant potential for practical applications in the food industry. This review highlights the molecular interactions underlying their antimicrobial action and discusses future directions for optimizing their safety and efficacy.

Keywords: Electrostatic interaction, Cationic materials, Antimicrobial activity, Food safety

Food contamination by pathogenic bacteria remains a critical challenge in food production and distribution systems[1]. In response, various sterilization techniques have been employed to eliminate foodborne pathogens linked to the consumption of contaminated food or water[2,3]. Among them, chemical disinfectants such as sodium hypochlorite and hydrogen peroxide are widely used in food processing environments[4]. However, their long-term effectiveness is limited due to chemical degradation, reduced available chlorine, and risks of chemical migration into food products[5]. Furthermore, the emergence of biofilm-forming bacteria, including *Staphylococcus aureus*, *Listeria monocytogenes*, and *Salmonella enterica*, has reduced the efficacy of oxidizing disinfectants, complicating bacterial control[6,7].

To address these limitations, alternative antimicrobial strategies that facilitate rapid and sustained interactions with bacterial cells have gained increasing attention[8]. In particular, ensuring close proximity between antimicrobial agents and bacterial surfaces is crucial to enable prompt action at the early stages of colonization[9]. This approach disrupts bacterial adhesion and prevents biofilm formation, providing a proactive means of microbial control. Agents that interact directly with bacterial membranes can compromise structural integrity and halt proliferation[10].

Cationic antimicrobial agents, in particular, operate through electrostatic interactions with negatively charged bacterial membranes[11]. These interactions promote swift adhesion to bacterial surfaces and enable contact-active bactericidal mechanisms[12]. Such electrostatic mechanisms also facilitate effective delivery and retention of antimicrobial agents on target cells, thereby enhancing the efficacy of biocidal formulations[8].

To address the necessity for the prompt inhibition of bacterial growth, this review categorizes cationic antimicrobials based on their fundamental electrostatic mechanisms of adhesion and disruption. Additionally, it emphasizes positively charge-based formulation strategies, including immobilization, nanostructure-based systems, and integration into biopolymer matrices, which are essential for improving antimicrobial effectiveness and ensuring material compatibility in food-related applications. Notably, it features recent studies that demonstrate the utilization of cationic agents in food packaging, surface coatings, and water purification. This study emphasizes the importance of electrostatic interactions as a fundamental mechanism underlying the bactericidal activity of cationic agents. By relating these interactions to practical applications in food safety systems, we propose a strategy framework for

*Correspondence to: Yoonjee Chang, Department of Food and Nutrition, Kookmin University, Seoul 02707, Korea
Tel: +82-2-910-5103, Fax: +82-2-910-5249
E-mail: ychang@kookmin.ac.kr

Copyright © The Korean Society of Food Hygiene and Safety. All rights reserved. The Journal of Food Hygiene and Safety is an Open-Access journal distributed under the terms of the Creative Commons Attribution Non-Commercial License(http://creativecommons.org/licenses/by-nc/3.0) which permits unrestricted non-commercial use, distribution,and reproduction in any medium, provided the original work is properly cited.

creating next-generation antimicrobial materials that improve food hygiene and preservation.

Cationic Functionalized Materials and Nanoparticles

Cationic antimicrobial agents impart a positively charged functionality to various substrates, including surfaces and nanoparticles[13]. Cationic compounds, such as quaternary ammonium compounds, polyethyleneimine, carbosilane dendritic polymers, and cationic liposomes, facilitate bacterial adhesion to their surfaces and disrupt bacterial structural integrity[14]. These antimicrobial agents exhibit high bactericidal activity through electrostatic interactions with bacterial cell membranes and are widely utilized in water purification, food packaging, and surface coatings within food processing facilities[11,15,16]. This mechanism includes the attraction of positively charged functional groups to the negatively charged components of bacterial membranes, including lipopolysaccharides or phosphate-containing lipids[13,17,18]. This interaction promotes bacterial adherence, impairs membrane integrity, and allows antimicrobial agent distribution[19,20]. Herein, comprehensive overviews of representative cationic materials were selected based on their prevalence in recent research studies and demonstrated relevance to food system applications, focusing on their properties, antimicrobial mechanisms, and formulation strategies (Table 1). Other types of cationic compounds were intentionally excluded to maintain a clear and focused scope, ensuring the discussion centers on the most widely investigated agents with established applicability in food-related systems.

Quaternary ammonium compounds (QACs)

QACs are representative of positively charged antimicrobial compounds. QACs such as dioctadecyldimethylammonium bromide (DODAB), dioctadecyldimethylammonium chloride (DODAC), and benzalkonium chloride (BAC) consist of a central quaternary ammonium ion bonded to three or four positively charged substituents with negatively charged bromide or chloride[21].

QACs have been integrated into diverse materials to prevent microbial contamination on food contact surfaces[22]. Several studies have shown antimicrobial films with QAC immobilization and functionalization on the substrate surface to increase bacterial cell membrane permeability[20]. Lee and Pascall[23] tested antimicrobial efficacy against surrogates for *L. monocytogenes* and *E. coli*, using silane QACs polymerization and immobilization on stainless steel for direct contact with food surfaces. Spray-applied surface coatings resulted in bacterial eradication (>5-log reduction) for Gram-positive bacteria and a 3- to 4-log reduction for Gram-negative bacteria, respectively.

In a similar study, Rukmanikrishnan et al.[24] developed a quaternary ammonium silane (QAS)-incorporated composite film based on agar/polyacrylamide hydrogel solution. Agar/polyacrylamide/QAS-based composite film demonstrated bacterial cell wall penetration, especially exhibiting the highest bacterial growth inhibition against *S. aureus*. This outcome revealed that hydrophobic antimicrobial agents enhanced cytoplasmic membrane permeability and increased bacterial susceptibility[25].

In addition to QAC immobilization on the surface, cationic functionalization with nanoparticles could provide a higher surface area, thus increasing the extent of surface modification with positive charges[26]. Based on these advantages, Eskandari et al.[27] developed zinc oxide nanoparticles (ZnONPs) coated with imidazolium (IM), a type of QAC, and evaluated antimicrobial activity against methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE). Imidazolium-functionalized zinc oxide nanoparticles (IM@ZnONPs) suspension showed a minimum inhibitory concentration (MIC) of 32 μg/mL against MRSA and VRE, while unmodified ZnONPs and zinc ions showed much higher MICs of 256 μg/mL and over 512 μg/mL, respectively[27].

Furthermore, Wang et al.[28] indicated that incorporating ZnO and CuO nanoparticles with QACs onto chitosan-based films enhanced the uniform distribution of positive charges while increasing the effective surface area accessible for microbial interaction. This dual alteration provided a synergistic antibacterial activity against both Gram-negative and Gram-positive bacteria, exceeding single-agent systems. These results revealed that penetration into the bacterial cell membrane was effectively promoted. Therefore, the nanoparticles coated with positively charged QACs facilitate strong electrostatic interactions with the negatively charged bacterial cell walls, suggesting that bacteria were effectively disrupted at a lower MIC[29].

Considering the various formulations reported in prior research, QAC immobilization onto surfaces or within polymeric matrices presents an effective method for maintaining prolonged antimicrobial efficacy while preventing bacterial migration into food systems[30]. Therefore, the immobilized processes, including covalent bonding, surface functionalization of nanoparticles, and integration into polymer matrices indicate that non-leachable retention of QACs is crucial for preserving antimicrobial effectiveness and ensuring durability.

