Received: 14 November 2023 | Revised: 20 May 2024 | Accepted: 27 May 2024

DOI: 10.1111/1541-4337.13394

COMPREHENSIVE REVIEW

Comprehensive REVIEWS in Food Science and Food Safety WILEY

Production, characterization, and potential applications of lipopeptides in food systems: A comprehensive review

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Abstract

Lipopeptides are a class of lipid–peptide-conjugated compounds with differing structural features. This structural diversity is responsible for their diverse range of biological properties, including antimicrobial, antioxidant, and anti-inflammatory activities. Lipopeptides have been attracting the attention of food scientists due to their potential as food additives and preservatives. This review provides a comprehensive overview of lipopeptides, their production, structural characteristics, and functional properties. First, the classes, chemical features, structure–activity relationships, and sources of lipopeptides are summarized. Then, the gene expression and biosynthesis of lipopeptides in microbial cell factories and strategies to optimize lipopeptide production are discussed. In addition, the main methods of purification and characterization of lipopeptides have been described. Finally, some biological activities of the lipopeptides, especially those relevant to food systems along with their mechanism of action, are critically examined.

KEYWORDS

fermented food, functional properties, gene expression, lipopeptide identification, lipopeptides

1 | INTRODUCTION

Lipopeptides are a class of oligopeptides comprising lipids or other compounds with lipophilic hydrocarbon tails attached to peptides. A lipopeptide is formed by the interaction of a fatty acyl chain (typically comprising C12 to C18) to the N-terminus of either a cyclic or linear short (between 4 and 12 amino acids) polypeptide (Hamley, 2015; Vecino et al., 2021). Typically, lipopeptides are low-molecular-mass compounds (typically ranging from 500 to 1500 Da) (Janek et al., 2010). These molecules possess "membrane-active" amphiphilic properties due to having a hydrophilic head and a hydrophobic tail. Lipopeptides are known for their high structural variation and their considerable potential for reduction of surface (SFT) and interfacial (IFT) tension (Mnif & Ghribi, 2015; Mnif et al., 2021).

Lipopeptides are produced naturally on the surfaces of microbial cells, are secreted extracellularly, and are commonly referred to as "microbial surfactants." They are considered to be secondary metabolites produced by many fungi (e.g., echinocandin and peptaibiotics), yeasts, and bacteria (Mnif et al., 2021; Zhao et al., 2019). Owing to the presence of hydrophobic and hydrophilic moieties in

lipopeptides, they can lower the SFT and IFT between liquids, solids, and gases. Consequently, lipopeptides have high dispersion in water and other fluids. Moreover, they have high surface activity and low critical micelle concentration (CMC), making them potential alternatives to synthetic surfactants. They exhibit better characteristics than their synthetic counterparts, such as higher biodegradability, higher stability against harsh environments (extreme temperature, salinity, and pH), low toxicity, and environment compatibility (Meena & Kanwar, 2015). Renewable raw materials can be used in fermentation substrates that are considered cost-effective synthesis starting materials to produce microbial surfactants (Banat et al., 2014). These factors have led to an increasing demand for biosurfactants, which is expected to reach about USD 53 billion by 2025 (Sharma, 2021). During the past few years, several classes of lipopeptide antibiotics, namely polymyxin B (PMB) and daptomycin, have received full approval from the Food and Drug Administration for treating infections caused by multidrug-resistant pathogens (Gotze & Stallforth, 2020; Pirri et al., 2009).

Lipopeptides provide different functions, including emulsifying, pore-forming, foaming, viscosity reduction, dispersing, and solubilizing activities, as well as acting as mobilizing agents (Mnif et al., 2021). Therefore, these molecules have potential for use in food products as additives and preservatives, in cosmetic and pharmaceutical fields as emulsifiers, and environmental areas for oil recovery and bioremediation. In addition, they have been reported to have various bioactive properties, such as antimicrobial (Gotze & Stallforth, 2020), anti-inflammatory (Park et al., 2013; Zhang et al., 2015), and anticancer (Cheng et al., 2016; Dey et al., 2017; Meena et al., 2020) activities. This review provides comprehensive information on the classification, structure, and functionalities of lipopeptides and their potential applications. Furthermore, the structure–activity relationship (SAR) of lipopeptides is delineated, with the aim of establishing the best strategies to produce tailored products for specific bioactivities and food applications.

2 | CLASSIFICATION AND STRUCTURE–FUNCTION RELATIONSHIPS OF LIPOPEPTIDES

2.1 | Classification of microbial lipopeptides

Different ways of classifying lipopeptides have been proposed, based either on their chemical structures, sources (or production mechanism), or net charge. Based on their chemical structures, lipopeptides have been classified into two groups: (1) linear lipopeptides and (2) cyclic lipopeptides (see Figure 1) (Meena & Kanwar, 2015). Based on charge, lipopeptides can be either cationic or non-ionic. Linear lipopeptides usually have the fatty acyl chain connected to either the α-amino group, or to other hydroxyl groups. The cerexins, the tridecaptins, the corrugatins, and the syringafactins that have been isolated from *Paenibacillus* spp., *Bacillus* spp., and *Pseudomonas* spp., are examples of linear lipopeptides (Götze & Stallforth, 2020; Sani et al., 2023). There is limited research on this group despite their being easier to produce and purify than their cyclic counterparts (Cochrane & Vederas, 2016).

Cationic cyclic lipopeptides, such as polymyxins, polypeptins, and octapeptins, are cyclized at the C-terminus by either an ester or an amide bond, and the lipid tail is incorporated through acylation of the N-terminal amino acid by non-ribosomal peptide synthetases (NRPS). Non-cationic cyclic lipopeptides are the most active and constitute peptides with a cyclic lactone or lactam ring of amino acid residues linked to a lipophilic moiety. Such molecules involve a complex mixture of *D*- and *L*-amino acids and non-proteinogenic residues (Schneider et al., 2014). Cyclization of lipopeptides stabilizes their structure, and is often required to enable interaction with the biological target, hence the activity of linear lipopeptides is typically not as good as their cyclic counterparts (Hamley, 2015). The most studied cyclic lipopeptides are the viscosins, surfactins, iturins, fengycins, amphisins, lichenysins, and putisolvins (Mukherjee & Das, 2010).

2.2 | Structure–activity relationships and congeners or homology in lipopeptides

As the name suggests, SAR is a term used to describe the relationship that links the chemical structure of a compound to its biological properties. A subset of SAR, referred to as quantitative SAR (Q-SAR), involves using mathematical models and in silico tools to study, predict, and relate the unique structural features of a compound with endpoint properties, such as bioactivity, physicochemical, and environmental properties (Mohapatra, 2020). Q-SAR models work on the premise that, for most 3D-conformed molecules, "structure determines activity" and that a high degree of correlation exists between the structure of the compound and the biological properties exhibited by that compound under various conditions. This phenomenon is exploited in several research areas, including toxicology (Mohapatra, 2020), pharmaceutics (Sable et al., 2017), and bioactive peptides (Manzanares et al., 2019).

As a case in point, there is a structural basis to the ability of a peptide and of peptide mimetics to exhibit

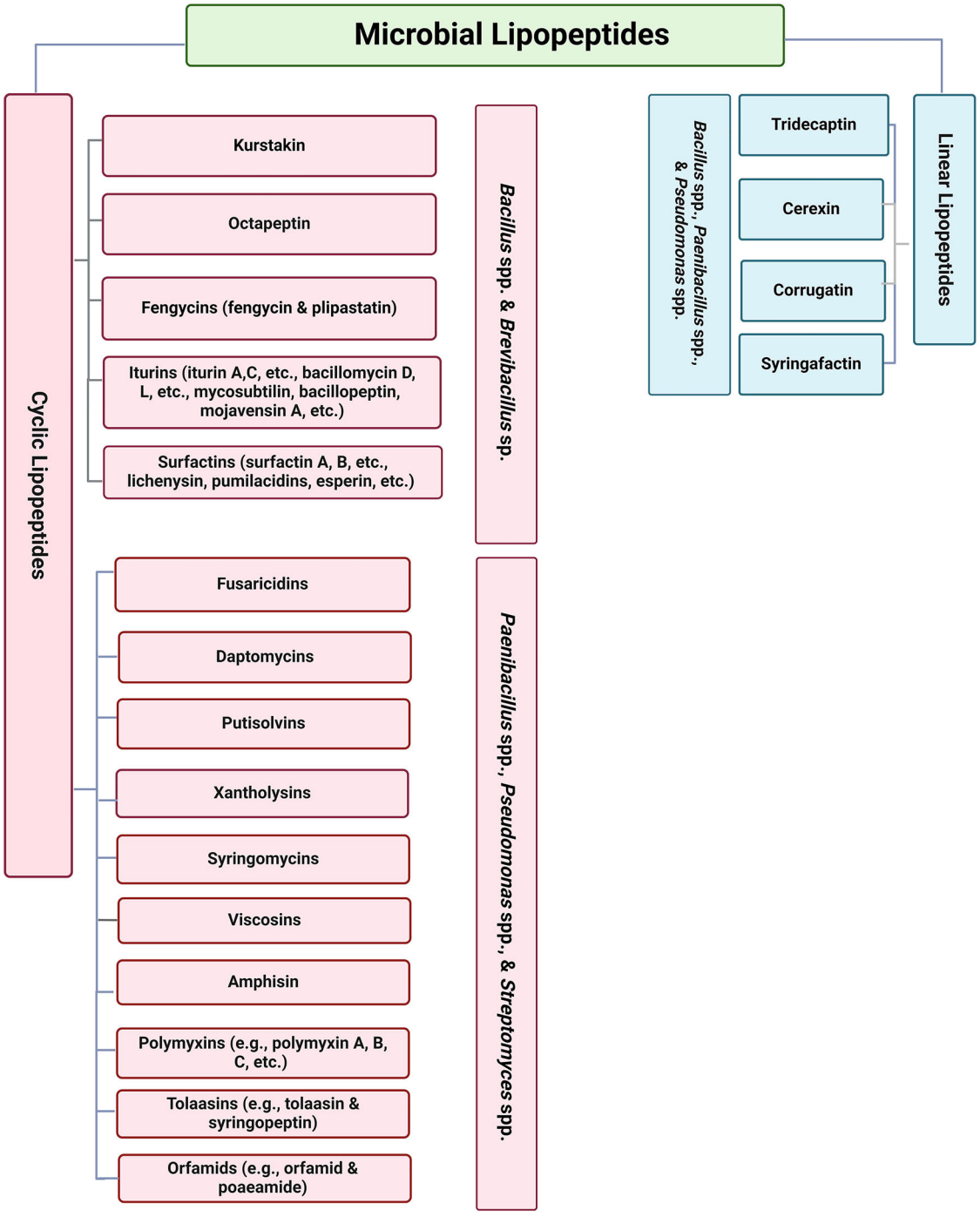

FIGURE 1 Current microbial lipopeptide classification (Wang et al., 2023; Zhao et al., 2017).

antimicrobial properties. To display antimicrobial properties, a peptide or peptide-containing biomolecule needs structural features that allow for easy adsorption onto the cell membrane of a microbial target. Peptide–microbe interaction is facilitated by features such as being cationic (to be able to interact electrostatically with negatively charged microbial cells), having a low molecular weight (to allow for quick and easy diffusion across the cell envelope), and having the ability to adopt an amphipathic helical conformation that permits the insertion of the lipopeptide into the microbial cell membrane (Fewer et al., 2021; Oh et al., 1999; Tossi et al., 2000). Other structural features of antimicrobial peptidic compounds are the primary and secondary sequence and hydrophobicity (Fjell et al., 2011; Oren & Shai, 1998; Powers & Hancock, 2003; Tossi et al., 2000).

Lipopeptides comprise a variety of structures based on the arrangement of both the peptide and lipid components which encompass linear and cyclic forms. It is worth

mentioning that the variations in length and branching of the fatty acid chains and amino acid substitutions lead to remarkable lipopeptide diversity and activities (Aleti et al., 2015; Sharma et al., 2014). While the initial classification of lipopeptides is usually focused on linear and cyclic lipopeptides, the structural diversity inherent in lipopeptides is brought about through branching. In this regard, Janiszewska et al. (2012) reported that the branching of lipopeptides, particularly in combination with a C12 lipid chain, appears to substantially impact their antimicrobial activity, selectivity against *Candida*, and mode of action against fungal cells. The more branched structures with the C12 chain demonstrate enhanced potency and specificity, making them promising candidates for further development as antifungal agents.

There is also the possibility of isoforms or congeners of the same lipopeptides (i.e., lipopeptides that share the same peptide chain but differ in their acyl chains) (Beltran-Gracia et al., 2017; Carolina et al., 2021). For example, Vahidinasab et al. (2022), reported the production of different lipopeptides and their congeners from two *Bacillus velezensis* strains (UTB96 and FZB42). While both strains were able to produce the three major lipopeptide families (surfactin, fengycin, and iturin), the well-established *B. velezensis* FZB42 strain was able to exclusively produce bacillomycin D, while the relatively novel *B. velezensis* UTB96 strain exclusively produced iturin A. Moreover, it was observed that the microorganisms produced different concentrations of congeners of the exclusively produced lipopeptides. Mass spectrometry analysis showed that under the conditions used in cultivating the *B. velezensis* FZB42, the concentration of the congeners of bacillomycin D was in the order C15 (~45%), followed by C14 (~35%), C16 (~15%), and then C17 congeners (~5%). In contrast, C14, C15, and C16 congeners of iturin A were produced at similar concentration (~34%, 33%, and 30%, respectively), but the C17 congener production was relatively low (~3%). In the same study, both strains produced a mixture of fengycin homologs, depending on the peptide moiety and acyl chain length and type. For example, in both strains, fengycin A and B conjugated to saturated or unsaturated fatty acid chains with C14–C18 atoms were detected, although the saturated fatty acid chain variants were more abundant. A number of different surfactin congeners with saturated fatty acid chains (between C12:0 to C17:0) were also detected in both strains. Another remarkable finding from this study was that varying substrates (initial glucose concentration, and amino acid type and availability) in the growth medium considerably altered the yields and antifungal activities of the three lipopeptide families (Vahidinasab et al., 2022). This study demonstrated the sheer diversity of lipopeptides that can be obtained from a single microbial species. Other studies have reported the presence of congeners of iturin A in *B. velezensis* FUA2155 (Li et al., 2023), surfactin congeners in *Bacillus subtilis* strain PB2-L1 (Jiang et al., 2016), and *Bacillus amyloliquefaciens* ST34 (Ndlovu et al., 2017), bacillomycin Lc congeners in *B. subtilis* (Eshita et al., 1995), syringafactins congeners in *Pseudomonas* sp. SZ57 (Zhang et al., 2021), pseudodesmin congeners from *Pseudomonas* sp. (De Vleeschouwer et al., 2020), xantholysin congeners in *Pseudomonas putida* BW11M1 (Li et al., 2013), fusaricidin congeners in *Paenibacillus* spp. (Cochrane & Vederas, 2016; Li & Chen, 2019), and *Bacillus polymyxa* (Bionda et al., 2016), among others.

2.2.1 | Description of specific bioactivities in lipopeptides

The SAR driving the biological properties of iturin, fengycin, and surfactin are presented in Table 1.

Fundamentally, these lipopeptides consist of a short-cyclic peptide connected to a fatty acid acyl chain (Figure 2), and each component in the structure performs a key function.

Iturin is an example of a family of cyclic antimicrobial peptides whose biological properties have been well reported. Iturins inhibit the growth of fungi (Wang et al., 2022; Zhou et al., 2020), cancer cells (Dey et al., 2015; Zhao, Yan, et al., 2021), and to a limited extent, bacteria (Kim et al., 2020). A growing body of research has found that the fungicidal properties of iturins are due to structurally controlled phenomena such as the formation of β-turn conformations that create pores for binding to and conducting ions, thereby increasing the electrical conductance of microbial cell membranes (Wan et al., 2022). These β-turn conformations are also used to chelate metal ions (especially Na^+), which might be important for the optimal growth of the microbial cell (Rautenbach et al., 2000). The fatty acid acyl chain component of iturins also can interact via hydrophobic bonding with phospholipids and sterols present in microbial cell membranes. The absence of charged amino acids in the peptide moiety of the iturin lipopeptide class gives the peptide a relatively poor affinity for bacterial cells compared with fungal cells (Arrebola et al., 2010; Fewer et al., 2021; Gong et al., 2015). The cumulative effect of the interactions between the lipopeptide and the microbial cell is the leakage of intracellular components of the microbial cell, leading to cell death.