Carbosilane dendritic system

A dendritic system is characterized by a highly branched

Table 1. Characteristics, antimicrobial mechanisms, and formulations of various cationic functionalized materials and nanoparticles

Antimicrobials	Composition	Mechanisms	Formulations	Antibacterial effects	References
Quaternary ammonium compounds (QACs)	Quaternary ammonium ion with alkyl substituents and a negatively charged counterion	• Adherence to bacterial cell walls attributed to cationic structure • Interaction with alkyl chains, leading to the disruption of bacterial membrane	Spray coating on stainless steel	>5-log reduction against *L. innocua*	23)
			Composite film based on agar/ Polyacrylamide hydrogel solution	85% bacterial reduction	24)
			Cationic functionalized zinc oxide nanoparticles	More than 90% bacterial reduction	27)
			AgCl-based nanoparticles and nanocolloids	4-log reduction against *L. monocytogenes*	103)
Carbosilane dendritic system	Dendritic polymers (dendrons and dendrimers)	• Increase in cationic charge density with augmented generation of dendritic components • Superior interaction with bacterial membranes through relatively higher cationic functional groups	Iron oxide magnetic nanoparticles	>1-log reduction against *E. coli*	15)
			Thiol-modified hyaluronic acid hydrogel	Significantly larger inhibition zone	104)
			Dendrimer-crosslinked hydrogel	4-log reduction against *S. aureus*	105)
			Imidazolium-terminated carbosilane dendrimers	>5-log reduction against *E. coli*	106)
Polyethyleneimine (PEI)	Primary, secondary, and tertiary amine groups with a linear or branched structure	• Electrostatic interactions with the Gram-negative bacterial outer membrane and penetration by facilitating adhesion to bacterial cells	Polylactide nanoparticles loaded with carvacrol	>3-log reduction against *S. aureus*	45)
			Microbicidal coating on a hydroxylated glass slide	100% reduction of *E. coli* and *B. subtilis*	107)
			Corn starch-chitosan/PEI film	2.5-log reduction against *E. coli*	108)
			Polysaccharide-based film derived from distillers dried grains with solubles	2.3-log reduction against *S. aureus*	109)
Cationic liposome	Cationic lipids with helper lipids and counterions	• Disrupting with negatively charged phosphate groups in the bacterial outer membranes through electrostatic interactions between liposomes and bacteria	Polyethylene oxide and soybean lecithin through the electrospinning process	6-log reduction against *L. monocytogenes*	50)
			Mixture of DPPC, stearylamine, and cholesterol	3-log reduction against *S. aureus*	110)
			Cationic liposome-encapsulated polyhexamethylene biguanide	More than 99% bacterial reduction	111)
			DOTAP-based cationic nanoliposomes encapsulating *L. sakei* bacteriocins	4-log reduction against *L. monocytogenes*	112)

and hierarchical molecular architecture, which serves as an effective approach for enhancing the cationic surface modification of nanoparticles. This system consists of dendritic polymers (dendrons and dendrimers) and provides a relatively large surface and multifunctionality[31]. Dendrimers, with their highly branched and symmetric architecture, allow precise control over surface functionality and present a high density of cationic groups, which enhance electrostatic interactions and improve capture efficiency[32]. In contrast, dendrons, with their directional and asymmetric architecture, may result in lower overall surface charge density and more spatially restricted interactions, potentially influencing selective capture depending on the bacterial membrane structure[32].

The antimicrobial properties of dendrons and dendrimers are dependent on the generation of dendronized components[33]. This generation indicates the hierarchical expansion from the core, with an increasing number of repetitive branching patterns and functional groups with each successive level[34]. As a result, the cationic dendritic system exhibits an increase in positively charged functional groups as the generation advances[35].

Especially, magnetic nanoparticles (MNPs), incorporating the cationic dendritic system, have been widely studied using their sensitivity to external magnetic fields[36]. In this regard, Quintana-Sánchez et al.[15] investigated the bacterial capture ability of iron oxide MNP, which applied cationic carbosilane (CBS) dendrons and dendrimers on the Fe_3O_4 surface. It indicated that MNPs functionalized with dendrons significantly improved bacterial capture efficacy for both Gram-positive and Gram-negative strains. Conversely, the dendrimer-based MNPs displayed selective activity, depending on the structural differences in bacterial cell walls.

This distinction is due to the different outer membrane architectures of Gram-positive and Gram-negative bacteria. The lipopolysaccharide (LPS) of Gram-negative bacteria possessed a higher negative charge than the teichoic acid-embedded peptidoglycan of Gram-positive bacteria, leading to different capture efficiency[37]. As the size of dendritic structures grafted onto the MNP surface became smaller, the electrostatic interactions with bacterial cell walls were more restricted[38]. Overall, MNPs with a lower surface dendron density required effective bacterial contact at higher concentrations. Whereas, MNPs functionalized with relatively higher-generation dendrons exhibited a greater positive charge density, suggesting superior bacterial capture efficiency through strong bacterial attachment[39].

Additionally, the ability to control molecular size, charge, and branching density in a generation-dependent manner enhances their targeted delivery to specific sites[34]. Nonetheless, higher-generation dendritic polymers require more complex synthetic methodologies, and elevated charge density results in structural instability owing to intramolecular electrostatic repulsion[35]. Consequently, the implementation of dendritic systems within the food industry necessitates regulation of the incorporation of functional groups in accordance with the generation of the dendrimer. Furthermore, it is imperative to assess the optimal cationic charge density needed to effectively inhibit bacterial proliferation, ensuring the durability, stability, and antimicrobial effectiveness of these systems.

Polyethyleneimine (PEI)

PEI is a synthetic polymer characterized by a sequence of repeating amine groups and is categorized into linear or branched forms based on its structural configuration[40]. Linear PEI is composed of secondary amines, while branched PEI encompasses a combination of primary, secondary, and tertiary amine groups[40]. These structural differences have an impact on their antimicrobial properties[41]. Linear PEI, with its flexible backbone and uniform charge distribution, has shown stronger activity against certain Gram-positive bacteria, whereas branched PEI, with its higher charge density and multivalent architecture, is more effective against Gram-negative strains[42]. Due to its cationic functional groups, water solubility, and excellent chemical tunability, PEI is extensively utilized in various applications[43]. Furthermore, alkylated PEI, which enhances both cationic and hydrophobic properties, increases bacterial membrane permeability and strengthens its antimicrobial efficacy[44].

To confirm that the cationic properties of PEI enhance bacterial interactions, Niza et al.[45]. developed a positively charged nanoparticle, which coated polylactide (PLA) nanoparticles with PEI. Moreover, this study assessed the effect of PEI coating on bacterial membrane permeability. CAR-(PEI)NP, PEI-coated PLA nanoparticles loaded with carvacrol (CAR), demonstrated lower MICs against both Gram-negative (*E. coli* and *S. enterica*) and Gram-positive (*L. monocytogenes* and *S. aureus*) bacteria, indicating its sustained high antimicrobial activity. While negatively charged PLA-NPs exhibit aggregation and repulsion that lead to diminished CAR activity, positively charged PLA-NPs revealed that the antimicrobial efficacy was improved due to facilitated bacterial cell penetration and uptake, enabled by uniform distribution.

PEI has the potential to demonstrate synergistic effects when utilized in conjunction with antimicrobial agents like CAR, which are frequently employed in the food industry[45,46]. Specifically, these robust electrostatic interactions allow for prompt bacterial adhesion within food packaging films, even in

the absence of active compound release[47]. Therefore, it is recommended that a polymer-based formulation incorporating both PEI and antimicrobial agents could synergistically improve bacterial surface targeting. This approach is expected to promote rapid antimicrobial activity and diminish the likelihood of bacterial persistence.

Cationic liposome

Liposomes, enclosed in a phospholipid bilayer, are self-assembled structures that serve as carriers for loading active compounds, and thus they are essential for toxicity reduction, stability improvement, and controlled release[48]. The capacity to encapsulate both hydrophilic and lipophilic drugs is also considered essential for an efficient antimicrobial delivery system. In particular, cationic liposomes enhance antimicrobial delivery through their superior structural stability and targeted interaction with bacteria[49].

Based on this electrostatic attraction, Li et al.[50]. formulated a cationic liposome loaded with basil essential oil (BEO) as the primary antimicrobial agent. The BEO-loaded cationic liposome (BCL) was subsequently incorporated into nanofibers composed of polyethylene oxide (PEO) and soybean lecithin (SL) through the electrospinning process. This system was designed for the controlled release of BEO, which is responsive to the bacterial phospholipase secreted by *L. monocytogenes*. As a result, the antimicrobial activity of BCL-loaded nanofibers (BCL-NF) against *L. monocytogenes* showed inhibition zones of 15.5 mm and 23.2 mm for PEO and PEO/SL composites, respectively. This suggests that the secretion of phospholipases by *L. monocytogenes* initiated the degradation, resulting in a marked increase in BEO.

Cationic liposomes, characterized by amphiphilic bilayer architecture, have shown a remarkable ability to effectively encapsulate a diverse range of antimicrobial agents[51]. The combination of electrostatic interactions and encapsulation renders them particularly advantageous as multifunctional delivery systems. They exhibit a strong affinity for bacterial membranes and facilitate enhanced penetration, which in turn allows for the stable delivery of active compounds. Moreover, the lipid constituents or the encapsulated antimicrobials within the liposomes are designed for stimuli-responsive release mechanisms, which are activated by factors such as pH, enzymes, or temperature. This suggests that they are promising agents in active packaging systems with controlled antimicrobial release in response to various environmental stimuli. While various cationic functionalized materials demonstrate promising antimicrobial efficacy, their safety and regulatory considerations are critical for their practical application in food systems. These aspects are further discussed in Section 4.