Another cyclic lipopeptide with strong antifungal properties is fengycin. A study by Sur and Grossfield (2022), using molecular dynamics simulations, showed that the unique structural features of fengycin give it the ability to aggregate and bind to fungal membranes (rich in phosphatidylcholine), as opposed to bacterial membranes

TABLE 1 Structure–activity relationship determined for some lipopeptides.

Name of lipopeptide	Compound description	Peptide moiety	Acyl chain	Biological property of interest	Structure–activity behavior necessary for biological action	Ref.
Iturin A	Closed loop decapeptide α-amino acid with one β-amino acid peptide coupled to a fatty acid acyl chain	L-Asn-D-Tyr-D-Asn-L-Gln-L-Pro-D-Asn-L-Ser	C11	Antifungal properties	Presence of β-turns that form pores for conducting ions and increasing the electrical conductance of microbial cell membrane	Gong et al. (2015)
					β-turns allow iturins to bind to metal ions such as sodium	Rautenbach et al. (2000)
					Acyl chains that associate via hydrophobic interactions with phospholipids and sterols in microbial cell membranes	Gong et al. (2015)
					The absence of a charged amino acid in the peptide moiety results in the relatively poor affinity of the lipopeptide for binding to bacterial cells, as opposed to fungal cells	Fewer et al. (2021)
Fengycin	Negatively charged cyclic decapeptide coupled at the N-terminus to a β-hydroxy fatty acid chain	L-Glu-D-Orn-L-Tyr-D-allo-Thr-L-Glu-D-Ala-L-Pro-L-Glu-D-Tyr-Ile	C15	Antifungal properties	Amphiphilic behavior that allows adsorption of the peptide into the interface of water and the membrane bilayer	Horn et al. (2013)
					Interaction between lipopeptide acyl tail and hydrophobic membrane	Horn et al. (2013)
					The net negative charge of the peptide alters the ionic environment of the fungal membrane, resulting in changes in the membrane potential	Epand & Epand (2011) and Horn et al. (2013)
Surfactin	Amphiphilic heptapeptide linked to β-hydroxy fatty acid tail	L-Glu-L-Leu-D-Leu-L-Val-L-Asp-D-Leu-L-Leu	C12–17	Biosurfactant activity	Amphiphilic properties allow self-assembly and interfacial tension reduction behavior—a feature that confers foaming, emulsification, and drug delivery properties and application	Theatre et al. (2021)
				Surface-acting behavior	The net negative charge (due to the presence of Glu and Asp) influences the physicochemical properties of surfactins	Liu et al.(2012) and Theatre et al. (2021)
				Antiviral properties	The cyclicity of surfactins confers surface-acting behavior that mediates antiviral behavior (by inhibiting membrane-fusion between virus and host cell)	Liu et al. (2012) and Yuan et al. (2018)

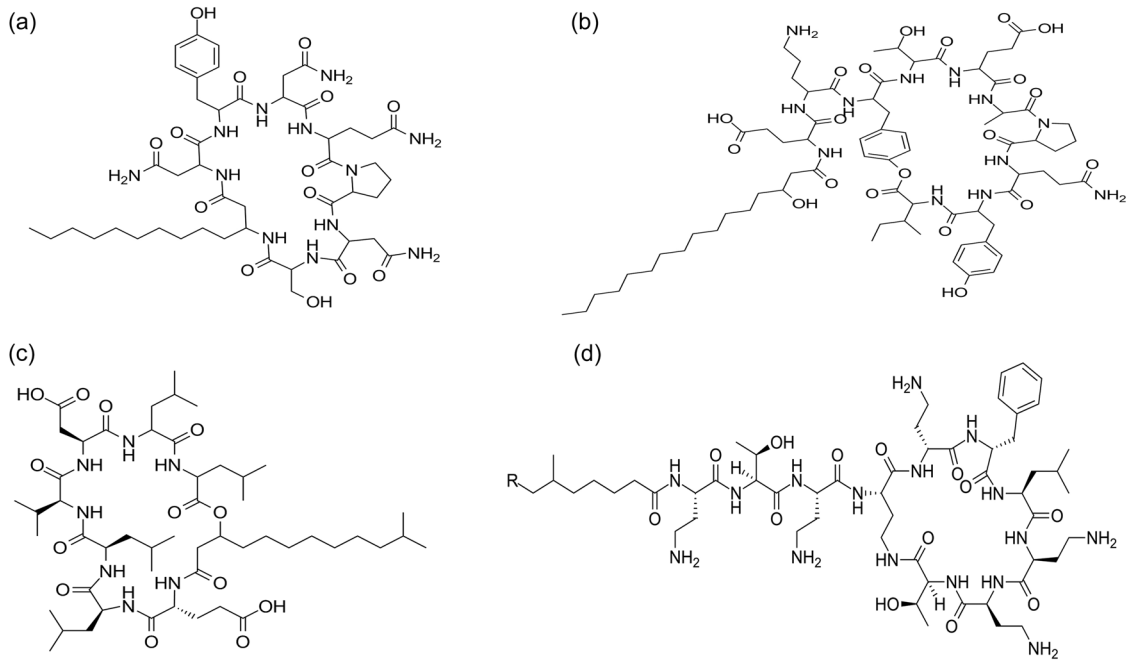

FIGURE 2 Chemical structures of (a) iturin, (b) fengycin, (c) surfactin, and (d) polymyxin.

(rich in phosphatidylethanolamine and phosphatidylglycerol). The binding of fengycin to phosphatidylcholine-rich membranes is mediated by the insertion of the acyl chain into the hydrophobic core of the membrane, changing the curvature and integrity of the membrane (Horn et al., 2013). The presence of charged amino acids in the fengycin lipopeptide structure in the vicinity of the membrane, also induces changes in the ionic strength and the voltage across the membrane (Epand & Epand, 2011; Horn et al., 2013), which compromises the structural integrity of the membrane. Horn et al. (2013) invoked the "interfacial activity model" proposed by Rathinakumar et al. (2009), to explain that fengycin is adsorbed to the bacterial cell membrane and re-organizing the water-bilayer interface. Moreover, the model describes how structural features such as molecular size, amphiphilicity, and electrostatic forces are all important in the binding mechanism of fengycin to microbial hosts.

Surfactin is another lipopeptide whose structural diversity and biological properties have been reported in the literature. Generally, surfactins are cyclic heptapeptides linked to β-hydroxy fatty acid tails (see Figure 2c). Theatre et al. (2021) reported three main structural features responsible for the biological properties of surfactins: (a) the cyclic nature of the compound, (b) the combinations of unique peptides and fatty acids representing the polar and non-polar groups, respectively, and (c) the net charge of the polar group. Collectively, these features afford surfactins the ability to act at interfaces and demonstrate a surface-acting behavior. Interestingly, surfactins have shown no antifungal properties on their own (Gong et al., 2015). However, they appear to be able to enhance the antifungal properties of other lipopeptides such as fengycin (Desmyttere et al., 2019), mycosubtilin (Deravel et al., 2014), and bacillomycin D (Tanaka et al., 2015). Other studies have reported antibacterial and anti-yeast properties (against *Candida* species and a broad range of bacteria species, including *Staphylococcus aureus* and *Escherichia coli*) (Sharma et al., 2020), and antiviral effects (against porcine epidemic diarrhoea virus and transmissible gastroenteritis virus) (Yuan et al., 2018) of surfactins. These observed bioactivities, together with the antifungal enhancing effects of surfactin, are all due to the ability of surfactins to disrupt the integrity of cell membranes in hosts—an ability that is due to the hydrophilic peptide loop found in surfactin (Theatre et al., 2021).

Knowledge of lipopeptide SAR is useful in several areas, such as predicting the biological properties of novel lipopeptides, and designing lipopeptide analogues with desired features and properties. It could also allow the design of lipopeptide targets to control antimicrobial-resistant microbes. Further research is required to understand the Q-SAR of lipopeptides and their analogues to tap the full potential of this interesting class of biomolecules.

3 | GENE EXPRESSION AND BIOSYNTHESIS OF LIPOPEPTIDES

Understanding and designing a lipopeptide synthesis process is essential for advanced lipopeptide production and effective industrial applications (Zhu et al., 2021). In addition to the various methods that are traditionally used in the biosynthesis of lipopeptides, including optimizing the nutrient supply and culture growth conditions of microbial resources (Xia & Wen, 2022), genetic engineering techniques have been proposed for the development of high lipopeptide-producing microorganism strains (Dang et al., 2019; Jiao et al., 2017; Sun et al., 2018; Xu et al., 2020).

Lipopeptides are generated by NRPS that are encoded by large biosynthetic gene clusters (BGCs; Clements et al., 2019). NRPSs are mega enzymes that recognize amino acid intermediates and bind them to produce polypeptide sequences. These enzymes play a key role in the synthesis of multiple polypeptide sequences with different structural properties and high structural diversity (Ines & Dhouha, 2015). The employment of NRPSs leads to remarkable diversification among the lipopeptides concerning the sequence, number (2–25), and type (e.g., acidic, aromatic, basic, aliphatic, and cyclic), and the configuration of amino acid residues (*L/D*) in the peptide chain, and the length (C_6–C_{18}), type (e.g., OH groups, iso-, anteiso-methyl branched forms), and branching of the fatty acid chain (Ongena et al., 2007). For an efficient lipopeptide synthesis process, three processing steps are considered crucial, involving supplying of precursors, assembling of lipopeptides, and extending the peptide chain (Zhu et al., 2021). In particular, the synthesis of side chain fatty acids, activation and loading of fatty acids, and lengthening of the peptide chain (Yang et al., 2020), appear to play an important role in the lipopeptide structure and bioactivity. The synthesis of lipopeptides is done through NRPSs which are described as large multi-modular enzymes. Each NRPS module adds one amino acid to the peptide moiety and typically consists of domains, such as adenylation (A), thiolation (T), condensation (C), starter condensation (Cs), epimerization (E), and thioesterase (TE). The order of these domains varies based on the lipopeptide structure. The A domain activates amino acids, the T domain elongates the peptide chain, and the Cs domain condenses lipid and peptide moieties at the N-terminus. Lipidation, involving the attachment of a fatty acid moiety, is a crucial step, with various mechanisms, such as direct integration and involvement of hybrid enzymes (Pilz et al., 2023). Termination of peptide elongation is facilitated by the TE domain where the hydrolysis or macrocyclization of the peptide occurs (Kopp & Marahiel, 2007; Strieker et al., 2010). The lipopeptide cyclization occurs during or after the elongation of the peptide chain and is facilitated by the NRPS domains. The cyclic structure can be achieved through various mechanisms, leading to the formation of macrolactones, β-lactams, or other macrocycles (Pilz et al., 2023; Schwarzer et al., 2003). Cyclization can involve the attachment of the N- or C-terminal amino acid to the lipopeptide backbone moieties, resulting in the formation of diverse cyclic lipopeptide structures (Schimana et al., 2002). It is worth mentioning that microorganisms belonging to the *Bacillus* and *Pseudomonas* genus have been identified as the most common lipopeptide producers (Pilz et al., 2023). Figure 3a. illustrates the biosynthetic machinery of lipopeptides. Starting from a precursor, assembly of lipopeptides involves extension of the peptide chain, attachment of fatty acids, and export of the final product.

Microorganisms that belong to *Bacillus* spp. initiate the biosynthesis of lipopeptides once the microorganisms stop sporulation. For instance, Wang et al. (2022) found that enhancement of lipopeptide production could be achieved by deleting genes responsible for the sporulation activation in *B. amyloliquefaciens* WH1. These microorganisms do not take mRNA as a template or tRNA as a carrier; fatty acids bind to NRPS in the form of acetyl-CoA for straight-chain fatty acids, and isobutyryl-CoA, isovaleryl-CoA, and methylbutyryl-CoA for branched fatty acids (Zhang et al., 2022; Zhu et al., 2021). After the fatty acids are activated and loaded onto peptide synthase systems, the next step in the synthesis of lipopeptides is the extension of the peptide chains. For the extension function, repeating units of the NRPSs are used in three steps (Yang et al., 2020). Particular amino acids present in the substrate are recognized and activated by the adenylation domain with ATP consumption, forming enzymatically stabilized aminoacyl adenylate. Afterward, the thiolation domain ensures the amino acid residues are bound to each other and form polypeptides (Zhang et al., 2022). Peptide bond formation of two consecutively bound amino acids is catalyzed by the condensation step (Roongsawang et al., 2010). The basic molecule carrying the three domains is copied to perform the peptide-elongation function (Zhang et al., 2022). After the biosynthesis process, the lipopeptide can be subjected to some modifications (glycosylation, halogenation, etc.) by specific enzymes (Ines & Dhouha, 2015), which can impact the functionality of the compound.

It is worth highlighting the importance of genome mining and in silico approaches in efficiently identifying and predicting lipopeptide BGCs (Aleti et al., 2015). Many novel antimicrobial compounds have been discovered using genome analysis, including cyclic lipopeptides (De Bruijn et al., 2008; Nikolouli & Mossialos, 2012). Aleti et al. (2015) identified several novel clusters of lipopeptides in the Bacillales from genomes deposited in the database, using web-based prediction tools. The authors summarized

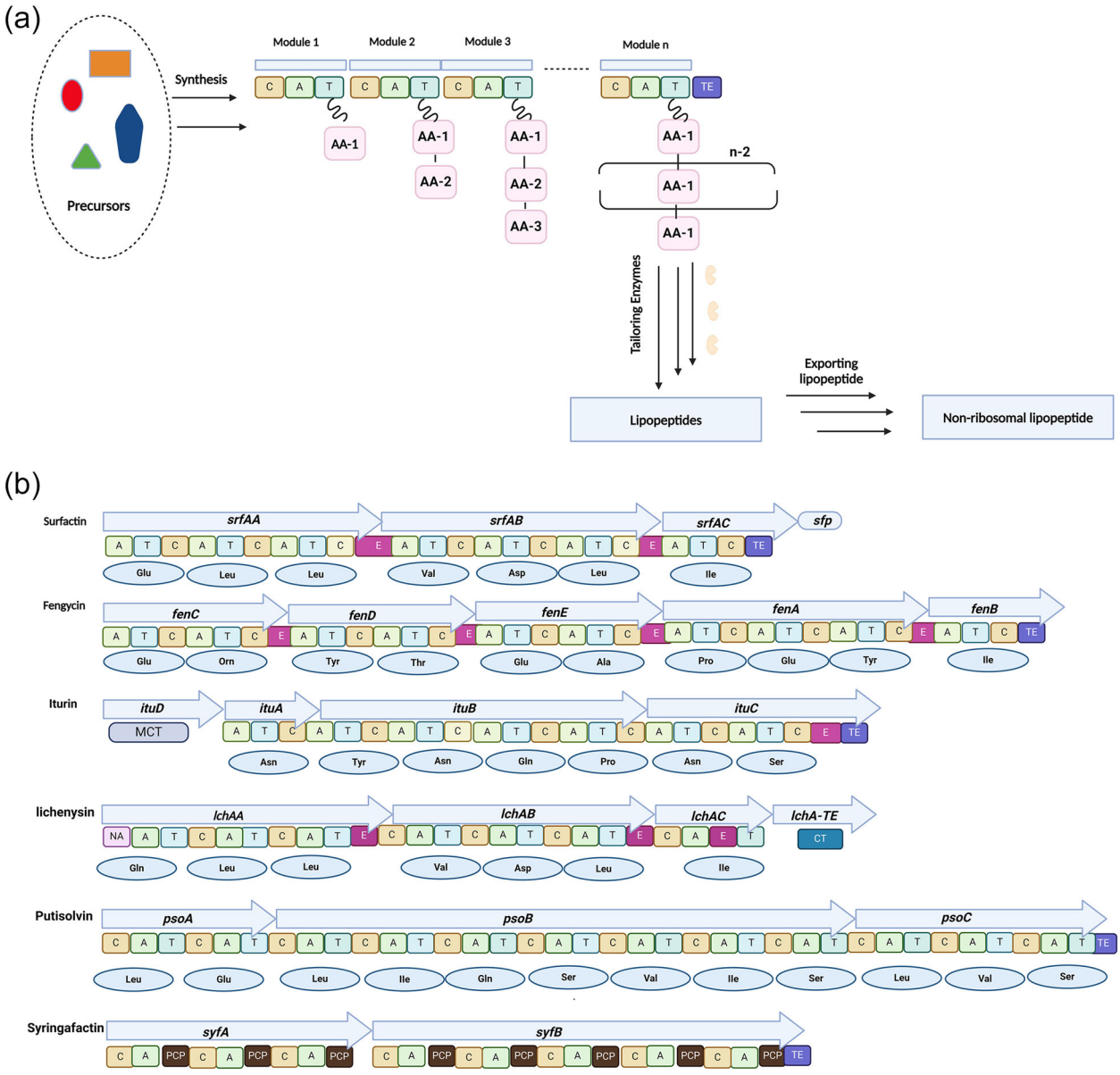

FIGURE 3 (a) Synthesis of lipopeptides via non-ribosomal peptide synthase (NRPS) and (b) schematic biosynthetic presentation of surfactin, fengycin, iturin, putisolvin, lichenysin, and syringafactin The NRPS modules consist of condensation domains (C), the adenylation domains (A), thiolation domains (T), epimerization domains (E), the thioesterase domain (TE), *N*-acylation domain (NA), C-terminal thioesterase (CT), and peptidyl carrier protein (PCP). Created with BioRender.com and adapted from Zhang et al. (2022) and Gudiña and Teixeira (2022).

the structural diversity and underlined gene clusters of lipopeptides in the Bacillales and evaluated the metabolic potential of these bacteria to produce lipopeptides using in silico genome analysis. Through genome analysis of *Bacillus aryabhattai*, Yaraguppi et al. (2021) identified lipopeptides with antimicrobial properties including iturin A, surfactin A, syringomycin E, bacitracin A, tyrocidine A, and fengycin. In silico studies highlighted iturin A as a promising biosurfactant, exhibiting strong binding affinity (−10.4 kcal/mol) to (1,3)-*β*-D-glucan synthase.

3.1 | Biosynthesis of linear and cyclic lipopeptides

Linear lipopeptides refer to a group of compounds comprising a linear peptide linked to the lipid tail or other moiety with lipophilic nature. Linear lipopeptides also have biological activities that include antimicrobial as well as antifungal activity along with surfactant properties (Mandal et al., 2013). Unlike cyclic lipopeptide, fewer studies have mentioned the biosynthesis of linear lipopeptides

(Berti et al., 2007), on the other hand many research reports have investigated the chemical synthesis of lipopeptides (Desjardine et al., 2007; Huang et al., 2017; Moon & Huang, 2019). In the last few years, various studies have discovered and evaluated several novel linear lipopeptides with various biological activities (Chakraborty et al., 2020; Qiushuang et al., 2023; Tareq et al., 2014a, 2014b), however, only some of them have reported the biosynthesis of these molecules. Dhali (2016) reported that the biosynthesis of either a linear or cyclic lipopeptide form occurs at the termination domain of NRPS, during the final step of molecule production. The termination domain facilitates either circular arrangement (macrocyclization) or breakdown into simpler components (hydrolysis), ultimately determining the structure of the resulting molecule. Similarly, Tareq et al. (2014a) proposed biosynthetic pathways for gageotetrins A–C, which are unique linear lipopeptides that have been identified in a marine *B. subtilis* that produced independently of ribosomes by NRPS.

In a study conducted by Qiushuang et al. (2023), a cryptic BGC (*lsh*) in *Lysobacter* sp. DSM 3655 was activated through promoter engineering and expressed in *Streptomyces* sp. S001. This led to the discovery of two novel linear lipopeptides, lysohexaenetides A and B (compound B was suggested to be a degradation product of A, as it lacks glycine and valine residues). The biosynthetic pathway for lysohexaenetides involves one polyketide synthase (PKS) and four NRPS modules, with the release facilitated by the thioesterase (TE) domain of lshB. The iterative bacterial PKS, LshA, likely assembles the corticrocin moiety. Despite identifying key components, such as lsh3 and host enzymes, some aspects of the biosynthetic process, including the formation of the carboxyl group at C14, remain unknown. Another linear lipo-octapeptide is produced by *P*seudomonas *syringae* pv. tomato DC3000, that is called syringafactin. The biosynthetic genes of syringafactin, identified from the genome, include *syfA* and *syfB*, that encode three and five NRPS modules, respectively. The N-acyl domain of *SyfA* suggests that there is an N-terminal fatty acid chain. *SyfB* has tandem Te-domains. The structure is likely fatty acyl-*D*-Leu1-*D*-Leu2-*D*-Gln3-Leu4-*D*-Thr5-Val6-*D*-Leu7-Leu8. The N-terminal C-domain of *SyfA* shares sequence similarity with ArfA. The syringafactin NRPS system evolved from arthrofactin, with three deleted modules, including the cyclization-involved threonyl residue, resulting in a linear form (Berti et al., 2007).

As the name suggests, cyclic lipopeptides have a cyclic lactone or lactam ring of amino acid residues linked to a lipophilic moiety. It is a complex mixture of *D*- and *L*-amino acids and non-proteinogenic residues (Schneider et al., 2014). Cyclic lipopeptides are produced as a result of NRPS biosynthesis catalyzed by surfactin synthetase (see Figure 3b), a sizeable multienzyme peptide synthetase complex. The *SrfA* operon, and including *srfAA, srfAB, srfAC*, and *srfAD* open reading frames (ORFs), encode the NRPS that is responsible for the synthesis of surfactin from *Bacillus* spp. The first two ORFs only contribute to combining the six amino acids. *SrfAC* is involved in encoding the TE domain for the extension and the peptide product release, besides incorporating the seventh amino acid. *Sfp* is the other gene responsible for encoding the phosphopantetheinyl transferase enzyme (PPTase), which regulates the peptidyl carrier protein (PCP) domain. Similarly, fengycin synthesis (see Figure 3b) consists of a linear arrangement of the PCP, adenylation, condensation, and many epimerization fields. All these steps are encoded by the *fenA-E* operon containing the *ppsA, ppsB, ppsC, ppsD*, and *ppsE* ORFs (Geissler et al., 2019). Unlike the lipopeptides mentioned above, the synthesis of iturin (see Figure 3b) is accomplished by the PKSs-NRPS system, encoded by the *iturin A* operon, which contains the *ituD, ituA, ituB*, and *ituC* ORFS. The malonyl coenzyme A transferase encoded by *ituD* catalyzes the side chain between fatty acids, and the rest of the ORFs are involved in the assembly between amino acids (Yang et al., 2020). Three genes (*psoA*, *psoB*, and *psoC*) were identified and shown to encode NRPS involved in putisolvin biosynthesis (see Figure 3b) (Dubern et al., 2008). In addition, the gene cluster (*lchA*) consists of four ORFs, including *lchAA*, *lchAB*, *lchAC*, and *lchA-TE*, which are involved in lichenysin biosynthesis (see Figure 3b), encoding the lichenysin synthetase LchAA, LchAB, LchAC, and thioesterase LchA-TE, respectively (Nerurkar, 2010).

4 | SOURCE AND PRODUCTION OF LIPOPEPTIDES

4.1 | Fermented foods as sources of lipopeptides

Food fermentation is an ancient preservation technique that has been used in the food industry to extend shelf life and to enhance the nutritional and organoleptic properties of foods (Verardo et al., 2020). Fermented foods are an important source of lipopeptide-producing bacteria. A summary of lipopeptides obtained by bacteria isolated from traditional fermented foods is shown in Table 2.

During fermentation, microorganisms are involved in converting raw materials into considerable amounts of secondary metabolites that possess excellent health benefits, such as antimicrobial, antioxidant, and immunostimulatory activities (Cho et al., 2015; Kanno et al., 2012; Voidarou et al., 2020). Recent studies have focused on lipopeptides produced by bacteria isolated from fermented foods due

TABLE 2 Lipopeptides produced by microorganisms isolated from fermented foods.

Fermented foods	Microorganism isolated	Types of lipopeptide	Functional properties	Ref.
Kinema	*Bacillus tequilensis*	Surfactin	Enhanced seed germination and plant growth	Chaurasia et al. (2020)
Budu, Cincalok, Tempehm, and Tapai ubi kayu	*Bacillus subtilis*	Surfactin	Strong antibacterial activity against *Bacillus cereus* and *Klebsiella pneumoniae*	Isa et al. (2020)
Chungkookjang	*Bacillus* sp. LM7	Bacillomycin D and surfactin	Considerable inhibitory effect on *B. cereus, Listeria monocytogenes, Saccharomyces cerevisiae, Aspergillus* spp., *and Fusarium moniliforme* under a range of pH and temperature	Lee et al. (2016)
Puba	*Bacillus* sp. P5	Surfactin, iturin, and fengycin	Substantial antimicrobial activity against *Listeria monocytogenes* and *B. cereus*	Perez et al. (2017)
Traditional Chinese fermented food	*Bacillus siamensis*	Iturin	Substantial antifungal activity against *Fusarium graminearum*	Huang et al. (2022)
Kimchi	*Bacillus siamensis*	Cyclic lipopeptide MS07	Considerable antibacterial activity against both Gram-positive and Gram-negative pathogens and antibiofilm effect on *Escherichia coli* and *Pseudomonas aeruginosa*	Khan et al. (2020)
Natto	*Bacillus amyloliquefaciens*	Iturin A	Inhibitory effect against *Rhizoctonia solani* and *Fusarium oxysporum*	Murata et al. (2013)
Kanjang	*Bacillus pumilus* HY1	Iturin	Strong antifungal activities against *Aspergillus flavus* and *Aspergillus parasiticus*	Cho et al. (2009)
Soumbala and Bikalga	*Bacillus subtilis/B. cereus*	Surfactin	Antimicrobial activities	Savadogo et al. (2011)
Bikalga	*Bacillus amyloliquefaciens*	Iturin, fengycin, and surfactin	Antibacterial activity against both Gram-positive and Gram-negative bacteria and fungi	Compaoré et al. (2013)
Budu, Cincalok, Tapai, and Tempeh	*Bacillus subtilis* and *Bacillus amyloliquefaciens*	Surfactin	Strongest antibacterial activities against Gram-positive and Gram-negative bacteria particularly *B. cereus* and *K. pneumoniae*	Mohd Isa et al. (2020)
Iru and palm oil mill effluents	*Lysinibacillus fusiformis, Lysinibacillus boronitolerans*, and *Bacillus* spp.	Surfactin, fengycin, and iturin	Emulsifying and dispersing abilities	Akintayo et al. (2022)

to their perceived safety track record. To utilize bacteria from fermented foods in the production of lipopeptides, the bacteria are first isolated from the food and tested for their ability to produce lipopeptides, subsequently characterized and assessed for their technological and biological activities (Chaurasia et al., 2020; Isa et al., 2020). Chen et al. (2020) detected surfactin from *Bacillus* spp. present in Moutai liquor (a traditional Chinese fermented alcoholic drink) using ultra-performance liquid chromatography coupled with triple quadrupole mass spectrometer (UPLC–MS/MS). These authors also quantified the concentration of surfactin during the liquor production process and discovered that the surfactin concentration during the stacking fermentation stage (1524 ± 17 μg/kg) is significantly higher compared to that found in the distilled product (0.02–0.36 μg/L). A wide range of

lipopeptides have been generated by bacterial isolates found in Chungkookjang (Savadogo et al., 2011), Puba (Perez et al., 2017), Natto (Murata et al., 2013), and Soumbala and Bikalga (Savadogo et al., 2011) (Table 2). These lipopeptides were classified into the surfactin, iturin, and fengycin families. For example, *Bacillus* spp. isolated from Kinema (a fermented soybean product rich in protein, fat, and free fatty acids) produced 754 mg/L of surfactin lipopeptide (Chaurasia et al., 2020). Previous studies confirmed the antimicrobial and antioxidant activities of the lipopeptides extracted from the bacteria species found in Bikalga (Compaoré et al., 2013), African fermented food condiments (Fadahunsi, 2020), and Chinese fermented foods (Huang et al., 2022). According to Juola et al. (2014), Natto (a Japanese fermented food) contains 2.2 mg/g surfactins, hence a consumer intake would be about 80–100 mg surfactins per single 50 g Natto serving. A previous study has shown a substantial antimicrobial activity of the *Bacillus natto* TK-1 lipopeptides against *Salmonella typhimurium*, *Botrytis cinerea*, *Fusarium moniliforme*, and *Micrococcus luteus*. Other biological activities of the Natto, namely, anticancer, antioxidant, and anti-inflammatory properties, have been reported, which may be associated with its bioactive compounds such as surfactin, nattokinase, and soybean isoflavone (Afzaal et al., 2022; Cao et al., 2009), and warrant further research. Although much work has been done on lipopeptides in the last few decades, most of these studies have been focused on lipopeptides isolated from microorganisms obtained from marine ecosystems and contaminated soil and much less on microorganisms obtained from fermented foods (Table 2).

4.2 | Microbial sources of lipopeptides

Microorganisms produce different biosurfactants, among which lipopeptide low-molecular-weight biosurfactant compounds are well recognized, due to their diverse functional properties (Liu et al., 2015; Zajic et al., 1983). Bacterial species, particularly *Bacillus* spp., *Pseudomonas* spp., *Paenibacillus* spp., *Streptomyces* spp., and actinomycetes, are well-known lipopeptide producers. These bacterial species are predominantly found in soil, the marine environment, and fermented foods (see Figure 4).

However, researchers are still working to discover potential new lipopeptides from several environments that can be classified into the existing classes or a new group; for instance, xantholysins (Li et al., 2013) and bananamides (Nguyen et al., 2016), have been recently added to the lipopeptide classification. The growth curve of a bacterial culture is composed of a lag phase, exponential (log) phase, and stationary phase, followed by death (Arima et al., 1968; Rolfe et al., 2012). The biosynthesis of surfactins commonly occurs during the transition from the exponential to stationary phase, and fengycins and iturins are synthesized in the stationary phase. Hence, lipopeptides are a primary metabolite associated with cell growth (Dhanarajan et al., 2014; Vater et al., 2002).