Antimicrobial Peptides (AMPs)

AMPs are integral components of the innate defense systems found in all living organisms and typically consist of several amino acids[52]. These peptides, compounds that exhibit inhibitory activity against microorganisms, are increasingly recognized as a promising alternative to conventional antibiotics[53]. The inherent structural characteristics of peptide-based antimicrobials are determined by amino acid sequences, frequently possessing lysine (Lys), arginine (Arg), tryptophan (Trp), and hydrophobic amino

Table 2. Comparative characteristics and functional application of AMPs and chitosan

Category	Antimicrobial peptides (AMPs)	Chitosan and derivatives
Source	• Peptides produced naturally by the innate immune systems of organisms	• Derived from chitin by alkaline deacetylation
Chemical structure	• Short peptides with amphipathic and cationic features	• Linear polysaccharide of N-acetyl-D-glucosamine and D-glucosamine
Functional groups	• Cationic and hydrophobic amino acids, including Lys, Arg, and Trp	• Amino and hydroxyl groups, modifiable with various polar or charged substituents (e.g., quaternary ammonium, carboxyl, sulfonic, phosphate).
Antimicrobial mechanism	• Membrane disruption via electrostatic and hydrophobic interaction	• Membrane destabilization via cation displacement and pore formation
Delivery strategies	• Immobilized on polymeric films • Encapsulated in nanoliposomes for sustained release	• Incorporated into films or immobilized on polymers • Used in nanocomposites with metal/metal oxides for enhanced stability and release
Limitations	• Reduced stability in food matrices • Decreased effectiveness by hydrophobic binding	• Poor solubility at neutral pH • Unmodified metal oxides prone to aggregation
Enhancement strategies	• Spatial control via immobilization • Nanocarrier	• Modified functional group • Nanoparticle integration

acids[54]. Based on these AMP characteristics, they present a cationic charge and effectively target foodborne pathogens.

AMPs are amphipathic molecules distinguished by their significant proportions of cationic and hydrophobic amino acids, contributing to their antimicrobial activities[55]. According to these compositions, the antimicrobial mechanism of AMPs is attributed to electrostatic interactions between negatively charged phospholipids present in bacterial membranes and the positively charged AMPs[56]. The general characteristics of AMPs are summarized in Table 2.

Following initial membrane interaction, AMPs exert bacterial cell lysis through additional membrane-disruptive mechanisms driven by hydrophobic interactions[57]. These AMP mechanisms are generally categorized into three models: the barrel-stave model, the toroidal-pore model, and the carpet-like model[58]. Consequently, a comprehensive analysis of each antimicrobial mechanism was conducted (Table 3). In the barrel-stave model, AMPs initially attach to the bacterial membrane in their monomeric form and subsequently oligomerize to create a cylindrical pore structure. During this process, the AMPs insert perpendicularly into the lipid bilayer, where their hydrophobic regions lead to the formation of transmembrane channels through interaction with the membrane core. These channels ultimately induce membrane collapse, allowing leakage of ions and intracellular contents[59]. Conversely, the AMPs in the toroidal-pore model align with lipid molecules rather than inserting vertically, resulting in peptide-lipid complex formation. The complexes bend the membrane by distorting the bacterial phospholipid, thereby promoting pore formation and insertion into the bilayer[60]. Additionally, in the carpet-like model, the hydrophobic regions of AMPs align with the membrane surface and disrupt the bilayer by forming micelle-like structures with phospholipids. As the bacterial membrane is gradually disintegrated, intracellular content leakage occurs via cell membrane lysis[61].

AMPs have been utilized in the food industry through various strategies as components of intelligent packaging systems[62]. However, the direct integration of AMPs into food matrices can lead to interactions with certain food components, potentially compromising their structural stability and consequently diminishing their antimicrobial effectiveness[63]. To mitigate this limitation, various immobilization techniques have been developed to facilitate effective AMP delivery, thereby overcoming the constraints of AMP-based coating and dipping methods. This suggests that AMP immobilization contributes to reducing peptide loss and promotes a sustained release profile with prolonged antimicrobial efficacy. Layer-by-layer (LBL) coating systems integrate AMPs alongside other compounds to form a “sandwich-like” structure[64]. This system maintains the initial interaction with food components and enables the gradual release of the AMPs, ensuring antimicrobial efficacy over an extended period[63,65].

In light of these findings, Placido et al.[66] developed an active packaging system utilizing the LBL deposition technique, incorporating a cationic peptide and cashew gum (CG). The incorporation of the cationic peptide augmented electrostatic interactions with *E. coli*, resulting in significant antimicrobial efficacy with a MIC ranging from 15.62 to 31.25 μg/mL. Importantly, films comprising a greater number of bilayers exhibited markedly enhanced inhibition zones.

In another study, Hernandez-Montelongo et al.[67] successfully immobilized the cationic peptides (Tet-124 and its brominated derivative) onto the surface of a polyethyleneimine film via electrostatic attraction. To improve antimicrobial efficacy, a linker was utilized to regulate the spatial orientation of Tet-124, ensuring that its active site was positioned away from the surface. The AMP-functionalized films achieved extended antimicrobial effects with inhibition rates up to 77%.

Moreover, the encapsulation of AMPs within polymer-coated nanoliposomes has increased to improve their stability and antimicrobial effectiveness. Cantor et al.[68] developed a modified Alyteserin-1c, which consists of 23 amino acids with cationic AMP characterized by a native net charge of +2. This modification involved structural alterations aimed at increasing both amphipathic and positively charged properties, while simultaneously decreasing hydrophobicity. Utilizing the ethanol injection method, the surface of nanoliposomes was modified with the polymer Eudragit E-100 and subsequently assessed the antimicrobial efficacy against *L. monocytogenes* and *E. coli*. The results indicated a superior enhancement in antimicrobial activity with approximately 2000-fold and 12.5-fold increase, respectively. This suggests that the Eudragit coating improves liposome stability and enables the controlled release of peptides at the bacterial interface[65].

Consequently, AMPs, determined by a significant presence of cationic amino acids, exhibit targeted antimicrobial delivery via membrane interaction. Furthermore, the spatial arrangement and positioning of AMPs within polymeric matrices is based on their ability, allowing for structural design that regulates the accessibility of active sites. These precision-targeted antimicrobial approaches suggest that AMP-based films and coatings with optimized orientation enhance contact and antimicrobial activity, particularly on food surfaces exhibiting curved or porous surfaces. Although AMPs have demonstrated significant potential for integration into food packaging, their biocompatibility and safety profiles require careful consideration. A more detailed

discussion of safety issues and advances in their food applications is provided in Section 4.

Chitosan and Derivatives

Chitosan is an ionic polymer obtained from chitin via alkaline deacetylation with sodium hydroxide, which is a copolymer consisting of *N*-acetyl-D-glucosamine and D-glucosamine units[69]. The extent of deacetylation, acetylation, and molecular weight vary depending on the ratio of the two monomeric units, subsequently affecting the antimicrobial properties of chitosan[70].

The antimicrobial efficacy of chitosan is influenced by the composition of the bacterial cell[71]. This attribute is especially effective in promoting bacterial inactivation as an outer membrane is present (Fig. 1). In Gram-negative bacteria, the outer membrane is composed of lipopolysaccharides (LPS), phospholipids, and lipoproteins with divalent cations serving to stabilize the negatively charged LPS. Chitosan displaces these divalent cations, consequently diminishing the interactions among the LPS molecules. LPS with weakened interactions promotes pore formation, permitting the diffusion of hydrophobic molecules and enhancing membrane permeability[72]. In contrast, Gram-positive bacteria lack an outer membrane, which enables the rapid binding of chitosan to the bacterial wall and results in relatively more potent antimicrobial effects[73].

However, considering that the antimicrobial properties of chitosan are influenced by its solubility, recent research has increasingly focused on antimicrobial effectiveness through chemical functionalization or combination with other antimicrobial agents[74]. Specifically, the chemical modification of functional groups attached to specific carbon positions within the chitosan structure, which is namely the amino group at C-2, the secondary hydroxyl group at C-3, and the primary hydroxyl group at C-6[75]. The principal structural and functional characteristics of chitosan are summarized in Table 2.