Lipopeptide-producing Bacilli, such as *Bacillus licheniformis, B. amyloliquefaciens, Bacillus mojavensis*, and *B. polymyxa*, are mainly isolated from deep-sea sediments, fermented food, and the human gastrointestinal tract. Most of them are classified into the surfactin, iturin, and fengycin families (Pathak & Keharia, 2014) (Figure 1). Surfactin, the most studied cyclic lipopeptide, is mainly generated by *B. subtilis* (Sarma & Prasad, 2021), *B. licheniformis* (Li et al., 2010), and *B. amyloliquefaciens* (Tanaka et al., 2015). Its name is derived from its exceptional potential to lower the SFT of water from 72 to 27 mN/m with concentrations as low as 0.005% (w/v) (Shaligram & Singhal, 2010) and a CMC of 10^{-5} M (Ishigami et al., 1995). The surfactin structure is formed by incorporating a β-hydroxy fatty acid of chain length C13 to C16, into the first amino acid of the heptapeptide ring, particularly if it is *L*-Glu, as in the amino acid sequence *L*-Glu-*L*-Leu-*D*-Leu-*L*-Val-*L*-Asp-*D*-Leu-*L*-Leu. Finally, a lactone bond is formed by connecting the first and last amino acids with an ester linkage (Theatre et al., 2021). There are different variants of surfactin, namely surfactin A, B, and C, lichenysin, esperin, and pumilacidin A-F, which differ in terms of the peptide moiety and fatty acid residues (Ongena & Jacques, 2008; Zhao et al., 2017). Surfactin is the strongest biosurfactant known, as it has an excellent ability to reduce the IFT of hexadecane/water from 43 to 1 mN/m (Lang, 2002; Rosenberg & Ron, 1999). The molecular assembly of surfactin molecules in aqueous solution, or at the interface of air and water exploits the β-sheet structure, forming a horse-saddle conformation, which is believed to contribute to its broad range of biological activity (Wu et al., 2017). Similarly, different strains of *B. subtilis* produce various forms of iturin with the sequence *L*-Asn-*D*-Tyr-*D*-Asn-*L*-Gln-*L*-Pro-*D*-Asn-*L*-Ser (Isogai et al., 1982), linked to C14–C17 β-amino fatty acid (Achi & Halami, 2016). However, cyclization forms between amino acids via amide bonds. This lipopeptide was named iturin due to its first isolation from the Ituri region in Congo (Delcambe, 1952). Following this, several lipopeptides belonging to this family, namely iturin A and C1 (Stein, 2005); mycosubtilin (Peypoux et al., 1976, 1986); bacillomycin D, L, and F (Besson et al., 1977; Mhammedi et al., 1982; Peypoux et al., 1981, 1980); mojavensin A (Ma et al., 2012); and bacillopeptin (Jacques, 2011) were identified. Fengycin/plipastatin varies from the families mentioned above due to the presence of amino acids such as ornithine and allo-threonine in the sequence (Moyne et al., 2001). Fengycin is a decapeptide with a typical sequence of *L*-Glu-*D*-Orn-*L*-Tyr-*D*-Thr-*L*-Glu-*D*-Ala-Val-

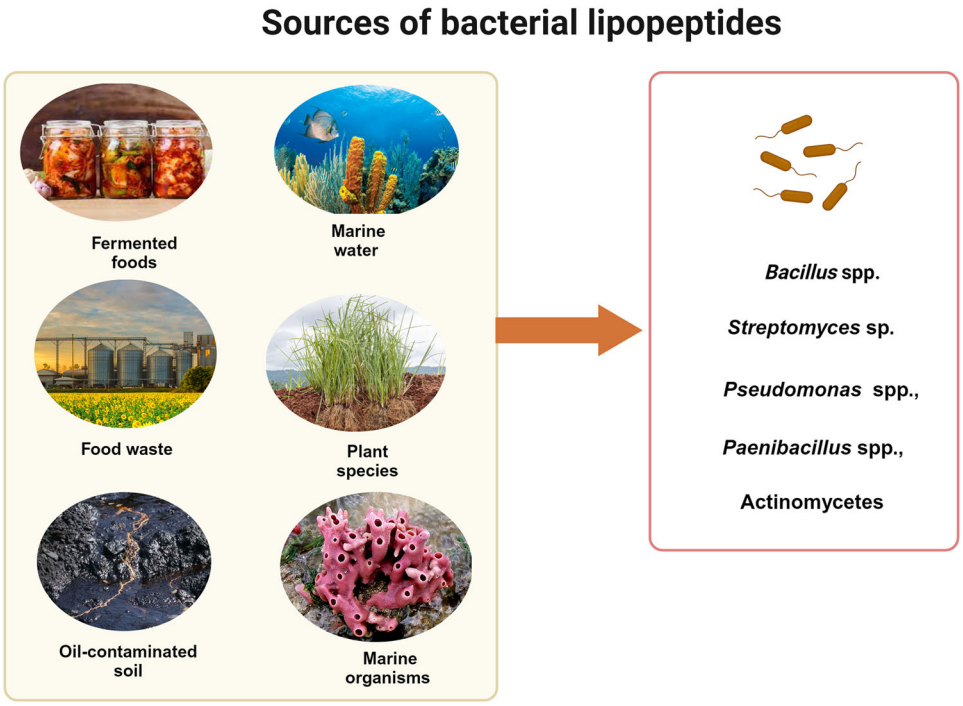

FIGURE 4 Classes of microorganisms that produce lipopeptides.

L-Pro-*L*-Gln-*D*-Tyr-*L*-Ile, linked to the β-OH of a fatty acid of chain length C14–C18 (Steller et al., 1999). The cyclization of the structure occurs when the phenol side chain of a Tyr at position 3 is connected to the C-terminal Ile at position 10 via a lactone bond. Fengycin A and B are the main variants, differing only in the amino acid type at position 6 (Tang et al., 2014). Fengycin B contains a *D*-Val at position six instead of *D*-Ala in fengycin A (Steller et al., 1999). Additionally, two new families, kurstakins (Hathout et al., 2000) and locillomycin (Luo et al., 2015), have been added to this list. *Bacillus thuringiensis* kurstaki HD-1 and *B. subtilis* 916 synthesize kurstakins and locillomycin, respectively. For the kurstakins structure, the first amino acid residues with the sequence of Thr-Gly-Ala-Ser-His-Gln-Gln was connected to a fatty acid of various chain length via an amide bond. The cyclization occurs between Ser at position 6 and the C-terminal Gln at position 7. Locillomycin is composed of Thr, Gln, Asp, Gly, Asn, Asp, Gly, Tyr, and Val, and its lactone bond is between the fourth and seventh amino acids. Only Gln is in the *D* configuration (Hathout et al., 2000; Luo et al., 2015).

In several studies, lipopeptide-producing *Pseudomonas* isolates are mainly collected from the rhizosphere, oil spills, drinking water reservoirs, and marine organisms (Arai, 2011; Raaijmakers et al., 2010). Unlike *Bacillus* lipopeptides, *Pseudomonas* lipopeptides have more diverse chemical structures. To date, 136 *Pseudomonas* lipopeptides have been identified and classified into 15 families, among which viscosins, syringomycins, tolaasins, and syringopeptins are the most abundant, and structurally are cyclic (Figure 1). Some *Pseudomonas* cyclic lipopeptides have been classified into the separate groups orfamide, amphisin, xantholysins, and putisolvin. They are formed when a linear 3-hydroxy fatty acid of chain length C5–C16 is linked to an oligopeptide of 2–25 amino acids, and is subsequently cyclized to form a lactone structure (Nybroe & Sørensen, 2004; Reder-Christ et al., 2012). Only two linear lipopeptide groups, including syringafactin and corrugatin, have been identified and exhibit limited structural differences. They are the products of plant pathogenic bacteria, such as *Pseudomonas cichorii* and *Pseudomonas corrugate*, which exhibit antimicrobial and phytotoxic activities (Berti et al., 2007; Pauwelyn et al., 2013). The minimum SFT of *Pseudomonas* lipopeptides recorded was 24.16 mN/m (Geudens & Martins, 2018). The viscosin family lipopeptides contain nine amino acids (*L*-Leu, *D*-Glu, *L*-Val, *L*-Leu, *D*-Ser, *L*-Leu, *D*-Ser, *L*-Ile, and allo-Thr) and a 3-hydroxydecanoic fatty acid, and are synthesized involving the products of three genes *viscA*, *viscB*, and *viscC*. In general, the lactone ring is usually formed between the *D*-allo-Thr at the third amino acid position and the C-terminal amino acid in the peptide chain. The first isolation of *Pseudomonas* lipopeptide is dated to 1951 and was found to exhibit an inhibitory effect on tubercle bacillus (Raaijmakers et al., 2006; Saini et al., 2008). The CMC and γCMC of viscosin were found to be 48 mmol/L and 28 mN/m (in water at 25°C), respectively (Gotze & Stallforth, 2020). The viscosin isolated from a plant pathogen,

Pseudomonas fluorescens SBW25, was found to exhibit biofilm formation, swarming motility, anti-oomycete and antiviral activities (De Bruijn et al., 2007; Raaijmakers et al., 2006). Syringomycins have a similar number of amino acids to viscosin, however, they differ in their amino acid composition, and the lipid tail of the syringomycins may be either a 3,4-dihydroxy or 3-hydroxy fatty acid of chain length C10–C14 (Raaijmakers et al., 2006). Several genes are reported to be involved in syringomycin production, including *syrD*, *syrP*, *syrC*, *syrB1*, *syrB2*, and *syrE* (Scholz-Schroeder et al., 2001).

Tolaasin is another lipopeptide that was first isolated from *Pseudomonas tolaasii*, a severe bacterial disease of edible fungi (Rainey et al., 1991). This lipopeptide is more diverse and unique than its counterparts due to differences in peptide length, ranging from 19 to 25 amino acids, and having unusual amino acids such as homoserine and 2,3-dihydro-2-aminobutyric acid (Dhb), and the type of lipid (3-hydroxydecanoic acid/3-hydroxyoctanoic acid) (Lo Cantore et al., 2006).

Daptomycin is the most well-known isolate from the soil saprotroph *Streptomyces roseosporus*. It is a calcium-dependent cyclic lipodepsipeptide with a cyclic decanoyl lipid chain linked to 13 amino acids cyclized to form a 10-membered macrolactone ring with three exocyclic residues (Isogai et al., 1982).

The most studied cyclic cationic lipopeptides are the polymyxins, which include paenibacterin, gavaserin, octapeptins, polypeptins, and fusaricidins (Grady et al., 2016). Limited linear cationic lipopeptides, such as tridecaptins, jolipeptin, and saltavalin, have been identified in the *Paenibacillus* species (Cochrane & Vederas, 2016). In 1947, polymyxins were purified from *B. polymyxa* with five diverse compounds (polymyxin A–E) (Stansly et al., 1947). Still, some years later, polymyxins were listed in the *Paenibacillus* group (Ash et al., 1993). Although polymyxins exhibit broad activity against resistant pathogens particularly Gram-negative bacteria (e.g., *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*), their application highlights the need for alternatives due to their considerable nephrotoxicity and neurotoxicity (Mohapatra et al., 2021; Wagenlehner et al., 2021). Polymyxins are composed of a cyclic heptapeptide with a tripeptide sidechain with a fatty acid acylated at the N-terminal amino acid. A connection between the carboxyl group of the C-terminal *L*-Thr residue at position 10 and the amino group of the side chain on a diaminobutyric acid (Dab) residue at position 4 generates an intramolecular cyclic heptapeptide loop. The difference between polymyxins B and E is the type of amino acid at position 6 (Yu et al., 2015).

The production of lipopeptide friulimicin (Aretz et al., 2000), amphomycin (Schneider et al., 2014), and lasparto-mycin (Wang et al., 2011) were confirmed by the activities of the actinomycetes *Actinoplanes friuliensis, Streptomyces canus*, and *Streptomyces viridochromogenes*, respectively. They consist of 10 amino acids that form a ring structure and 1 exocyclic amino acid to which an acyl residue is linked. They differ in terms of the amino acid sequence, having one to three non-conservative residues and diverse lipid tails (chain length, position of the double bond, and configuration) (Heinzelmann et al., 2003). Each family includes variants with the same peptide length but different residues at certain positions. Each variant may have various homologs resulting from diverse fatty acid chain lengths and isomers (Raaijmakers et al., 2010). Few lipopeptides have been isolated from yeasts and fungi so far. Among the most prominent were *Candida* (Diniz Rufino et al., 2014), *Aspergillus* (Yao et al., 2021), *Fusarium* (Qazi et al., 2014), and *Actinoplanes* (Aretz et al., 2000) lipopeptides.

4.2.1 | Methods for screening bacteria-originating lipopeptides

Figure 5 illustrates the production process of lipopeptides. The potential of bacterial isolates for lipopeptide production should be tested by several qualitative methods, namely, the Du-Nouy-Ring, oil displacement, drop collapse, emulsification capacity/emulsification index (E_{24}), and microplate tests, before their isolation and assessment of their biological activity. These methods are mostly based on the SFT and IFT measurements of biosurfactants.

SFT is a physical phenomenon in which a surface of a liquid is in contact with a gas phase (usually air) and acts as an elastic plate. If the surface is between two fluids (such as the interface between water and oil, or liquid and liquid), a tensile force (IFT) is observed. Lipopeptides are known to be capable of lowering the SFT and IFT at the surface and interface. In this regard, surfactin, iturin A, and fengycin at a 100 mg/L concentration in a dodecane/water environment had IFT of 2.45, 16.27, and 13.46 mN/m, respectively (Deleu et al., 1999).

The Du-Nouy-Ring technique is a direct measurement of SFT and IFT of a culture supernatant. An automated tensiometer is used to measure the force required to separate a ring/loop from an interface/surface. The main advantages of this method are accuracy and easy operation. Generally, biosurfactants are able to reduce the surface tension of a liquid to ≤40 mN/m (Dalili et al., 2015), which is substantially lower than the ST of water (72 mN/m).

The oil displacement assay is a rapid and simple method that can be used to detect biosurfactant-producing bacteria, with no requirement of complicated equipment. It just requires a small amount of culture supernatant to be placed in the middle of a thin oil layer which is formed by

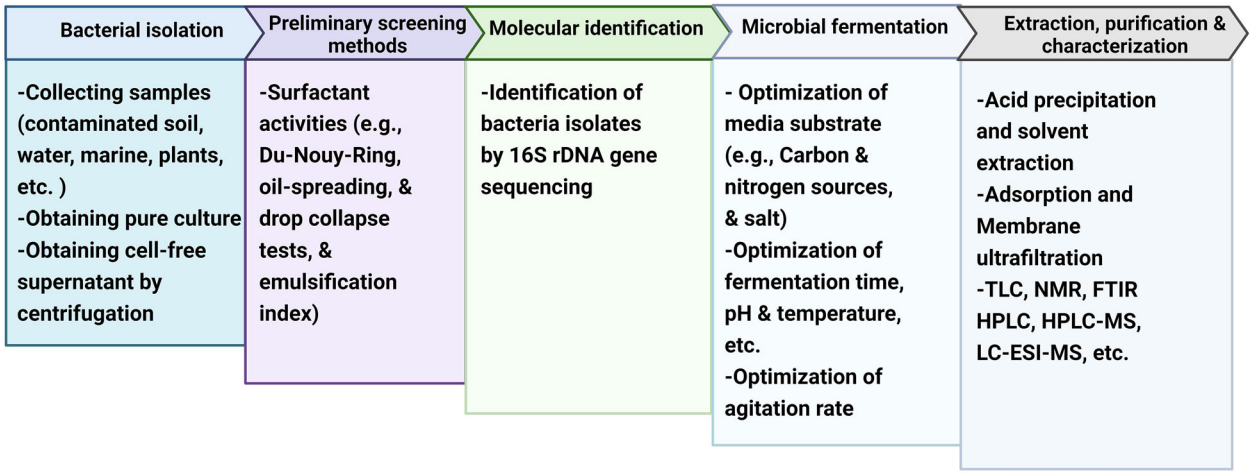

FIGURE 5 Microbial production and characterization of lipopeptides. FTIR, Fourier-transform infrared spectroscopy; HPLC, high-performance liquid chromatography; LC-ESI-MS, liquid chromatography-electrospray ionization mass spectrometry; MALDI-TOF, matrix-assisted laser desorption ionization time-of-flight mass spectrometry; NMR, nuclear magnetic resonance; TLC, thin-layer chromatography.

the addition of crude oil to the surface of distilled water. If any type of biosurfactant is present, the oil is displaced, and a clearing zone appears. There is a direct relationship between the diameter of the clear zone on the oil surface and the surface activity, hence the effect is called oil displacement activity (Walter et al., 2010).

The drop collapse test screens for the destabilization of liquid droplets by surfactants. For this purpose, a droplet of a culture supernatant, or a cell suspension, is placed on an oily surface. If a surfactant is present in the sample, the droplet collapses or spreads and is unable to retain integrity as a droplet, because the force or IFT between the hydrophobic surface and the liquid droplet is decreased. Generally, the SFT, IFT, and surfactant concentrations are important parameters in the stability of droplets. The main disadvantage of these tests is the requirement of having a considerable lipopeptide concentration in the sample to obtain an acceptable result (Walter et al., 2010).

In the E_{24} assay, a hydrophobic solution, consisting of mainly hydrocarbon liquid, such as kerosene or hexadecane, is added to the aqueous lipopeptide-containing sample and then the mixture is vortexed for a few minutes and the height of the stable emulsion layer is measured after 24 h. The E_{24} is calculated based on the ratio of the height of the emulsion layer and the total height of liquid which is dependent upon the surfactant concentration (Cooper & Goldenberg, 1987).

The microplate assay is a qualitative measurement of the surface activity of cell-free culture supernatants. In this method, 100 µL of the supernatant is transferred to a well of a 96-well plate, and then the shape formed in the plate well is observed. If biosurfactants are present in the sample, a concave surface can be observed, as opposed to a flat surface with pure water.

Polymerase chain reaction (PCR) and gene sequencing are rapid and accurate screening tools to identify microbial producers and the genes responsible for lipopeptide synthesis. This methodology can identify the genotypic and phenotypic features of the microbial isolates used for lipopeptide production (Jozala, 2017). PCR-based techniques are used to identify genes involved in lipopeptide synthesis, such as *ituC*, *itu*D, *srfAA, srfAB, fen, srfAC, bmyB, bioA, and yngG* (Wu et al., 2021; Xu et al., 2018). The principle of the method is simple, as when a unique PCR product of the 16S gene is obtained, sequenced, and aligned against a bacterial DNA database, the bacterium can be identified (Barghouthi, 2011).

With the advent of global genome mining tools, particularly Antibiotics and Secondary Metabolite Analysis Shell (anti-SMASH), it is possible to detect lipopeptide BGCs that encode NRPS and PKS enzymes using the complete sequence of bacterial isolates either available in the National Center for Biotechnology Information (NCBI) database or next-generation sequencing (NGS). These tools have been employed in recent studies to assess secondary metabolites, such as lipopeptides generated by bacterial species (Clements-Decker et al., 2022; Gutiérrez-Chávez et al., 2021). For example, Xiong et al. (2022) identified iturin A produced by *B. velezensis* isolates through identification of various ORFs (e.g., *ituD, ituA, ituB*, and *ituC*) and the promoter P_{itu} involved in the iturin A production, using anti-SMASH and BActeriocin GEnome mining tooL (BAGEL) tools. Likewise, Adeniji et al. (2019), Zhang et al. (2022), and Medeot et al. (2023)

detected several gene clusters in the *B. velezensis* genome that are involved in the synthesis of lipopeptides such as surfactin, fengycin, mersacidin, bacillibactin, and oocydin.

4.3 | Production of microbial lipopeptides

Microbial lipopeptides can be produced by fermentation using water-miscible (submerged fermentation, SmF) or immiscible (solid-state fermentation, SSF) substrates. A comparative study (Zhu et al., 2013) was conducted to determine the difference between the lipopeptides produced by SmF and SSF. The results obtained demonstrated that gene expression relating to biosynthesis of lipopeptide pathways, such as *srfAA* and *sfp*, under SSF was higher than that of SmF, but there was no substantial difference in the general structure of lipopeptides produced by these two methods. Lipopeptide production with SmF exhibited better emulsification and antagonistic properties and higher amino acid proportions, than production with SSF (Zhu et al., 2013). Similarly, surfactin production with SSF was found to be substantially higher than that with SmF. In SmF fermentation, there is a homogeneous distribution of water and nutrients on an aqueous medium that exceeds the cell growth rate, but not the production of secondary metabolites. In contrast, bacterial cell growth in SSF fermentation is considerably lower because nutrients gradually dissolve in the aqueous phase from the solid substrate, and cell growth occurs on the solid surface, which might restrict the nutritional supply to the bacteria and increase the accumulation of secondary metabolites (Ohno et al., 1995). SSF fermentation has been found also to pose a problem due to foam formation during production (Nalini et al., 2016).

4.3.1 | Submerged fermentation

Submerged fermentation is a typical process for lipopeptide production in a bioreactor controlled system. In this method, the composition and yield of lipopeptide depends on the bacteria strain, environmental conditions (pH and temperature), fermentation substrate (carbon and nitrogen sources, mineral salts, and trace elements added), oxygen availability, and agitation speed. Therefore, optimizing these parameters during fermentation can achieve enhanced biomass growth and lipopeptide production (Table 3).

The growth medium needs to contain sufficient amounts of carbon, nitrogen, minerals, and vitamins in the appropriate quantities for optimum lipopeptide production (Batista et al., 2010). Lipopeptides can be produced by bacteria utilizing a broad range of hydrophobic carbon sources; vegetable oils and hydrocarbons and hydrophilic carbon substrates; sugars (e.g., glucose, galactose, fructose, and sucrose); and carbohydrate (e.g., starch) (Mnif et al., 2012). Therefore, the type of carbon and nitrogen sources can be selected based on the microorganism used and desired lipopeptides being produced. Different carbon sources, including vegetable oils, and sucrose, were used to produce *B. subtilis* lipopeptides, but the results revealed that glucose is the best option due to its efficient uptake and utilization by this bacterial strain (Ghribi & Ellouze-Chaabouni, 2011). Glucose was found to be an excellent carbon source for production of lipopeptide by *B. mojavensis* A21 (Hmidet et al., 2017), and *B. mojavensis* I4 (Ghazala et al., 2017). An initial increase in the glucose concentration could improve lipopeptide production, but the concentration can have a negative impact on the later stage of production, which might be associated with utilization of additional glucose for bacterial cell growth, instead of lipopeptide production (Ghribi & Ellouze-Chaabouni, 2011). On the other hand, it is reported that various organic (i.e., yeast extract, tryptone, soybean flour peptone, casein acid hydrolysate, and glutamic acid) and inorganic (i.e., urea, ammonium sulfate, ammonium nitrate, sodium nitrate, and sodium glutamate) nitrogen sources can be used for lipopeptide production (Mnif et al., 2012). The obtained results from comparative studies on various nitrogen sources showed that a maximum lipopeptide yield was isolated from *B. mojavensis* A21 and *B. mojavensis* I4 in a culture containing glutamic acid (Ghazala et al., 2017) and yeast extract alone, or in combination with glutamic acid (Hmidet et al., 2017). One study maximized the yield of iturin A isolated from *B. subtilis* by using rapeseed as the nitrogen source instead of peptone and ammonium nitrate (Gu et al., 2005). More recently, research has shifted emphasis to the utilization of cheaper/renewable sources, mainly agricultural residues/agro-industrial and food wastes and food byproducts containing a large amount of carbon source, as a feasible and low-cost substitute for microbial-based conversion into biosurfactant production (Santos et al., 2017; Sharma et al., 2020; Solaiman et al., 2004). In particular, using waste frying oil can remove a large amount of waste from the environment, especially in the most populous countries, such as the United States (1.2 million tons), China (5.6 million tons), and India (1.1 million tons) (Teixeira et al., 2018). In most cases, the carbon source accounts for almost half of the total production (Rufino et al., 2007). Waste oils such as canola and olive oils, rich in saturated or unsaturated fatty acids with 16–18 carbon atoms, are a great source of carbon for bacterial fermentation (Dumont & Narine, 2007). Moreover, substantial amounts of agricultural waste, such as rice and wheat

TABLE 3 The effect of different fermentation conditions on the synthesis of microbial lipopeptides.

Organisms	Lipopeptide types	Fermentation type	Yield	Optimization tools	Fermentation conditions	Ref.
Bacillus megaterium MTCC 8280	Fengycin and surfactin	SmF	5.34 g/L	RSM	IV: 4.67%, MV: 340 mL, AG: 121 rpm	Rangarajan et al. (2015)
Bacillus subtilis THY-7 (genetically modified strain)	Surfactin	SmF	8.61 g/L	NR	T: 37°C, pH: 7, FT: ~3 D, AG: 150 rpm, C: 10% (v/v) sunflower oil and 1 g/L glycerol, N: 55 g/L ammonium bicarbonate	Jiao et al. (2017)
B. licheniformis	NR	SmF	7.8 g/L	NR	T: 37°C, pH: 7, AG: 200 rpm, C: 70 g/L sucrose, N: 1 g/L yeast extract	Jayalatha & Devatha (2019)
B. subtilis SPB1	NR	SmF	4.92 g/L	NR	T: 37°C, AG: 200 rpm, pH: 7, FT: 2 D, C: 40 g/L glucose, N: 5 g/L urea and ammonium chloride, C/N: 7	Ghribi et al. (2011)
Bacillus sp. HIP3	Surfactin	NR	5.35 g/L	NR	T: 30°C, AG: 200 rpm, pH: 7, FT: 6 D, C: 2% (v/v) cooking oil, N: 0.1 g/L yeast extract and 7 g/L $NaNO_3$ (7.0)	Md Badrul Hisham et al. (2019)
Brevibacterium aureum MSA13	Brevifactin	SSF	18 g/L	RSM	T: 30°C, pH: 7, FT: 6 D, C: olive oil and pre-treated molasses, N: 2% acrylamide, MC: > 80%, C/N: 0.5	Kiran et al. (2010)
Aneurinibacillus thermoaerophilus MK01	NR	NR	6.75 g/L	RSM	T: 45°C, AG: 200, FT: 4–7 D, C: 28 g/L sunflower oil, N: 3.8 g/L sodium nitrate, 1.25 g/L yeast extract	Sharafi et al. (2014)
B. megaterium	NR	NR	6.58 g/L	ANN + PSO	T: 33.3°C, pH: 6.7, FT: ~ 2 D, AG: 458, AR: 128 L/h C: 30 g/L noodle processed water supplemented with chemical fertilizers, N: 4.5 g/L urea	Dhanarajan et al. (2014)
B. licheniformis NIOT-AMKV06 (genetically modified strain)	NR	NR	11.78 g/L	NR	T: 38°C, pH: 7, FT: 2–7 D, C: glucose up to 4% (w/v), N: yeast extracts, NaCl: 1.5% (w/v); HS: 1%–2.5% (v/v) crude oil	Lawrance et al. (2014)
Candida lipolytica UCP 0988	NR	NR	8 g/L	NR	C: 6% (v/v) waste soybean oil, N: 1% (w/v) glutamic acid, pH: 7, FT: 2 D	Diniz Rufino et al. (2014)
Serratia marcescens UCP 1549	NR	SSF	52.0 g/kg dry substrate	NR	C: 5 g wheat bran and 5% (w/v) waste soybean, N: 1 g/L ammonium sulfate, T: 28°C, FT: 5 D	Dos Santos et al. (2022)

(Continues)

TABLE 3 (Continued)

Organisms	Lipopeptide types	Fermentation type	Yield	Optimization tools	Fermentation conditions	Ref.
B. cereus SNAU01	NR	SSF	NR	RSM	C: 8.18 g/L peanut oil cake, pH: 7, T: 30°C	Nalini et al. (2016)
Pseudomonas sp. OXDC12	NR	NR	1.17 g/L	RSM+ OFAT	C: ~0.003 g/L, glucose, N: ~0.003 g/L yeast extract, FT: 2.5 D, T: 32.5°C	Chauhan et al. (2021)
Pseudomonas sp. DSS73	Amphisin	NR	16.51 g/L	RSM	C&N: 6.6% black cumin cake, Salt: 8.0 mM, FT: 6.5 D	Ciurko et al. (2023)

Abbreviations: AG, agitation rate; AR, aeration rate; C, carbon source; D, day; FT, fermentation time; IV, inoculum volume; MC, moisture content; N, nitrogen source; NR, not reported; OFAT: one factor at a time; RMS, response surface methodology; SmF, submerged fermentation; SSF, solid-state fermentation.

straw, are being produced worldwide, most of which are discarded by open air burning, leading to substantial financial and environmental implications (Panjiar et al., 2020). One of the best strategies to manage such wastes might be converting wastes containing a range of fatty acids, such as oleic, linolenic, and linoleic acids, into value-added products such as lipopeptides (Pathania et al., 2022). Several studies have used different waste frying oils, particularly sunflower and rice bran oils (Vedaraman & Venkatesh, 2011), kitchen waste oil (Chen et al., 2018), as well as a combination of waste frying oil, steep corn liquor, and molasses (Almeida et al., 2017), to produce diverse biosurfactants. In a study by Das and Kumar (2019), a soil bacterium, *Bacillus safensis* J2, was found to produce 0.92 g/L surfactin by utilizing bagasse as the sole carbon source. The isolated lipopeptide exhibited good stability to various environmental stresses, emulsification properties, and enhanced oil recovery efficiency. Verma et al. (2020) utilized sugarcane molasses (a byproduct of the sugar cane industry) as a sole carbon source, to produce lipopeptides from *B. subtilis* RSL-2. Strain RSL-2 grown in 5 % (w/v) molasses produced 12.34 g/L of lipopeptides. Molasses is an ideal substrate choice for microorganisms for lipopeptide production because it is a rich source of dry matter, proteins, no organic sugar matter, minerals, and other components (Marcelino et al., 2019). In general, oils are hydrophobic and have low water solubility, which prolongs their resistance to degradation and consumption by microorganisms. For example, in a comparative study, after 24 h of *B. subtilis* MTCC2423 culture for surfactin production, the glucose concentration of the growth media considerably decreased, while the concentration of waste frying sunflower oil and waste frying rice bran oil decreased by only 20%. Once the surfactin production started, the oil consumption increased, possibly due to the increasing cell surface lipophilic nature (Vedaraman & Venkatesh, 2011). *B. subtilis* BDCC-TUSA-3 produced a maximum concentrations of surfactin (36.1 g/L) and cell biomass (31.8 g/L) by utilizing 204 g Maldex-15 (a byproduct of fructose syrup) (Amin, 2014). Mnif et al. (2021) found that an optimum lipopeptide yield was produced by *B. mojavensis* BI2 when cultured in a growth medium containing 25% leugmi/date juice (as a C and N source) in 0.1% Na_2HPO_4 during a 24 h incubation. Similarly, *Bacillus* sp. HIP3 cultivated in a cooking oil substrate could produce 5.35 g/L surfactin (Md Badrul Hisham et al., 2019). The lipopeptide produced, which ranged from 1.88 to 2.25 g/L, were isolated from *Bacillus stratosphericusx* FLU5 grown on olive oil, corn oil, and residual frying oil as carbon sources in the culture medium at 37°C, shaken at 180 rpm for 10 days (Hentati et al., 2019). It should be noted that the use of different microorganisms and substrates can have a major impact on the rate of lipopeptide production.

For example (Oliveira & Garcia-Cruz, 2013), reported that the highest yield of biosurfactant obtained from *Bacillus pumilus* (20.4 and 27.7 g/L) was achieved using 5% vinasse (a byproduct of ethanol production) as the carbon source, after 24 and 48 h of fermentation at pH 7.0 and 37°C, which is much faster than the study reported by Hentati et al. (2019). Apart from the sources of carbon and nitrogen used, the carbon–nitrogen ratio remarkably affects microbial growth, and the nature of and production of lipopeptides (Mnif et al., 2012; Sen, 1997). A high carbon to nitrogen ratio restricts bacterial growth but promotes cell metabolism for metabolite production (Nurfarahin et al., 2019). Trace elements and divalent cations such as copper, nickel, magnesium, manganese, zinc, and iron are critical parameters in producing lipopeptides. For instance, it is reported that the addition of Mn to the culture medium can increase the lipopeptide yield rates from 0.33 to 2.6 g/L (Wei & Chu, 2002).

An average culture agitation speed of 150 to 200 rpm results in considerable production of lipopeptides, as oxygen is another critical parameter in lipopeptide synthesis. In a study by Rangarajan et al. (2015), oxygen availability in relation to lipopeptide production was assessed by optimizing three parameters: medium volume, agitation speed, and inoculum volume. The results revealed a direct relationship between oxygen availability and fengycin production yield.