Its chemical modifications involve the incorporation of diverse functional groups, such as quaternary ammonium, carboxyl, sulfonic, and phosphate groups[76]. Notably, quaternization is identified as a particularly effective method for improving the solubility of chitosan. It is defined as a chemical process that modifies the primary amino and hydroxyl groups with a chitosan backbone, resulting in the formation of quaternary ammonium groups internally or on the surface of the polymer structure[77]. QAC derivatives,

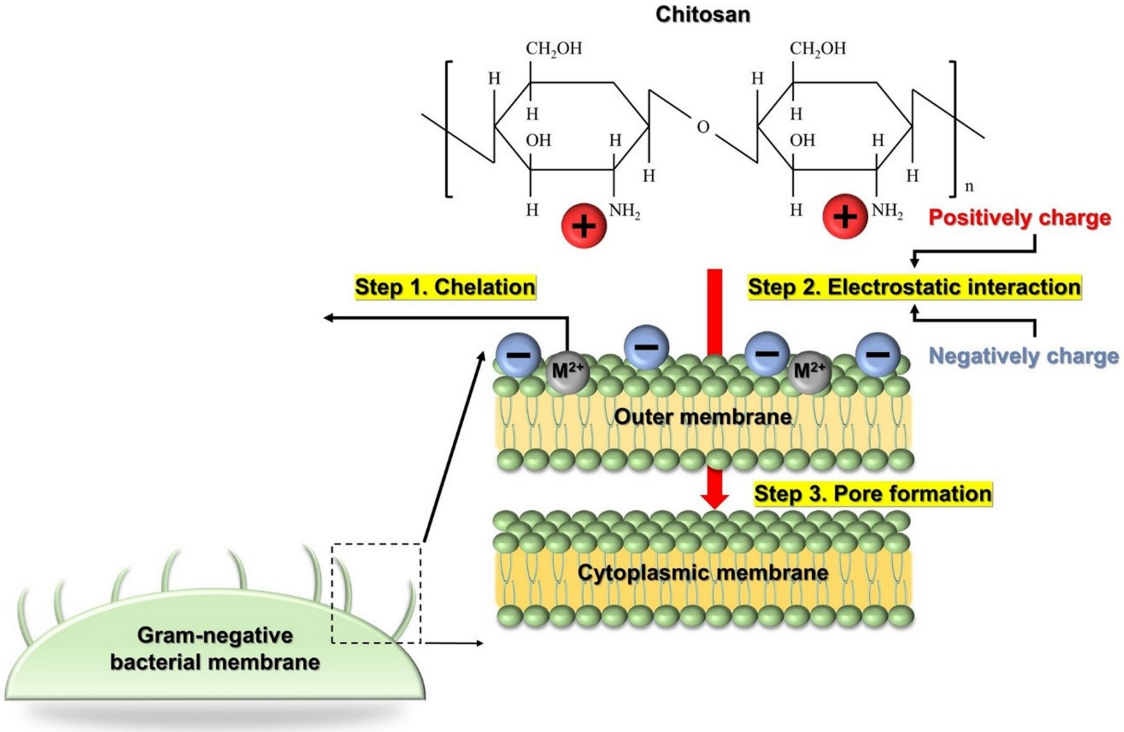

Fig. 1. Antibacterial mechanism of chitosan on Gram-negative bacteria.
Chitosan, a biopolymer with a positive charge, affects the outer membrane of Gram-negative bacteria through a three-step mechanism: (Step 1) the chelation of divalent cations such as magnesium (Mg^{2+}) and calcium (Ca^{2+}), which serve to stabilize the lipopolysaccharide (LPS) layer; (Step 2) the electrostatic interaction with the negatively charged LPS; and (Step 3) the pore formation resulting from the destabilization of the LPS, which ultimately leads to an increase in membrane permeability.

Table 3. Comparison of antimicrobial mechanisms of AMPs

Types of mechanisms	Mode of membrane permeabilization	Role of structural components in pore formation	Stability and specificity of interactions
Barrel-stave model	• Establishment of stable transmembrane pores exclusively comprised of AMPs	• Penetration of the lipid bilayer in a perpendicular orientation	• Relatively stable and sustainable
Toroidal-pore model	• Development of adaptable membrane-spanning pores that incorporate both AMPs and lipid constituents	• Engagement with membrane lipids to facilitate the formation of toroidal, curved pore structures	• Dynamic and transient
Carpet-like model	• Complete disruption of membrane that occurs without the formation of distinct pores	• Adhesion to membrane surface in uniform coverage of the surface	• Non-specific and widespread disruption

including trimethyl chitosan (TMC) and hydroxypropyl trimethyl ammonium chitosan chloride (HTCC), are synthesized to enhance the solubility of chitosan and to provide stable cationic charges. These modifications significantly improve antimicrobial efficacy even in neutral pH environments, by promoting more robust electrostatic interactions with bacterial membranes[78,79].

To implement QAC-based antimicrobial films in food packaging, Min et al.[80] formulated a coating consisting of quaternary ammonium salt-modified chitosan (HACC) and poly (vinyl alcohol) (PVA) and its effectiveness in inhibiting the bacterial growth. Identification of their functional groups revealed that they were associated with the C–H stretching of methyl groups ($–CH_3$) and the N–H stretching of amino groups ($–NH_2$) present in HACC within the HACC/PVA composite coating. Furthermore, remarkable hydrogen bonding interactions between HACC and PVA were detected, suggesting the establishment of a stable network structure. Based on these functional groups, the antimicrobial activity of the HACC/PVA coating, which was applied to strawberry surfaces, demonstrated enhancement with an increase in HACC content, exhibiting significant inhibition against all three tested microorganisms. Upon reaching a HACC mass ratio of 3%, the inhibition rate surpassed 99%, confirming the sustained antimicrobial properties within the composite film.

In other research based on HACC, Zhou et al.[81] implemented surface modifications through the application of hyperthermal hydrogen-induced cross-linking (HHIC) to enhance the HTCC immobilization on inert polyethylene (PE) surfaces. With the application of this method in food packaging, this research revealed that an antimicrobial film was considered highly effective as the antimicrobial activity value R surpasses 2.0, which corresponds to a bacterial reduction of over 99%. The PE cross-linked HTCC film (PE-c-HTCC) demonstrated an R-value of 6.2 against both *S. aureus* and *E. coli*. It is noteworthy that bacteria adhering to the PE-c-HTCC surface exhibited membrane disruption and intracellular content leakage[81]. This observation suggests that the immobilized quaternary ammonium polymer within the film effectively performed its function as a cationic surfactant.

Meanwhile, composite film is formulated through the incorporation of chitosan with metals and metal oxides to improve their antimicrobial properties. Various nanoparticles, including titanium dioxide (TiO_2), zinc oxide (ZnO), and silver (Ag), are integrated into chitosan matrices to create nanocomposites with improved functionality[82]. These chitosan-based nanocomposites mitigate the limitations associated with the metal oxides used independently, including diminished activity and aggregation-induced decline[83].

For instance, Mizwari et al.[84] developed an innovative porous chitosan-metal oxide nanocomposite by integrating MgO and NiO into a chitosan matrix. This composite demonstrated improved interactions with sulfhydryl and phosphorus-containing compounds within bacterial cell membranes, attributed to the protonated amino groups of chitosan and the metal ions derived from the nanoparticles. These interactions were observed to disrupt DNA replication and damage the bacterial structure. In a separate investigation, Al-Naamani et al.[85] applied a coating of chitosan and ZnO nanoparticles to PE films, which were treated with oxygen plasma. This process improved the stability and antimicrobial efficacy of the metal oxide. The chitosan-coated PE surface exhibited high antimicrobial activity attributed to the presence of positively charged amine groups. Moreover, the chitosan-ZnO nanocomposite indicated complete bacterial inhibition, suggesting a synergistic interaction between the two antimicrobial agents.

Based on its antimicrobial properties, chitosan has been advanced into food packaging systems through the incorporation and immobilization within polymeric films. In particular, through the integration of metal-based nanoparticles into chitosan, this structural disruption

promotes the rapid penetration of metal ions into the bacterial cells[86]. Moreover, as a natural biopolymer recognized as Generally Recognized as Safe (GRAS), it is effectively combined with other cationic antimicrobial agents to improve its applicability and to facilitate efficient bacterial eradication[87]. Chitosan-based composite antimicrobial systems exhibit improved bactericidal efficacy due to promoting bacterial adhesion and the synergistic effects of the antimicrobial agents incorporated within the chitosan matrix.