4.3.2 | Solid-state fermentation

Recently, SSF has been receiving increased attention due to advantages such as a shorter time required for fermentation, cost of production, and energy requirement, as well as higher lipopeptide yields and simplicity of the method (Jozala, 2017; Zhu et al., 2014). With a long history of food production by diverse microorganisms, this fermentation technique has extended its applications in production of antibiotics, enzymes, biocides, and biosurfactants. In this method, microorganisms grow on a moist solid substrate, namely agro-industrial wastes, in the absence of free water, which can reduce production costs and produce a diverse range of molecules. Producing a smaller volume of effluent is another essential advantage that makes it possible to perform the process in non-sterile conditions (Farinas et al., 2011). The SSF is commonly used when the production of some enzymes and secondary metabolites is insignificant using SmF. The yield of diverse compounds achieved by this technique is usually considerably higher than that obtained by SmF because the growth conditions provided for bacteria are very similar to that of their natural habitats (Castilho et al., 2000). A comparative study found that more lipopeptide yield was obtained from *B. pumilus* UFPEDA by SSF than by SmF (Slivinski et al., 2012). Despite the above-mentioned benefits of SSF, its application at an industrial scale is still challenging. It would be difficult to control all the variables required for optimal fermentation, particularly temperature and humidity. Because microbial fermentation under aerobic conditions generates heat, which can negatively affect metabolism and growth of the microorganisms. In a flowing water free environment, removing this extra heat is challenging, and one effective way is by evaporation cooling, which itself leads to drying of the culture growth (Farinas et al., 2011). As with SmF, the quantity and quality of lipopeptides synthesized by SSF depends on several physical and chemical parameters, such as fermentation time, incubation temperature, initial moisture content, substrate components, inoculum size, and supplementary nutrients (mineral salts and metals) (Sharma & Arora, 2010). Based on the substrate composition, the maximum concentration of lipopeptides is normally achieved over a certain fermentation time. Once the maximum production time is reached, the lipopeptide concentration is found to decrease (Zhu et al., 2014). The maximum lipopeptide production produced by *Bacillus* spp. was commonly achieved after 48 h of fermentation (Table 3).

The optimum temperature for any type of bacterium is within a relatively specific range, at which the bacteria species perform most effectively. Although increasing the temperature accelerates microbial metabolism and increases the speed of chemical reactions, but above a certain level can impede bacterial growth and metabolic processes. As shown in Table 3, the optimal temperature for growth and biosynthesis of most lipopeptides is between 30 and 40°C. Thus the fermentation temperature needs to be managed to enable maximum bacterial growth and subsequent biosynthesis of lipopeptides. Most studies have been conducted at 30 to 37°C for production of lipopeptides by *Bacillus cereus* (Nalini et al., 2016), *S. canus* (Fu et al., 2015), *B. subtilis* (Ghribi et al., 2012), and *Brevibacterium aureum* (Kiran et al., 2010). Zhu et al. (2014) studied the effects of isothermal and non-isothermal temperature on lipopeptide production by *B. amyloliquefaciens* XZ-173 using SSF. The results showed a maximum lipopeptide yield of 55.83 mg/gds (per g dry substrate) after 44 h of culture, when the fermentation temperature was adjusted to 30°C for maximum bacterial growth, and then later in the fermentation the temperature was increased to 37°C for lipopeptide production. The 7°C increase in temperature improved the bacterial activity and accelerated transformation of the substrate, while still resulting in cell division and lipopeptide production. A lower yield of 50.1 mg/gds was obtained in fermentations that were maintained at 30°C for the whole fermentation process.

Another major factor that should be paid attention to is using an appropriate solid substrate in relation to its cost and availability. Agro-industrial byproducts such as peanut oil cake (Nalini et al., 2016), molasses (byproducts of the sugar production), ground nut oil cake, rice bran (Kiran et al., 2010), and wheat bran (Dos Santos et al., 2022), have been used as carbon sources in many studies due to their containing high levels of carbohydrates, protein, and lipids (Table 3). In a comparative study, several solid substrates, such as potato peel, millet, barley flour, barley bran, orange peel, banana peel, chickpea flour, soya meal, corn starch, rice flour, and soya bean meal, were used to produce biosurfactant by *B. subtilis* SPB1. The highest biosurfactant yield (14.5 mg of biosurfactant per g of the substrate) was achieved using millet as a substrate and 24 h of fermentation (Ghribi et al., 2012). One of the critical issues of using solid materials is their tendency to form a compact mass during SSF, which leads to reduced productivity even at a small scale and hinders heat and mass transfer processes in the bioreactor. To tackle this issue, Slivinski et al. (2012) added sugarcane bagasse as bulking agent to Okara as substrate to reduce compacting of the solid medium, as well as employing a pre-hydrolysis step with the Okara to increase the availability of free amino acids in the culture. This process was found to increase surfactin production to 6.5 g/kg dry solids from *B. pumilus*, which was twice as much as that reported by Ohno et al. (1995), which might be due to an increase in porosity caused by the addition of bulking agent. The effect of the pre-hydrolysis step on lipopeptide yield was insignificant due to the relatively high production of proteases during SSF (Slivinski et al., 2012). For example, 18.1 g/L lipopeptide was produced by the marine actinobacterium *B. aureum* MSA13 using SSF with pre-treated molasses, olive oil, and acrylamide (Kiran et al., 2010). Inoculum size and pH can affect lipopeptide-producing strains. Reduction in inoculum density may result in the production of insufficient biomass to inhibit the growth of unwanted organisms. Conversely, the inoculum density should not be too high as the biomass may deplete nutrients rapidly, leading to hindering production of lipopeptide. An optimal inoculum size was found to be 2.5 mL based on a response surface methodology (RSM) model (Nalini et al., 2016).

4.3.3 | Strategies for optimizing microbial lipopeptide yields

To determine optimal levels for the factors affecting the production of lipopeptides and their properties, it is required to evaluate experimental designs. To control the number of repetitions, an appropriate statistical analysis such as RSM, or artificial neural network (ANN), can be useful (see Table 3) to optimize the fermentation process along with saving time and resources, leading to better lipopeptide yield (Zhang et al., 2010).

RSM is a collection of applied mathematics and statistical techniques for modeling multivariate experiments such as lipopeptide production. It is used to predict the optimum range of independent variables, which leads to reducing the number of tests and maximizing the lipopeptide yield and productivity. First, a Plackett–Burman design (PBD) is applied to detect the most influential factors, namely substrate composition (e.g., C and N sources) and production conditions (e.g., pH, temperature, and agitation rate) on lipopeptide synthesis. Then a central composite design (CCD) is applied to detect the optimum level for each factor, and the interactions among factors are used to construct a RSM to obtain the optimum conditions for production. In most studies, the predicted conditions for maximum yield were verified experimentally (Mohana et al., 2008). A maximum production of lipopeptide (3.1 g/L) by *B. subtilis* SPB1 was obtained using RSM coupled with PBD under a medium composition of 15 g/L glucose, 7.5 g/L urea, and 1 g/L K_2HPO_4, which was twice as much as the original production reported (Mnif et al., 2012). The same authors could successfully obtain a lipopeptide product from a *B. mojavensis* BI2 fermentation, with the highest ST and oil dispersing activity (ODA), under optimum factors of 25% date juice (leugmi) (as C and N sources), 0.1% Na_2HPO_4 and incubation time of 24 h, using RSM based on a Box–Behnken design (BBD) (Mnif et al., 2021). Rangarajan et al. (2015) reported a maximum fengycin production (5.34 ± 0.1 g/L) by a *Bacillus megaterium* MTCC 8280 isolate through optimizing processing factors that included 340 mL medium volume (in 1 L conical flask), 4.67% (v/v) inoculum volume, and 121 rpm agitation speed, which resulted in about a two fold increase in lipopeptide production, compared to the original unoptimized production process. Likewise, 28 g/L sunflower oil, 3.8 g/L sodium nitrate, and yeast extract 1.25 g/L, were the optimum medium concentrations that resulted in a 6.75 g/L lipopeptide (*Aneurinibacillus thermoaerophilus* MK01 isolate) yield (Sharafi et al., 2014).

ANN is a type of artificial intelligence that can be used to model nonlinear systems, simulate the chaos bioprocess, and predict outputs. In this method, the human brain learning pattern is simulated using several neurons. The neurons are classified into several hidden layers linked by synapses called weights (Schlusselhuber et al., 2018; Sivapathasekaran & Sen, 2013). It has several advantages over the RSM due to having an overwhelming ability to manage nonlinear situations between independent variables and responses (Patel & Brahmbhatt, 2016). In a study by Peng et al. (2014), an ANN-GA model based on a uniform design (UD) was employed to enhance the iturin A

yield from *B. subtilis* ZK8. The optimum yield of iturin A (titer measurement, reflecting the antibiotic activities of this lipopeptide) was 13364.5 ± 271.3 U/mL. It was obtained by adding 0.155 g/L asparagine, 0.32 g/L glutamic acids, and 0.16 g/L proline under fed-batch fermentation, as compared to a yield of 9929.0 ± 280.9 U/mL for the unoptimized experiment. Furthermore, lipopeptide production by a *B. megaterium* isolate (6.58 ± 0.32 g/L) was significantly improved through optimizing the fermentation conditions (pH = 6.7, temperature = 33.3°C, agitation rate = 458 rpm, and aeration rate = 128 L/h) using ANN coupled with a particle swarm optimization (PSO) algorithm (Dhanarajan et al., 2014).

Genetic modification strategies are considered as another promising approach to enhance the production of lipopeptides. Various approaches encompassing precursor availability, knockout of lipopeptide degradation pathways, and manipulating promoters are employed to optimize lipopeptide production (Pilz et al., 2023). Increased lipopeptide titers involve precursor-derived strategies, such as feeding amino acid precursors, such as leucine or lipids, which demonstrated an up to a 20-fold increase in surfactin production (Wu, Zhi, et al., 2019). As the promoter plays a crucial role in gene expression regulation of lipopeptide synthesis, several studies have focused on modifying and substituting promoters. For instance, Dang et al. (2019) improved the transcription of the iturin A biosynthetic genes by inserting a robust constitutive promoter upstream of the *itu* operon. This modification resulted in the production of iturin A at a level of 37.35 mg/L. Jiao et al. (2017) successfully achieved a substantial increase in surfactin production by designing a synthetic promoter (P_{g3}) based on the P_{groE} promoter (as a native srfA promoter) in *B. subtilis* THY-7. As a result, the surfactin production reached 8.61 g/L, which was a substantial 15.6-fold increase compared to the wild-type strain. Furthermore, other studies have used the knockout technique to eliminate certain genes, resulting in varying degrees of upregulation of the expression level of other genes responsible for lipopeptide biosynthesis, as compared to the original strain. In this regard, Sun et al. (2018) maximized the production of bacillomycin D by ~40% via knocking out the *rapC* gene from the genome of *B. amyloliquefaciens* fmbJ using a marker-free biological technique. Similarly, the elimination of certain genes, such as *kinA* and *bdh*, from the genome of *B. amyloliquefaciens* WH1 increased the iturin titer to 17.0 mg/L, which was more than three times higher than that of the wild strain (Wan et al., 2022). In addition, the cloning of bacillomycin D gene cluster from *B. amyloliquefaciens* FZB42 to *B. subtilis* 1A751 using the Red/ET recombineering system could improve lipopeptide production (Liu et al., 2016). Red/ET recombineering has been proven to be a potent technique in the manipulation and replication of biosynthetic pathways involved in natural product synthesis (Abbasi et al., 2020).

5 | EXTRACTION, PURIFICATION, AND CHARACTERIZATION OF LIPOPEPTIDES

In the production process of biosynthetic products such as lipopeptides, a fermenter or bioreactor is used in the upstream processing, and the extraction, recovery/purification of the lipopeptides are in the downstream processing, which accounts for 60% of the total production cost. Therefore, the need to pay attention to downstream processes is economically important. Diverse chemical and physical methods can be used to obtain crude lipopeptides (see Table 4), with acid precipitation and foam fractionation being mostly used due to their cost-effectiveness. Most studies have used a combination of acid precipitation and solvent extraction for the extraction of lipopeptides (Hu et al., 2022).

5.1 | Extraction of lipopeptides

Acid precipitation is the oldest technique for lipopeptide purification. The first step is to separate the broth from the cell material by centrifugation and subsequent acidification (pH 2.0) of the supernatant with hydrochloric or sulfuric acid (Coutte et al., 2013). The precipitation is carried out overnight at 4°C, then the lipopeptides are isolated using organic solvents after obtaining the supernatant by centrifugation (Arima et al., 1968). Acid precipitation results in a relatively high recovery rate, but multiple extraction steps are required to achieve a product of reasonably high purity (Coutte et al., 2013).

Solvent-free/foam fractionation method separates the lipopeptides attaching to air bubbles from the culture medium. It endows a biosurfactant-rich solution, and subsequently decreases the volume of the product to be handled. This technique has been carried out in two different ways (Winterburn et al., 2011). The first is as an integral step of the biosurfactant production process, which provides a constant foam fractionation process, but a decrease of biomass concentration in the fermenter may occur due to uncontrolled foaming. The second way is in a sequential operation after the biosurfactant production, which has a module of foam fractionation separate from the fermenter, so it overcomes the foaming problem.

The physical extraction and enrichment of a specific compound from a mixture with the help of solvent is called "solvent extraction." Several factors such as pH, the type and concentration of the solvent, temperature,

TABLE 4 Techniques used for the extraction of lipopeptides.

Extraction and purification methods	Advantages	Disadvantages	Lipopeptides	Ref.
Acid precipitation	Simplicity, affordability, large quantities	Using multiple extractions	Fengycin and surfactin	Rangarajan et al. (2015) and Wei et al. (2010)
Solvent extraction	Large quantity recovery, partial purification, reuse of organic solvents	Expensive, high toxicity High selectivity due to the level of hydrophobicity and the nature of the solvent	*Stenotrophomonas* sp. IE-93 lipopeptides Surfactin, *Candida lipolytica* lipopeptides	Diniz Rufino et al. (2014), Karbalaei-Heidari et al. (2019) and Loiseau et al. (2015)
Acid precipitation and solvent extraction	Considerable productivity	Time consuming	Iturin, bacillomycin F surfactin, and fengycin	Hazra et al. (2015), Jemil et al. (2017) and Xu et al. (2018)
Reverse micellar systems	More economical and effective, high purity	Time consuming	Surfactin	Juang et al. (2012)
Ultrafiltration	Minimization of toxic compounds, increased production, reduced lipopeptide loss	Complicated pre-treatment processes, easily block the membrane, risk of fouling	Surfactin and mycosubtilin	Coutte et al. (2013), Hu et al. (2022), Kourmentza et al. (2021) and Lin & Jiang (1997)
Foam extraction and fractionation	Highly purification of lipopeptide product, best method for continuous retention process	High risk of contamination, possibility of culture medium loss	NR	Hu et al. (2022)
Adsorption	High production with considerable purification, reusable resin, fast approach, less degradation of product	Necessary use of organic solvents for desorption, high cost	*Streptomyces amritsarensis* lipopeptide, surfactin, iturin, and fengycin	Dhanarajan et al. (2015), Ines & Dhouha (2015), Sharma et al. (2014) and Wang et al. (2010)
Extraction–back extraction	Low energy consumption, equipment, and waste Low or no acid or alkali consumption. In addition, organic solvents, reusable	NR	NR	Hu et al. 2022)

Abbreviation: NR, not reported.

speed, and duration of the agitation are considered critical parameters in liquid-–liquid lipopeptide extraction (Mnif et al., 2013). Common organic solvents that have been used, either alone or in combination are acetone, ethanol, butanol, methanol (Mnif et al., 2013), chloroform, ethyl acetate, *n*-hexane, dichloromethane, or mixtures of chloroform–methanol (Khondee et al., 2015. Chloroform is highly toxic, not only harmful to the environment but also can have many adverse effects on human health. Instead, other solvents such as ethyl acetate (polar solvent) and *n*-hexane (non-polar solvent) have been employed (Karbalaei-Heidari et al., 2019). Dimkić et al. (2017) compared the type and yield of lipopeptide (from *Bacillus* spp.) obtained by ethyl acetate extraction, and by acid precipitation followed by methanol extraction. The results revealed that higher yield and more diversity of lipopeptides were achieved by ethyl acetate extraction.

The purity of surfactin when using acid precipitation alone was 53% (Chen & Juang, 2008b). A higher recovery (up to 78%) and increased purity (about 84%) can be achieved by repeated solvent extraction using ethyl acetate. Improved recovery (92%) was achieved by adding 5 mM tri-n-octylmethylammonium chloride (Aliquat 336) surfactant to *n*-hexane (Chen & Juang, 2008b). However, this approach is not useful for lipopeptide production since the possibility of irreversible degradation of the product and loss of its bioactivity due to partition into organic solvents and low purity. To resolve this issue, reverse micellar systems have been proposed (Mohd-Setapar et al., 2009), where high selectivity with minimal change in the nature and biological activity of the molecule, high efficiency, low energy requirement, and the possibility of continuous operation can be obtained. The method is carried out as steps of extraction (forward step) and stripping (backward extraction). In the forward extraction, a targeted product

such as protein and lipopeptide, moves from a liquid phase to a reverse micellar organic phase. Then, the target product is released from the reverse micellar phase and is transferred into an aqueous phase where the product can be easily recovered. The partition of the product between these two phases depends upon various factors, such as the pH and ionic strength of the aqueous solution (Zhao et al., 2010). Juang et al. (2012) reported that the reverse micellar extraction method improved the extraction efficiency of surfactin (3 g/L) to 92% compared to 70% using a batch stirred ultrafiltration (UF) process. The authors used two surfactants, 40 mM tri-n-octylamine and 5 mM Aliquat 336. In another investigation (Chen & Juang, 2008a), a microporous polyvinylidene fluoride (PVDF, pore size 0.2 μm) hollow fiber membrane, was used to enhance the extraction of surfactin from *B. subtilis* ATCC 21332 by *n*-hexane to avoid the foaming behavior and the formation of stable emulsions during extraction. Another strategy proposed to enhance the recovery of lipopeptides is the use of ultrasound treatment. In a study by Yuan et al. (2012), the authors reported substantial improvement (by 78%) in the recovery of iturin (*B. amyloliquefaciens* NJN-6) through the application of ultrasound-assisted extraction (8 min, 200 w). However, it was found that impurities are also extracted during the extraction process, so a further purification step, mainly using chromatography, is required to achieve higher purity (Peypoux et al., 1999).

5.2 | Purification of lipopeptides

Adsorption is an interesting method that is greatly influenced by the physicochemical properties of molecules such as lipopeptides. The commonly used adsorbents are macroporous resins (MAR) (Dhanarajan et al., 2015), activated carbon (Montastruc et al., 2008), and silica (Sharma et al., 2014), that have been used for the isolation of fengycin, surfactin, and an antimicrobial lipopeptide from *Streptomyces amritsarensis*. In recent years, the use of MAR has gained increasing attention due to the high non-polarity, adsorption and desorption abilities, and accessible regeneration capacity of the resin. The mechanism of MAR is based on hydrophobic/hydrophilic interactions between solute and resin surfaces (Ma et al., 2013). The use of a strong polar silica gel is challenging, because the amphiphilic behavior of the lipopeptides leads to rapid formation of micelles in a normal aqueous phase (Rangarajan & Clarke, 2016). In this type of purification, the separation is based on the difference in the surface adsorption of the mobile phase (involving a solvent such as hexane), and the stationary phase (such as silica gel). The mobile phase carries the components by passing through the stationary phase. The speed of movement of each component depends on the surface adsorption capacity of the stationary phase. In this way, the velocity of the low-adsorption compounds will be higher than that of the highly adsorbed material, and the components that are more adsorbable will be adsorbed at the top of the column, and the less absorbable objects will be adsorbed later in the column. Here, parameters such as adsorption and desorption ratios, thermodynamic functions (Gibbs free energy, enthalpy, and entropy), eluent flow rate and composition, and sample loading should be considered (Rangarajan & Clarke, 2016). In a comparative study, X-5, a non-polar resin, showed the highest adsorption capacity of lipopeptides obtained from *B. amyloliquefaciens* ES-2 among its counterparts (e.g., ADS-7, HPD-450, and HPD-600) (Wang et al., 2010). Dhanarajan et al. (2015) compared the purification and recovery of three lipopeptides (surfactin, iturin, and fengycin) when employing various macroporous adsorption resins for chromatography, including XAD-4, HP-2MG, HP-20, and XAD-7, along with different pH ranges and solvent composition. The highest purification and recovery was achieved for all three lipopeptides when HP-20 was used (because of its lower polarity and its higher surface area). Moreover, the optimum mobile phase for iturin was pH 4 and 40% acetone, for fengycin was pH 4 and 65% acetone, and for surfactin was pH 8 and 95% acetone.

Membrane ultrafiltration can achieve a level of purity by reducing the contents of low-molecular-weight impurities. This separation is supported by the ability of lipopeptides to produce micelles in water, which helps to separate lipopeptides from other products. Membrane ultrafiltration can be performed in a single process that removes low-molecular-weight impurities or it can be carried out in different steps that target low- and high-molecular-weight impurities, achieving considerable enrichment purification (Rangarajan & Clarke, 2016). Factors that must be considered to optimize this method include: type and molecular weight cut-off (MWCO) of the membrane, pH, retentate and permeate fluxes, and trans-membrane pressure (Sen & Swaminathan, 2005). In this case, several researchers have reported that they could successfully purify surfactin and mycosubtilin using membranes with a MWCO of 10 to 100 kDa (Coutte et al., 2013; Jauregi et al., 2013).

5.3 | Characterization of lipopeptides

The primary structure analysis of lipopeptides can be classified into parts: (1) analysis of the peptide and the fatty acid components and (2) comprehensive and compositional analysis of the lipopeptide component, especially the amino acid composition and sequence (Liu et al., 2007).

Chromatographic techniques such as thin layer chromatography (TLC), and high-performance liquid chromatography (HPLC), are two techniques often used for the preliminary identification and quantification of lipopeptides. For evaluation of lipopeptides by TLC, aliquots of the cell-free culture supernatants can be applied to silica gel plates and the components separated to obtain information on the biosurfactant production, and the separated components can be used to contribute to characterization of the chemical nature of the biosurfactant. Peptides can be detected on TLC as pink spots using the ninhydrin reagent. In the presence of iodine vapor lipids stain yellow on TLC. Both of these indicators can contribute to identification of a lipopeptide (Alajlani et al., 2016).

Based on the research reports available on PubMed, Fourier-transform infrared spectroscopy (FTIR) technology was first used in 1972, and has been further developed over the years (Fadlelmoula et al., 2022). This method can determine the chemical bonds and functional groups present in compounds. FTIR has been used to analyze many lipopeptide compounds, including surfactin (Sivapathasekaran et al., 2010), and iturin (Kumar et al., 2009). The intensity and position of the different IR bands can be analyzed to determine the presence of functional groups, or their protonation states. The various aspects of the spectrum and the peak assignments of the different compounds are used in the analysis of the FT-IR spectra of lipopeptides. These are useful in identifying the functional groups and the chemical properties of the compounds (Kong & Yu, 2007; Socrates, 2004). A typical FTIR system consists of a source, an interferometer, a detector, a computer, an amplifier, and a sample compartment. The radiation source passes through the sample and reaches the sensor through an interferometer. It then generates a signal that is amplified and then converted to digital using a digital converter. The signal is transmitted to a computer that performs the Fourier transform. This technique has various advantages, such as its ability to perform non-destructive analysis and retain the structure of the compounds. In addition, it can be easily performed and is a simple and inexpensive technique. However, the results might be influenced by certain environmental conditions. To overcome this issue, background scans and repeated scans of the same sample are required and choosing to perform analysis of an appropriate purification step (Biniarz et al., 2017).

Nuclear magnetic resonance (NMR) involves studying the absorption of radio frequency radiation by nuclei. NMR can generate valuable information about the structure of molecules in solution with a high resolution. Structural characterization using this method involves: (1) creating suitable conditions for recording spectra, (2) estimating a series of 1D (1H and 13C) or 2D (e.g., COZY, TOCSY, and ROSY) NMR spectra, and (3) merging cross peaks and conversion to upper distance ranges, and finally, the quality of the molecule structure is estimated. The samples are mixed with the reference compound solution, such as tetramethylsilane dissolved in DMSO-d6 for 1H NMR, adding to an NMR probe (in generally less than 2 mL), insertion into the instrument, and generating the NMR spectrum for analysis. This technique is useful to provide information for lipopeptide structure characterization of both the fatty acid and peptide components, along with providing information about the position of the linkage between these moieties. In this case, purified lipopeptide is first dissolved in deuterated chloroform, and a series of 1D and 2D NMR experiments are conducted. The obtained data are drawn from the NMR spectrum which relies on the impact of shielding by electrons orbiting the nucleus. Chemical shifts in the spectrum represent components of the molecular structure. The chemical shift for 1H NMR is determined as the difference (in ppm) between the resonance frequency of the observed proton, and that of a reference proton present in a reference compound set at 0 ppm (Biniarz et al., 2017).

A widely used tool for peptide analysis is HPLC. Lipophilic compounds such as lipopeptides can conveniently be separated, quantified, and analyzed using reversed phase HPLC (RPHPLC). The columns for RPHPLC have an aliphatic carbon chain coated hydrophobic stationary phase which interacts with hydrophobic regions of solute molecules. Bound compounds are sequentially eluted from the RPHPLC column with a gradient of organic solvent, which can be very effective at separating compounds based on differences in hydrophobicity. Peak detection of components can be achieved using ultraviolet (UV) absorbance, and components can be collected in fractions for further analysis. A commonly used mobile phase is methanol:water (80:20) for fractionation of lipopeptides, such as fengicins and iturins. Another mobile phase, acetonitrile:water, has been used for surfactins. Typically, C-18 aliphatic carbon chain coated RPHPLC columns of 150−250 mm length have been used for lipopeptide fractionation, with a stationary phase particle size of 5 μm (Yang et al., 2015).

HPLC-MS analysis was conducted to identify the differentially produced molecules by referencing their molecular weights in the MS database. In particular, the detection of lipopeptides/peptides using UV alone can be challenging due to co-elution caused by their similar chemical properties. However, coupling HPLC with a mass spectrometer (MS) allows for the acquisition of preliminary information regarding the molecular mass of each component. In such cases, (HP)LC-MS is considerably more useful in determining whether co-elution is taking place (McGenity et al., 2016; Rabbee & Baek, 2023).

Matrix-assisted laser desorption ionization time-of-flight MS (MALDI-TOF) has been used for identification of various lipopeptides. A sample is mixed with a matrix and then dried on a stainless-steel target plate, and a laser beam incident on the target volatilizes the compounds forming gaseous ions, which can be separated by time of flight (TOF) in a magnetic field and detected (Sajitha et al., 2016; Urajova et al., 2016). In a study using MALDI-TOF MS to analyze lipopeptides purified from *B. amyloliquefaciens* An6, surfactin, fengycin, and bacillomycin were able to be detected and identified (Ben Ayed et al., 2017), and similarly surfactin isolated from *B. mojavensis* was able to be identified (Fanaei & Emtiazi, 2018). The lipopeptide biosurfactants surfactin and iturin, produced by *B. subtilis* (KP7 and I0-1a) have been characterized by MALDI-TOF MS and also liquid chromatography MS/MS (LC-MS/MS) (Paraszkiewicz et al., 2018).

Liquid chromatography electrospray ionization mass spectrometry (LC-ESI-MS) is a comprehensive and sensitive ionization technique that can be applied for the structural identification and quantification of peptides and proteins in a mixture. A compound fractionated by liquid chromatography is sprayed into an MS under high vacuum and during the droplet evaporation process, electrical charge is transferred to molecules present in the droplet-producing multiple charged ions, which are separated in a magnetic field and then detected and analyzed, generating complex ESI spectra (Neagu et al., 2022). LC-ESI-MS analyses have been reported by Pecci et al. (2010) and Chen et al. (2017), for characterization of fengycin and surfactin from *B. licheniformis*. More than 40 novel lipopeptide variants, including cyclic and linear versions of surfactin, esperin, bacillomycin D, and fengycin A purified from marine *B. megaterium* have been analyzed by LC-ESI-MS (Ma et al., 2016).

6 | BIOLOGICAL ACTIVITIES OF LIPOPEPTIDES

6.1 | In vitro antimicrobial and antibiofilm activities

Due to the presence of both hydrophobic and hydrophilic moieties in lipopeptide structures, they can interact with pathogen cell membranes and act as amphiphilic membrane-like antibiotics that can control microbial growth and activity (Falardeau et al., 2013). A novel antibacterial lipopeptide purified from *S. amritsarensis* was found to be effective against a wide range of Gram-positive pathogens, particularly methicillin-resistant *S. aureus* (MRSA) (Sharma et al., 2014). Previous studies have demonstrated that lipopeptides with longer peptide chains exhibit better antibacterial activity (Tabben et al., 2011). However, few studies (see Figure 6) have focused on understanding the mechanisms involved in relation to the antimicrobial activity of lipopeptides.

Possible antibacterial mechanisms proposed for *Bacillus* lipopeptides, such as surfactin, iturins, and fengycin, include insertion into lipid bilayers, membrane solubilization, destabilization of membrane permeability by channel formation, chelation of mono- and divalent cations (Horng et al., 2019), and growth inhibition (Liu et al., 2023). To confirm the influence of lipopeptides on the cell wall permeability, the leakage of alkaline phosphatase (AKP), an intracellular enzyme located between the cell wall and the membrane, has been used to indicate cell damage. The AKP activity from *Clostridium difficile* ATCC 9689 increased after the administration of a lipopeptide obtained from *B. amyloliquefaciens* C-1 at ¼ MIC and ½ MIC (Lv et al., 2020), indicating cell damage involved in the antimicrobial effect.

The antimicrobial characteristics of lipopeptides are highly dependent on the lipopeptide-producing microorganisms and the type and structure of lipopeptides resulting from the microorganism substrate used, and the culture conditions employed in the production of lipopeptide. In a study by Reder-Christ et al. (2012), SB-253514 lipopeptide produced by *Pseudomonas* strain SH-C52 with unusual chemical structure (cyclocarbamate structure in the peptide moiety), exhibited substantial growth inhibition against several Gram-positive bacteria, such as *B. subtilis* 168 and *Arthrobacter crystallopoietes* DSM 20117 (MIC = 12.5 μg/mL), among another six *Pseudomonas* lipopeptides (MIC = 25–50 μg/mL). Most studies have found that Gram-negative bacteria are more resistant to lipopeptides than Gram-positive bacteria, owing to the presence of acidic components such as a hydrophilic lipopolysaccharide layer on the bacterial cell surface that limit the damaging effect of the lipopeptides. The antibacterial mechanisms of lipopeptides toward Gram-negative pathogens may differ from that of Gram-positive pathogens, due to the presence of teichoic acids in the outer cell wall membrane. In this case, cationic peptides can interact with the anionic cell surface, leading to loss of integrity of the cytoplasmic membrane (Hancock & Sahl, 2006). For instance, the cationic paenibacterin from *Paenibacillus thiaminolyticus* OSY-SE can attach to the anionic cell surface of *E. coli* and subsequently disrupt cytoplasmic membrane integrity, leading to cell death (Huang & Yousef, 2014). Similar results were obtained with battacin from *Paenibacillus tianmuensis* on *P. aeruginosa* ATCC 27853 and *E. coli* ATCC 35218 (MICs = 2–4 μg/mL), which was assayed using an agar dilution method (Qian et al., 2012). The antimicrobial potency of lipopeptides is a function of the concentration used. For instance, Ohadi et al.