Advances and Safety Issues in Food Applications

Cationic functionalized agents, including QACs, carbosilane dendritic polymers, PEI, and cationic liposomes, are promising antimicrobial agents through interaction with bacterial membranes[13]. These insights have facilitated the development of various formulations incorporating positively charged agents, with a multitude of research underscoring their exceptional antimicrobial effectiveness[88]. Despite these advantages, it is imperative to ensure the safe application of cationic agents in environments related to the food industry. Excessive density of cationic charge leads to cytotoxicity on bacterial cells as well as mammalian cells. For instance, high-density dendrimers and PEI with high molecular weight (25 kDa or higher), characterized by a substantial quantity of amine groups, have the potential to penetrate and compromise mammalian cell membranes due to non-specific electrostatic interactions[89,90]. Similarly, it has been observed that QACs and cationic liposomes cause cytotoxicity as the ratio of cationic charge in headgroups is increased[91,92].

Various AMPs and chitosan are naturally occurring substances that have been used extensively as antimicrobial agents, in contrast to synthetically derived cationic agents such as QACs[63,73]. In particular, certain AMPs, such as nisin, pediocin, and lysozyme, as well as chitosan, were certified as GRAS by the US FDA, and these substances are currently used in food packaging systems[56,87]. However, depending on the particular peptide type and degree of chitosan's chemical alteration, the increased cytotoxicity has raised safety concerns[93,94]. As a result, the introduction of functionally improved cationic agents into food systems requires rigorous regulatory control to assure their safe use.

In order to mitigate cytotoxicity, various surface modification strategies have been devised to partially neutralize the cationic charges, facilitating ability to specifically target foodborne pathogens[95]. Therefore, methods such as PEGylation[96] and acetylation[47] have been utilized to improve biocompatibility and reduce adverse effects on human cells. Notably, cationic chitosan has been crosslinked with polyethylene glycol (PEG) to preserve its antibacterial activity while increasing mechanical properties and reducing cytotoxicity[97,98]. Davidovich-Pinhas et al.[99] demonstrated that PEGylation of chitosan preserved its inherent antibacterial effects (>7-log reduction) while improving mechanical performance by a decrease in Young's modulus. Furthermore, Casettari et al.[100] found that PEGylation decreased cytotoxicity through charge-shielding effects, underlining its potential as a promising technique for the development of biocompatible materials. In addition, despite the high antimicrobial activity of certain peptides, their significant cytotoxicity may be exhibited[101]. However, Liu et al.[102] indicated that peptide HG2, which incorporates D-amino acid substitution and terminal stabilization, maintained over 80% cell viability, indicating its considerable potential for application in food systems. These techniques highlight the significance of optimizing cationic charge density to achieve antimicrobial efficacy and biocompatibility, contributing to the safety and applicability of food packaging systems.

Conclusion

In conclusion, cationic polymers are promising antimicrobial agents, offering rapid bactericidal activity by disrupting bacterial membranes through electrostatic interactions. Representatives such as quaternary ammonium compounds, polyethyleneimine, antimicrobial peptides, and chitosan effectively target foodborne pathogens by binding to negatively charged bacterial surfaces and compromising membrane integrity. Advances in material engineering, including surface immobilization, charge density control, and stimuli-responsive release systems, have further improved their efficacy. Incorporating these agents into biopolymeric matrices enhances biocompatibility, regulatory compliance, and sustained antimicrobial performance in food packaging. However, successful industrial application requires thorough toxicological evaluation and clear regulatory frameworks to address cytotoxicity concerns. Moving forward, the development of multifunctional, sustainable packaging that balances safety and efficacy is expected to accelerate the adoption of cationic antimicrobial technologies, advancing food safety and public health.

Acknowledgement

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (Ministry of Science and ICT) (RS-2025-00518970).

국문요약

본 총설에서는 음전하를 띠는 박테리아 세포막과의 상호작용을 통해 구조와 기능을 교란시키는 양전하성 항균제의 종류, 작용 기전, 그리고 최근 연구 동향을 종합적으로 분석하였다. 식품 안전성에 대한 우려가 증가함에 따라 기존 항생제를 대체할 수 있는 새로운 항균 전략에 대한 수요가 높아지고 있다. 특히, 4차 암모늄, 폴리에틸렌이민, 항균 펩타이드, 키토산 등의 양전하성 항균제는 박테리아 표면에 신속하게 부착하고 세포막을 손상시켜 초기 단계에서의 증식을 효과적으로 억제하는 강력한 항균 활성을 보인다. 이러한 물질들은 다양한 제형화 전략을 통해 설계되어 식품 산업에서의 실용적 응용 가능성을 높이는 데 기여한다. 본 총설에서는 이들의 분자 수준에서의 항균 작용 기전을 중심으로 고찰하고, 향후 안전성과 효능 향상을 위한 연구 방향을 제시하였다.

Conflict of interests

The authors declare no potential conflict of interest.

ORCID

Jaeyoung Ma https://orcid.org/0009-0007-9128-0296
Yoonjee Chang https://orcid.org/0000-0003-0275-9830

References

1. Shi, C., Kang, S., Foodborne pathogenic bacteria: prevalence and control–volume I. *Foods*, **13**, 1531 (2024).
2. Awad, D.A., Masoud, H.A., Hamad, A., Climate changes and food-borne pathogens: the impact on human health and mitigation strategy. *Clim. Change*, **177**, 92 (2024).
3. Membre, J.M., Guillou, S., Latest developments in food-borne pathogen risk assessment. *Curr. Opin. Food Sci.*, **8**, 120-126 (2016).
4. Abdelshafy, A.M., Neetoo, H., Al-Asmari, F., Antimicrobial activity of hydrogen peroxide for application in food safety and COVID-19 mitigation: an updated review. *J. Food Prot.*, **87**, 100306 (2024).
5. Gow, C.K., Weinhouse, C., Johnson, G.O., Saunders, K.E., Stability of free available chlorine levels in dilute sodium hypochlorite solutions over a 6-week period. *J. Am. Assoc. Lab. Anim. Sci.*, **61**, 181-187 (2022).
6. Capita, R., Alonso-Calleja, C., Antibiotic-resistant bacteria: a challenge for the food industry. *Crit. Rev. Food Sci. Nutr.*, **53**, 11-48 (2013).
7. Grande, R., Puca, V., Muraro, R., Antibiotic resistance and bacterial biofilm. *Expert Opin. Ther. Pat*, **30**, 897-900 (2020).
8. Uneputty, A., Dávila-Lezama, A., Garibo, D., Oknianska, A., Bogdanchikova, N., Hernández-Sánchez, J.F., Susarrey-Arce, A., Strategies applied to modify structured and smooth surfaces: a step closer to reduce bacterial adhesion and biofilm formation. *Colloid Interface Sci. Commun.*, **46**, 100560 (2022).
9. Xie, M., Gao, M., Yun, Y., Malmsten, M., Rotello, V.M., Zboril, R., Akhavan, O., Kraskouski, A., Amalraj, J., Cai, X., Lu, J., Zheng, H., Li, R., Antibacterial nanomaterials: mechanisms, impacts on antimicrobial resistance and design principles. *Angew. Chem. Int. Ed.*, **62**, e202217345 (2023).
10. Wang, Y., Yang, Y., Shi, Y., Song, H., Yu, C., Antibiotic-free antibacterial strategies enabled by nanomaterials: progress and perspectives. *Adv. Mater.*, **32**, 1904106 (2020).
11. Zhou, C., Wang, Y., Structure–activity relationship of cationic surfactants as antimicrobial agents. *Curr. Opin. Colloid Interface Sci.*, **45**, 28-43 (2020).
12. Haktaniyan, M., Bradley, M., Polymers showing intrinsic antimicrobial activity. *Chem. Soc. Rev.*, **51**, 8584-8611 (2022).
13. Carmona-Ribeiro, A.M., de Melo Carrasco, L.D., Cationic antimicrobial polymers and their assemblies. *Int. J. Mol. Sci.*, **14**, 9906-9946 (2013).
14. Chu, X., Yang, F., Tang, H., Recent advance in polymer coatings combating bacterial adhesion and biofilm formation. *Chin. J. Chem.*, **40**, 2988-3000 (2022).
15. Quintana-Sánchez, S., Barrios-Gumiel, A., Sánchez-Nieves, J., Copa-Patiño, J.L., de la Mata, F.J., Gómez, R., Bacteria capture with magnetic nanoparticles modified with cationic carbosilane dendritic systems. *Biomater. Adv.*, **133**, 112622 (2022).
16. Erkoc, P., Ulucan-Karnak, F., Nanotechnology-based antimicrobial and antiviral surface coating strategies. *Prosthesis*, **3**, 25-52 (2021).
17. Helander, I.M., Alakomi, H.L., Latva-Kala, K., Koski, P., Polyethyleneimine is an effective permeabilizer of Gram-negative bacteria. *Microbiology*, **143**, 3193–3199 (1997).
18. Campanh, M.T.N., Mamizuka, E.M., Carmona-Ribeiro, A.M., Interactions between cationic liposomes and bacteria: the physical-chemistry of the bactericidal action. *J. Lipid Res.*, **40**, 1495-1500 (1999).
19. Saverina, E.A., Frolov, N.A., Kamanina, O.A., Arlyapov, V.A., Vereshchagin, A.N., Ananikov, V.P., From antibacterial to antibiofilm targeting: an emerging paradigm shift in the development of quaternary ammonium compounds (QACs). *ACS Infect. Dis.*, **9**, 394-422 (2023).
20. Santoro, O., Izzo, L., Antimicrobial polymer surfaces containing quaternary ammonium centers (QACs): synthesis and mechanism of action. *Int. J. Mol. Sci.*, **25**, 7587 (2024).
21. Bure, F., Quaternary ammonium compounds: simple in structure, complex in application. *Top. Curr. Chem.*, **377**, 14 (2019).
22. Lainioti, G.C., Druvari, D., Designing antibacterial-based quaternary ammonium coatings (surfaces) or films for biomedical applications: recent advances. *Int. J. Mol. Sci.*, **25**, 12264 (2024).

23. Lee, J., Pascall, M.A., Reduction in microbial survival on food contact surfaces by a spray coated polymerized quaternary ammonium compound. *Food Sci. Nutr.*, **8**, 2472-2477 (2020).
24. Rukmanikrishnan, B., Ramalingam, S., Lee, J., Quaternary ammonium silane-reinforced agar/polyacrylamide composites for packaging applications. *Int. J. Biol. Macromol.*, **182**, 1301-1309 (2021).
25. Vaara, M., Agents that increase the permeability of the outer membrane. *Microbiol. Rev.*, **56**, 395-411 (1992).
26. Yao, Y., Ye, Z., Zhang, Y., Wang, Y., Yu, C., Quaternary ammonium compounds and their composites in antimicrobial applications. *Adv. Mater. Interfaces*, **11**, 2300946 (2024).
27. Eskandari, F., Mofidi, H., Asheghi, B., Mohammadi, F., Gholami, A., Bringing resistance modulation to methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *enterococci* (VRE) strains using a quaternary ammonium compound coupled with zinc oxide nanoparticles. *World J. Microbiol. Biotechnol.*, **39**, 193 (2023).
28. Wang, K., Yang, X., Liang, J., Rong, Y., Zhao, W., Ding, J., Liu, Y., Liu, Q., Preparation, characterization, antimicrobial evaluation, and grape preservation applications of polyvinyl alcohol/gelatin composite films containing zinc oxide@ quaternized chitosan nanoparticles. *Int. J. Biol. Macromol.*, **277**, 134527 (2024).
29. Joshi, A.S., Singh, P, Mijakovic, I., Interactions of gold and silver nanoparticles with bacterial biofilms: molecular interactions behind inhibition and resistance. *Int. J. Mol. Sci.*, **21**, 7658 (2020).
30. Khalil, R.K.S., Selective removal and inactivation of bacteria by nanoparticle composites prepared by surface modification of montmorillonite with quaternary ammonium compounds. *World J. Microbiol. Biotechnol.*, **29**, 1839-1850 (2013).
31. Fuentes-Paniagua, E., Sánchez-Nieves, J., Hernández-Ros, J.M., Fernández-Ezequiel, A., Soliveri, J., Copa-Patiño, J.L., Gómez, R., de la Mata, F.J., Structure–activity relationship study of cationic carbosilane dendritic systems as antibacterial agents. *RSC Adv.*, **6**, 7022-7033 (2016).
32. Sanchez-Milla, M., Gomez, R., Perez-Serrano, J., Sanchez-Nieves, J., de la Mata, F.J., Functionalization of silica with amine and ammonium alkyl chains, dendrons and dendrimers: synthesis and antibacterial properties. *Mater. Sci. Eng. C-Mater. Biol. Appl*., **109**, 110526 (2020).
33. Chen, C.Z., Cooper, S.L., Recent advances in antimicrobial dendrimers. *Adv. Mater.*, **12**, 843-846 (2000).
34. Vereroudakis, E., Bang, K.T., Karouzou, M., Ananiadou, A., Noh, J., Choi, T.L., Loppinet, B., Floudas, G., Vlassopoulos, D., Multi-scale structure and dynamics of dendronized polymers with varying generations. *Macromolecules*, **54**, 235-248 (2020).
35. de la Mata, F.J., Gómez, R., Cano, J., Sánchez-Nieves, J., Ortega, P., Gallego, S.G., Carbosilane dendritic nanostructures, highly versatile platforms for pharmaceutical applications. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.*, **15**, e1871 (2023).
36. Chandra, S., Mehta, S., Nigam, S., Bahadur, D., Dendritic magnetite nanocarriers for drug delivery applications. *New J. Chem.*, **34**, 648-655 (2010).
37. Tavares, T.D., Antunes, J.C., Padrão, J., Ribeiro, A.I., Zille, A., Amorim, M.T.P., Ferreira, F., Felgueiras, H.P., Activity of specialized biomolecules against Gram-positive and Gram-negative bacteria. *Antibiotics*, **9**, 314 (2020).
38. Li, L.L., An, H.W., Peng, B., Zheng, R., Wang, H., Self-assembled nanomaterials: design principles, the nanostructural effect, and their functional mechanisms as antimicrobial or detection agents. *Mater. Horizons*, **6**, 1794-1811 (2019).
39. Habib, S., Talhami, M., Hassanein, A., Mahdi, E., Al-Ejji, M., Hassan, M.K., Altaee, A., Das, P., Hawari, A.H., Advances in functionalization and conjugation mechanisms of dendrimers with iron oxide magnetic nanoparticles. *Nanoscale*, **16**, 13331-13372 (2024).
40. Jäger, M., Schubert, S., Ochrimenko, S., Fischer, D., chubert, U.S., Branched and linear poly (ethylene imine)-based conjugates: synthetic modification, characterization, and application. *Chem. Soc. Rev.*, **41**, 4755-4767 (2012).
41. Fox, S.J., Fazil, M.H.U.T., Dhand, C., Venkatesh, M., Goh, E.T.L., Harini, S., Eugene, C., Lim, R.R., Ramakrishna, S., Chaurasia, S.S., Beuerman, R.W., Verma, C.S., Verma, N.K., Loh, X.J., Lakshminarayanan, R., Insight into membrane selectivity of linear and branched polyethylenimines and their potential as biocides for advanced wound dressings. *Acta Biomater.*, **37**, 155-164 (2016).
42. Gibney, K.A., Sovadinova, I., Lopez, A.I., Urban, M., Ridgway, Z., Caputo, G.A., Kuroda, K., Poly (ethylene imine)s as antimicrobial agents with selective activity. *Macromol. Biosci.*, **12**, 1279-1289 (2012).
43. Chen, H., Deng, X., Ding, G., Qiao, Y., The synthesis, adsorption mechanism and application of polyethyleneimine functionalized magnetic nanoparticles for the analysis of synthetic colorants in candies and beverages. *Food Chem.*, **293**, 340-347 (2019).
44. Yudovin-Farber, I., Golenser, J., Beyth, N., Weiss, E.I., Domb A.J., Quaternary ammonium polyethyleneimine: antibacterial activity. *J. Nanomater.*, **2010**, 826343 (2010).
45. Niza, E., Božik, M., Bravo, I., Clemente-Casares, P., Lara-Sanchez, A., Juan, A., Klouček, P., Alonso-Moreno, C., PEI-coated PLA nanoparticles to enhance the antimicrobial activity of carvacrol. *Food Chem.*, **328**, 127131 (2020).
46. Briones, A.V., Sato, T., Bigol, U.G., Antibacterial activity of polyethylenimine/carrageenan multilayer against pathogenic bacteria. *Adv. Chem. Eng. Sci.*, **4**, 233-241 (2014).
47. Zhao, C., Zhou, B., Polyethyleneimine-based drug delivery systems for cancer theranostics. *J. Func. Biomater.*, **14**, 12 (2022).
48. Pinilla, C.M.B., Lopes, N.A., Brandelli, A., Lipid-based nanostructures for the delivery of natural antimicrobials. *Molecules*, **26**, 3587 (2021).
49. Domínguez-Arca, V., Sabín, J., García-Río, L., Bastos, M., Taboada, P., Barbosa, S., Prieto, G., On the structure and sta-

bility of novel cationic DPPC liposomes doped with gemini surfactants. *J. Mol. Liq.*, **366**, 120230 (2022).
50. Li, C., Bai, M., Chen, X., Hu, W., Cui, H., Lin, L., Controlled release and antibacterial activity of nanofibers loaded with basil essential oil-encapsulated cationic liposomes against *Listeria monocytogenes*. *Food Biosci.*, **46**, 101578 (2022).
51. Wang, D.Y., Van der Mei, H.C., Ren, Y., Busscher, H.J., Shi, L., Lipid-based antimicrobial delivery-systems for the treatment of bacterial infections. *Front. Chem.*, **7**, 872 (2020).
52. Hancock, R.E., Sahl, H.G., Antimicrobial and host-defense peptides as new anti-infective therapeutic strategies. *Nat. Biotechnol.*, **24**, 1551-1557 (2006).
53. Sang, Y., Blecha, F., Antimicrobial peptides and bacteriocins: alternatives to traditional antibiotics. *Anim. Health Res. Rev.*, **9**, 227-235 (2008).
54. Leon Madrazo, A., Segura Campos, M.R., Review of antimicrobial peptides as promoters of food safety: limitations and possibilities within the food industry. *J. Food Saf.*, **40**, e12854 (2020).
55. Keymanesh, K., Soltani, S., Sardari, S., Application of antimicrobial peptides in agriculture and food industry. *World J. Microbiol. Biotechnol.*, **25**, 933-944 (2009).
56. Erdem Büyükkiraz, M., Kesmen, Z., Antimicrobial peptides (AMPs): a promising class of antimicrobial compounds. *J. Appl. Microbiol.*, **132**, 1573-1596 (2022).
57. Savitskaya, A., Masso-Silva, J., Haddaoui, I., Enany, S., Exploring the arsenal of antimicrobial peptides: mechanisms, diversity, and applications. *Biochimie*, **214**, 216-227 (2023).
58. Luo, Y., Song, Y., Mechanism of antimicrobial peptides: antimicrobial, anti-inflammatory and antibiofilm activities. *Int. J. Mol. Sci.*, **22**, 11401 (2021).
59. Lei, J., Sun, L., Huang, S., Zhu, C., Li, P., He, J., Mackey, V., Coy, D.H., He, Q., The antimicrobial peptides and their potential clinical applications. *Am. J. Transl. Res.*, **11**, 3919-3931 (2019).
60. Sengupta, D., Leontiadou, H., Mark, A.E., Marrink, S.J., Toroidal pores formed by antimicrobial peptides show significant disorder. *Biochim. Biophys. Acta-Biomembr.*, **1778**, 2308-2317 (2008).
61. Baltutis, V., O'Leary, P.D., Martin, L.L., Self-assembly of linear, natural antimicrobial peptides: an evolutionary perspective. *ChemPlusChem*, **87**, e202200240 (2022).
62. Santos, J.C.P., Sousa, R.C.S., Otoni, C.G., Moraes, A.R.F., Souza, V.G.L., Medeiros, E.A.A., Espitia, P.J.P., Pires, A.C.S., Coimbra, J.S.R., Soares, N.F.F., Nisin and other antimicrobial peptides: production, mechanisms of action, and application in active food packaging. *Innov. Food Sci. Emerg. Technol.*, **48**, 179-194 (2018).
63. Singh, B.P., Rohit, Manju, K.M., Sharma, R., Bhushan, B., Ghosh, S., Goel, G., Nano-conjugated food-derived antimicrobial peptides as natural biopreservatives: a review of technology and applications. *Antibiotics*, **12**, 244 (2023).
64. Xu, K., Zhao, X., Tan, Y., Wu, J., Cai, Y., Zhou, J., Wang, X., A systematical review on antimicrobial peptides and their food applications. *Biomater. Adv.*, **155**, 213684 (2023).
65. Yang, Z., He, S., Wu, H., Yin, T., Wang, L., Shan, A., Nanostructured antimicrobial peptides: crucial steps of overcoming the bottleneck for clinics. *Front. Microbiol.*, **12**, 710199 (2021).
66. Plácido, A., Bragança, I., Marani, M., de Araujo, A.R., Vasconcelos, A.G., Batziou, K., Domingues, V.G., Eaton, P., Almeida Leite, J.R.S.A., Delerue-Matos, C., Antibacterial activity of novel peptide derived from Cry1Ab16 toxin and development of LbL films for foodborne pathogens control. *Mater. Sci. Eng. C-Mater. Biol. Appl.*, **75**, 503-509 (2017).
67. Hernandez-Montelongo, J., Ureña, Y.C., Machado, D., Lancelloti, M., Pinheiro, M.P., Rischka, K., Lisboa-Filho, P.N., Cotta, M.A., Electrostatic immobilization of antimicrobial peptides on polyethylenimine and their antibacterial effect against *Staphylococcus epidermidis*. *Colloid Surf. B-Biointerfaces*, **164**, 370-378 (2018).
68. Cantor, S., Vargas, L., Rojas, A.O.E., Yarce, C.J., Salamanca, C.H., Oñate-Garzón, J., Evaluation of the antimicrobial activity of cationic peptides loaded in surface-modified nanoliposomes against foodborne bacteria. *Int. J. Mol. Sci.*, **20**, 680 (2019).
69. Karrat, A., Lamaoui, A., Amine, A., Palacios-Santander, J.M., Cubillana-Aguilera, L., Applications of chitosan in molecularly and ion imprinted polymers. *Chem. Afr. J. Tunisian Chem. Soc.*, **3**, 513-533 (2020).
70. Li, J., Zhuang, S., Antibacterial activity of chitosan and its derivatives and their interaction mechanism with bacteria: current state and perspectives. *Eur. Polym. J.*, **138**, 109984 (2020).
71. Egorov, A.R., Kirichuk, A.A., Rubanik, V.V., Rubanik Jr, V.V., Tskhovrebov, A.G., Kritchenkov, A.S., Chitosan and its derivatives: preparation and antibacterial properties. *Materials*, **16**, 6076 (2023).
72. Je, J.Y., Kim, S.K., Chitosan derivatives killed bacteria by disrupting the outer and inner membrane. *J. Agric. Food Chem.*, **54**, 6629-6633 (2006).
73. Yusof, N.A.A., Zain, N.M., Pauzi, N., Synthesis of ZnO nanoparticles with chitosan as stabilizing agent and their antibacterial properties against Gram-positive and Gram-negative bacteria. *Int. J. Biol. Macromol.*, **124**, 1132-1136 (2019).
74. Chen, Y., Liu, Y., Dong, Q., Xu, C., Deng, S., Kang, Y., Fan, M., Li, L., Application of functionalized chitosan in food: a review. *Int. J. Biol. Macromol.*, **235**, 123716 (2023).
75. Aranaz, I., Alcántara, A.R., Civera, M.C., Arias, C., Elorza, B., Heras Caballero, A., Acosta, N., Chitosan: an overview of its properties and applications. *Polymers*, **13**, 3256 (2021).
76. Wang, W., Meng, Q., Li, Q., Liu, J., Zhou, M., Jin, Z., Zhao, K., Chitosan derivatives and their application in biomedicine. *Int. J. Mol. Sci.*, **21**, 487 (2020).
77. Qiu, Y.L., Li, Y., Zhang, G.L., Hao, H., Hou, H.M., Bi, J., Quaternary-ammonium chitosan, a promising packaging material in the food industry. *Carbohydr. Polym.*, **323**, 121384 (2024).

78. Wu, M., Long, Z., Xiao, H., Dong, C., Recent research progress on preparation and application of N, N, N-trimethyl chitosan. *Carbohydr. Res.*, **434**, 27-32 (2016).
79. Freitas, E.D., Moura Jr, C.F., Kerwald, J., Beppu, M.M., An overview of current knowledge on the properties, synthesis and applications of quaternary chitosan derivatives. *Polymers*, **12**, 2878 (2020).
80. Min, T., Zhu, Z., Sun, X., Yuan, Z., Zha, J., Wen, Y., Highly efficient antifogging and antibacterial food packaging film fabricated by novel quaternary ammonium chitosan composite. *Food Chem.*, **308**, 125682 (2020).
81. Zhou, H.F., Deng, W.Y., Guo, H.Q., Luo, W.H., Han, Z.Q., Cheng, Z., Lau, W.M., Xiao, N.Y., Zhang, X.Q., Antibacterial activity of polyethylene film by hyperthermal hydrogen induced cross-linking with chitosan quaternary ammonium salt. *Int. J. Biol. Macromol.*, **286**, 138335 (2025).
82. Bui, V.K.H., Park, D., Lee, Y.C., Chitosan combined with ZnO, TiO2 and Ag nanoparticles for antimicrobial wound healing applications: a mini review of the research trends. *Polymers*, **9**, 21 (2017).
83. Jana, S., Jana, S., 2020. Functional chitosan: drug delivery and biomedical applications, first ed., Springer Nature, Singapore, pp. 457-489.
84. Mizwari, Z.M., Oladipo, A.A., Yilmaz, E., Chitosan/metal oxide nanocomposites: synthesis, characterization, and antibacterial activity. *Int. J. Polym. Mater. Polym. Biomat.*, **70**, 383-391 (2021).
85. Al-Naamani, L., Dobretsov, S., Dutta, J., Chitosan-zinc oxide nanoparticle composite coating for active food packaging applications. *Innov. Food Sci. Emerg. Technol.*, **38**, 231-237 (2016).
86. Babaei-Ghazvini, A., Acharya, B., Korber, D.R., Antimicrobial biodegradable food packaging based on chitosan and metal/metal-oxide bio-nanocomposites: a review. *Polymers*, **13**, 2790 (2021).
87. Yan, D., Li, Y., Liu, Y., Li, N., Zhang, X., Yan, C., Antimicrobial properties of chitosan and chitosan derivatives in the treatment of enteric infections. *Molecules*, **26**, 7136 (2021).
88. Alkarri, S., Bin Saad, H., Soliman, M., On antimicrobial polymers: development, mechanism of action, international testing procedures, and applications. *Polymers*, **16**, 771 (2024).
89. Janaszewska, A., Lazniewska, J., Trzepiński, P., Marcinkowska, M., Klajnert-Maculewicz, B., Cytotoxicity of dendrimers. *Biomolecules*. **9**, 330 (2019).
90. Kafil, V., Omidi, Y., Cytotoxic impacts of linear and branched polyethylenimine nanostructures in a431 cells. *BioImpacts*, **1**, 23-30 (2011).
91. Inácio, Â.S., Costa, G.N., Domingues, N.S., Santos, M.S., Moreno, A.J., Vaz, W.L., Vieira, O.V., Mitochondrial dysfunction is the focus of quaternary ammonium surfactant toxicity to mammalian epithelial cells. *Antimicrob. Agents Chemother.*, **57**, 2631-2639 (2013).
92. Romøren, K., Thu, B.J., Bols, N.C., Evensen, Ø., Transfection efficiency and cytotoxicity of cationic liposomes in salmonid cell lines of hepatocyte and macrophage origin. *Biochim. Biophys. Acta-Biomembr.*, **1663**, 127-134 (2004).
93. Greco, I., Molchanova, N., Holmedal, E., Jenssen, H., Hummel, B.D., Watts, J.L., Håkansson, J., Hansen, P.R., Svenson, J., Correlation between hemolytic activity, cytotoxicity and systemic in vivo toxicity of synthetic antimicrobial peptides. *Sci. Rep.*, **10**, 13206 (2020).
94. Suryani, S., Chaerunisaa, A.Y., Joni, I.M., Ruslin, R., Aspadiah, V., Anton, A., Sartinah, A., Ramadhan, L.O.A.N., The chemical modification to improve solubility of chitosan and its derivatives application, preparation method, toxicity as a nanoparticles. *Nanotechnol. Sci. Appl.*, **17**, 41-57 (2024).
95. Kubczak, M., Michlewska, S., Karimov, M., Ewe, A., Noske, S., Aigner, A., Bryszewska, M., Ionov, M., Unmodified and tyrosine-modified polyethylenimines as potential carriers for siRNA: biophysical characterization and toxicity. *Int. J. Pharm.*, **614**, 121468 (2022).
96. Saqafi, B., Rahbarizadeh, F., Effect of PEI surface modification with PEG on cytotoxicity and transfection efficiency. *Micro Nano Lett.*, **13**, 1090-1095 (2018).
97. Yang, B., Liu, B., Gao, Y., Wei, J., Li, G., Zhang, H., Wang, L., Hou, Z., PEG-crosslinked O-carboxymethyl chitosan films with degradability and antibacterial activity for food packaging. *Sci. Rep.*, **14**, 10825 (2024).
98. Casettari, L., Vllasaliu, D., Castagnino, E., Stolnik, S., Howdle, S., Illum, L., PEGylated chitosan derivatives: synthesis, characterizations and pharmaceutical applications. *Prog. Polym. Sci.*, **37**, 659-685 (2012).
99. Davidovich-Pinhas, M., Danin-Poleg, Y., Kashi, Y., Bianco-Peled, H., Modified chitosan: a step toward improving the properties of antibacterial food packages. *Food Packaging and Shelf Life*, **1**, 160-169 (2014).
100. Casettari, L., Vllasaliu, D., Mantovani, G., Howdle, S.M., Stolnik, S., Illum, L., Effect of PEGylation on the toxicity and permeability enhancement of chitosan. *Biomacromolecules*, **11**, 2854-2865 (2010).
101. Dijksteel, G.S., Ulrich, M.M., Middelkoop, E., Boekema, B.K., Lessons learned from clinical trials using antimicrobial peptides (AMPs). *Front. Microbiol.*, **12**, 616979 (2021).
102. Vishweshwaraiah, Y.L., Acharya, A., Hegde, V., Prakash, B., Rational design of hyperstable antibacterial peptides for food preservation. *Npj Sci. Food*, **5**, 26 (2021).
103. Bajrami, D., Hossain, S.I., Barbarossa, A., Sportelli, M.C., Picca, R.A., Gentile, L., Mastrolonardo, F., Rosato, A., Carocci, A., Colabufo, N.A., Mizaikoff, B., Cioffi, N., A scalable route to quaternary ammonium-functionalized AgCl colloidal antimicrobials inhibiting food pathogenic bacteria and biofilms. *Heliyon*, **10**, e25260 (2024).
104. McMahon, S., Kennedy, R., Duffy, P., Vasquez, J.M., Wall, J.G., Tai, H., Wang, W., Poly (ethylene glycol)-based hyperbranched polymer from RAFT and its application as a silver-sulfadiazine-loaded antibacterial hydrogel in wound care. *ACS Appl. Mater. Interfaces*, **8**, 26648-26656 (2016).

105. Muñoz-Sánchez, S., Heredero-Bermejo, I., de la Mata, F.J., García-Gallego, S., Bifunctional carbosilane dendrimers for the design of multipurpose hydrogels with antibacterial action. *Chem. Mat.*, **36**, 266-274 (2023).
106. Skrzyniarz, K., Takvor-Mena, S., Lach, K., Łysek-Gładysińska, M., Barrios-Gumiel, Ó., Cano, J., Ciepluch, K., Molecular mechanism of action of imidazolium carbosilane dendrimers on the outer bacterial membrane–From membrane damage to permeability to antimicrobial endolysin. *J. Colloid Interface Sci.*, **665**, 814-824 (2024).
107. Xia, B., Dong, C., Lu, Y., Rong, M., Lv, Y.Z., Shi, J., Preparation and characterization of chemically-crosslinked polyethyleneimine films on hydroxylated surfaces for stable bactericidal coatings. *Thin Solid Films*, **520**, 1120-1124 (2011).
108. Zhang, J., Han, Y., Ben, Z., Han, T., Yin, P., Effect of branched polyethyleneimine and citric acid on the structural, physical and antibacterial properties of corn starch/chitosan films. *Int. J. Biol. Macromol.*, **231**, 123186 (2023).
109. Galaburri, G., Infantes-Molina, A., Melian Queirolo, C.M., Mebert, A., Tuttolomondo, M.V., Rodríguez-Castellón, E., Lázaro-Martínez, J.M., Composite films based on linear polyethyleneimine polymer and starch or polysaccharides from DDGS: synthesis, characterization, and antimicrobial studies. *Polymers*, **17**, 458 (2025).
110. Pu, C., Tang, W., The antibacterial and antibiofilm efficacies of a liposomal peptide originating from rice bran protein against *Listeria monocytogenes*. *Food Funct.*, **8**, 4159-4169 (2017).
111. Ahani, E., Montazer, M., Mianehro, A., Samadi, N., Toliyat, T., Rad, M.M., Preparation of long-lasting antibacterial wound dressing through diffusion of cationic-liposome-encapsulated polyhexamethylene biguanide. *React. Funct. Polym.*, **169**, 105092 (2021).
112. Malheiros, P.S., Cuccovia, I.M., Franco, B.D., Inhibition of Listeria monocytogenes in vitro and in goat milk by liposomal nanovesicles containing bacteriocins produced by Lactobacillus sakei subsp. sakei 2a. *Food Control*, **63**, 158-164 (2016).