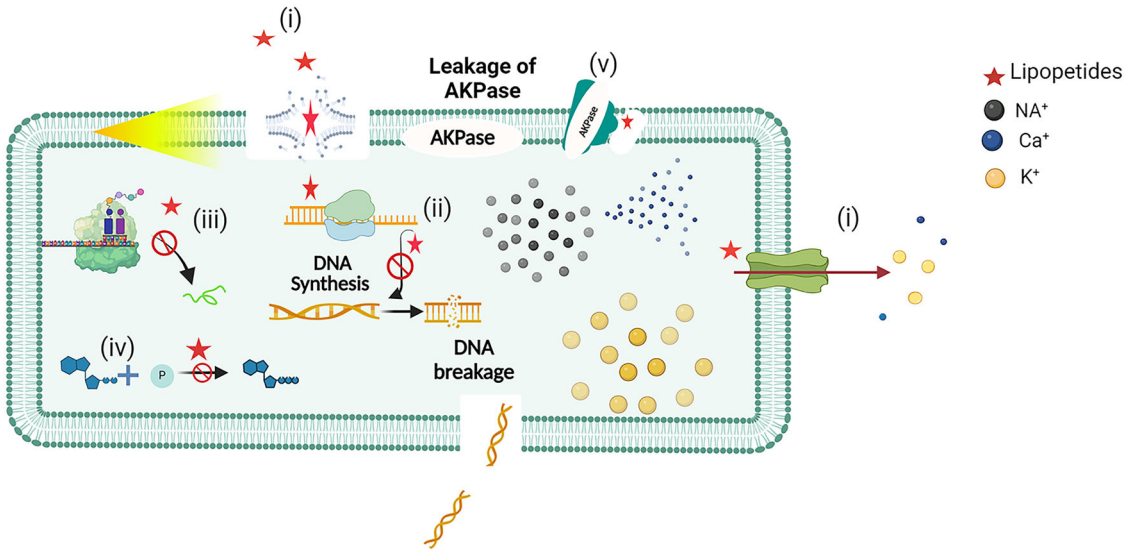

FIGURE 6 Common antibacterial mechanistic effects of lipopeptides. (i) antibacterial lipopeptide actions commonly include disruption of cell membrane integrity, pore formation, and osmotic imbalance, by either carrying cations across the membrane, such as is achieved by surfactin (Thimon et al., 1993), or insertion into the cell membrane such as is achieved by iturin (Nasir & Besson, 2011), or cell membrane depolarization and permeabilization, such as is achieved by daptomycins (Taylor & Palmer, 2016), leading to the leakage of intracellular components, namely Na^+ and K^+, and ultimately resulting in the bacterial cell death, (ii) lipopeptides can directly interact with DNA and subsequently inhibit secondary metabolite synthesis and gene expression, (iii) lipopeptides can hinder protein synthesis and the reproduction of bacteria (Mei et al., 2020), (iv) lipopeptides are able to kill cells through stopping ATP synthesis, and (v) the damaged cell wall and cell membrane resulting from lipopeptide interaction can enhance cell permeability and result in increased extracellular leakage of AKPase (Lv et al., 2020).

(2020) observed a negative relationship between the concentration of lipopeptides from *Acinetobacter junii* B6 and the mortality rate of bacteria, such as *S. aureus* and *P. aeruginosa*. The tested lipopeptide at a concentration near the CMC value was found to penetrate readily into the bacterial cell membrane, where it was completely miscible with the phospholipids, leading to modification of cytoplasmic membrane permeability, leakage of cell components, and cell death. At concentrations above the CMC, the lipopeptides formed micelles that were not able to cause microbial membrane damage. This means that a linear relationship cannot necessarily be expected, between the level of antimicrobial activity and the concentration of the lipopeptide. Furthermore, some lipopeptides such as daptomycin are highly dependent on the presence of Ca^{2+} to exhibit the highest antibacterial effectiveness. Daptomycin primarily enters into bacterial cell membranes in a Ca^{2+}-dependent fashion, leading to membrane depolarization, followed by loss of intracellular components such as ATP, K^+, and Mg^{+2} (Heidary et al., 2018). This antibacterial mode of action has been reported against *B. megaterium* and *S. aureus* upon exposure to daptomycin (Boaretti et al., 1993). The binding of metal ions to the peptides can boost their antimicrobial effects due to the influence on their charge, structure, and changing their mode of action (Walkenhorst et al., 2014). Divalent cations, in particular Cu^{2+} and Zn^{2+}, enhanced the antimicrobial activities of the lipopeptide pseudofactin II, via enhancing its penetration depth into the membrane of *Proteus mirabilis* ATCC 22100 and *Staphylococcus epidermidis* KCTC 1917. The accumulation of lipopeptide resulted in channel formation, and subsequently diffusion of ions out of the cell (Janek et al., 2016). In addition, a synergistic effect between bacterial-sourced antimicrobial peptides, such as nisin, and antimicrobial lipopeptides can be a potential option to enhance the effectiveness of antimicrobial agents. Kourmentza et al. (2021) demonstrated considerable antibacterial activity with a combination of surfactin and mycosubtilin with nisin against fungi, such as *Candida krusei* and *Rhizopus stolonifera*.

The biofilms can be defined as diverse microbial communities, initially comprising cells adhering to either an abiotic or a biotic surface, surrounded by a protective extracellular polymeric substance (EPS). EPS is made up of polysaccharides, protein, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and water, as a medium that aids the flow of nutrients inside a biofilm (Verderosa et al., 2019). Inhibition of adhesion is an effective strategy to control biofilm formation, so lipopeptides with surface anti-adhesive activity can be applied to reduce the adhesion between bacteria and a solid surface, removing bacteria before adherence and proliferation. Lipopeptides with

both hydrophilic and hydrophobic parts can exist between fluid phases resulting in the eradication of biofilms. A mixture of lipopeptides (surfactin, iturin, and fengycin) isolated from *B. subtilis* I'1a was found to decrease the adhesion of and biofilm formation by *Serratia marcescens* and *E. coli* (Moryl et al., 2015). Similar findings have been reported for coryxin (*Corynebacterium xerosis* NS5) lipopeptide against biofilm formed by *S. aureus, S. mutans, E. coli*, and *P. aeruginosa* (Dalili et al., 2015). The biofilm disruption of lipopeptide (from *B. licheniformis* V9T14) at 250 μg/mL concentration against biofilms of *P. aeruginosa* and *E. coli* was found to be substantial (Nalini et al., 2016). Rivardo et al. (2011) reported that the antibiofilm mechanisms of lipopeptides from *B. licheniformis* V9T14 were associated with forming pores and altering membrane integrity, leading to increased efficacy of the antibacterial agents.

7 | APPLICATION OF LIPOPEPTIDES IN FOOD SYSTEMS

During food processing, storage, transportation, and sale of food, food spoilage can occur due to two primary factors, microbial contamination and nutrient oxidation. To prevent spoilage and the growth of harmful bacteria, chemical preservatives have traditionally been used, but their use is hampered by concerns over their potential carcinogenic, toxic, and slow degradation properties. In response to consumer demand for safer preservatives, research has shifted toward natural compounds as alternatives.

Lipopeptides have considerable potential as food preservatives, due to their antimicrobial properties. The use of lipopeptides as antimicrobial agents can be accomplished in two main strategies, that is, either through the use of food-grade microorganisms to produce lipopeptides in situ during fermentations, or through the use of purified preparations of lipopeptides as food additives. The use of antimicrobial peptides as food preservatives is limited due to their inherent sensitivity to proteases. However, this sensitivity can be prevented by utilizing peptides that have a cyclic ring structure, such as lipopeptides (Meena & Kanwar, 2015). For example, the lipopeptide surfactin, is reported to inactivate *Salmonella enteritidis* (the leading cause of meat spoilage) under optimized conditions of 0.69 μM lipopeptide concentration at 5°C (Huang et al., 2009). Wu, Zhou, et al. (2019) have reported the antimicrobial effect of brevibacillin V and brevibacillin lipopeptides, produced by *Brevibacillus laterosporus* fmb70, after incubation at 30°C for 24 h, against different foodborne pathogens, at a minimum inhibitory concentration (MIC) of 2 and 16 μg/mL, respectively. Brevibacillin V at a concentration of 64 μg/mL could effectively inhibit the growth of *S. aureus* and *Listeria monocytogenes* in skimmed ultra-high temperature (UHT) milk stored at 4°C for up to 12 days. Lee et al. (2016) reported a high stability of bacillomycin D and surfactin synthesized by *Bacillus* sp. LM7, over a broad pH range of 4.0–9.0 and temperature range of 4 to 100°C for up to 30 min, indicating their potential use as food preservatives under a wide range of food processing conditions. These lipopeptides were found to possess a more substantial antimicrobial effect on Gram-positive bacteria, such as *B. cereus* and *L. monocytogenes*, than on Gram-negative bacteria, although their inhibitory effects were increased when combined with a positive control, such as polymyxin and nisin.

In addition to food spoilage microorganisms, lipid oxidation is another major cause of deterioration in food quality and organoleptic properties of food products. Lipopeptides are regarded as promising antioxidants with several advantages, such as maintaining their stability during food processing, and low toxicity (compared with chemical antioxidants such as tertiary butyl hydroquinone [TBHQ] and butylated hydroxytoluene [BHT]). Previous studies have also established the reactive compound scavenging activities of lipopeptides purified from *B. subtilis* B38 (Tabben et al., 2012) and *B. amyloliquefaciens* An6 (Ben Ayed et al., 2017). Crude preparations of lipopeptide DCS1 at 0.0125% (w/w of emulsion), isolated from *Bacillus methylotrophicus* DCS1 incubated for 72 h at 30°C, was found to delay lipid oxidation (according to the peroxide value and thiobarbituric acid reactive substances [TBARS]), of sunflower oil in a 23-day storage trial. Moreover, treatment of beef patties with the lipopeptide DCS1 (0.5%) and storage at 4°C was found to effectively delay lipid oxidation of meat (TBARS value of 0.35 mg MDA/kg meat), and extend meat shelf life by 14 days (Jemil et al., 2020).

Lipopeptides can also be employed as solubilizers, emulsifiers, and anti-adhesive agents (Mnif & Ghribi, 2015). One study (Mnif et al., 2013) investigated the potential use of a lipopeptide purified from *B. subtilis* SPB1 in bakery products and compared it with the commercial surfactant, soy lecithin. The results indicated that the lipopeptide could improve the textural properties of dough in terms of springiness, cohesion, adhesion, and hardness, as well as enhance the gas retention capacity of fermented dough. Similar results have been reported with the addition of *B. licheniformis* MS48 lipoepeptide, with gluten use in the formulation of cookies (Ravindran et al., 2023). In addition, the incorporation of the lipopeptide MSA31 in muffin formulation showed that the addition of 0.75% (w/w) lipopeptide remarkably enhanced the textural characteristics of the muffin, compared to the control in terms of chewiness, hardness, and color (Kiran et al., 2017).

Another study (Hoffmann et al., 2021) aimed to evaluate interfacial and emulsion properties of surfactin and

its suitability as an oil in water (O/W) emulsifier in food formulations, compared to use of synthetic surfactants (Tween). The results revealed that surfactin could not form strong viscoelastic interfaces, but it had a high interfacial charge, allowing it to maintain its stability in the pH range of 6–9. It also exhibited either a comparable, or better, performance to natural and synthetic chemicals such as lecithins. Studies have shown that the use of SPB1 biosurfactant could have a substantial impact on the development and maintenance of bread-making processes (Mnif et al., 2013, 2012). It could improve the texture and appearance of the dough and reduce the risk of microbial spoilage. In other developments, the food safety implications of the anti-adhesive activity of lipopeptides against the binding of *L. monocytogenes* to stainless steel and polypropylene (De Araujo et al., 2011; Moryl et al., 2015), and polystyrene surfaces, is well recognized. Moreover, another report indicates that some lipopeptides can hamper biofilm formation (Nitschke et al., 2009). In a very recent research study, the findings indicated that the addition of *Acinetobacter calcoaceticus* RAG-1 bio-emulsifier (0.5% w/w) could effectively reduce bread staling, without affecting sensory parameters such as chewability and porosity (Sadeghi et al., 2023).

7.1 | Lipopeptide formulation in food processing

Although diverse biological activities of lipopeptides have been reported, their use in certain applications, particularly in the food industry, are still limited due to their short half-lives and low stability (e.g., under high temperature and oxygen exposure) that can occur during some industrial processes. To overcome these issues, different fabrication strategies, namely, nanoparticles, coatings, and encapsulation have been evaluated in the recent literature. These techniques can also improve the efficiency of lipopeptides even at lower doses. Encapsulation can increase the stability of lipopeptides against harsh conditions, achieve controlled release, and retain functionalities during food processing and storage (Zhang et al., 2022). For example, the incorporation of lipopeptides (surfactin and iturin) and clay nanoparticles into polyvinyl alcohol (PVA; PVOH) film, enhanced their antimicrobial properties against *S. enterica serovar* Typhimurium and *Pythium myriotylum* (can impart antimicrobial activities to the film along with other functionalities such as barrier properties) (Jayakumar et al., 2021a). The same authors (Jayakumar et al., 2021b) reported an increase in the antimicrobial activities of a blend of PVOH (PVA) nanocomposite membrane containing zinc oxide nanoparticles and lipopeptide (from *B. subtilis*), against *S. aureus*, *K. pneumoniae*, and *P. aeruginosa*. In addition, the encapsulation of lipopeptides isolated from *B. subtilis* S1702 in solid lipid nanoparticles (SLNs), resulted in better antifungal activities against *Aspergillus* spp., through their gradual and controlled release, compared to the non-encapsulated ones. The encapsulated lipopeptides also exhibited improved stability during a 30-day storage period by reducing their oxidation (Lin et al., 2020). Microencapsulation of iturin A purified from *B. subtilis* X-01 has been achieved by a spray-drying method. Sodium alginate (SA)/poly-γ-polyglutamic acid was selected as the best encapsulation material due to the lower viscosity and higher encapsulation efficiency and yield, compared to counterpart agents, such as gelatin and sodium carboxymethyl cellulose. The microencapsulation technique could successfully maintain the storage stability of iturin up to 3 months as well as protect from ultraviolet irradiation (Yu et al., 2017). However, in another study, a mixture of maltodextrin and porous starch was found to be the best encapsulation material for preparing microencapsulated lipopeptide obtained from *B. amyloliquefaciens* ES-2 by spray drying, because it considerably improved the absorbability of materials and reduced the adhesiveness of microcapsules (Wang et al., 2014).

Additionally, chitosan derived from different types of organisms, mainly crustaceans, has great potential to be used in food preservation due to its antioxidant and antimicrobial activities, and can be used as a carrier to deliver lipopeptides. The application of bacillomycin D encapsulated in chitosan inhibited *R. stolonifer* and *B. cinerea* growth (MIC = 25 mg/L), while using the lipopeptide alone exhibited MICs of 0.1 and 0.05 g/L, respectively. The results revealed that encapsulated lipopeptides can extend the shelf life of tomatoes by approximately 15 days, based on measuring quality parameters such as weight loss and firmness, as compared to the use of lipopeptide alone (Lin et al., 2021). Similarly, surfactin incorporated with chitosan resulted in enhanced antifungal activity against *Lasiodiplodia* spp. by up to 46%, compared to surfactin alone (Yuan et al., 2014). Likewise, chitosan in combination with iturin A and succinaldehydic acid improved the antifungal activity against *Ceratocystis fimbriata* and *R. stolonifera* by about 20%, as compared to using iturin A alone, and encapsulation could effectively control the release of iturin A during storage (Yuan et al., 2020). The combination of chitosan with silver nanoparticles (AgNPs) and iturin has been found to be an effective strategy to enhance the antibacterial activity of chitosan against *E. coli* and *S. aureus* by two fold, based on measurement of inhibition zones (Zhou et al., 2021). In another study, the effectiveness of AgNPs containing iturin A on postharvest quality of orange fruits has been reported. However, the potential toxic effect of AgNPs has restricted its use in the food sector. To overcome this, its concentration has

been reduced and replaced by adding iturin A, and then the antimicrobial capacities were compared. In comparison with AgNPs stabilized with polyvinyl pyrrolidone, iturin-AgNPs exhibited a higher inhibitory effect on different pathogens, such as *E. coli*, *S. aureus*, and *Aspergillus niger*, by 20% to 50% (Zhao, Wang, et al., 2021). Lipopeptides can be applied in food packaging for improving food shelf life and safety. In a recent study (Verónica et al., 2023), it was found that the incorporation of *B. amyloliquefaciens* PGPBacCA1 lipopeptides into films based on pectin and a mixture of starch and gelatin, could substantially inhibit the growth of *S. enteritidis*, *L. monocytogenes*, and *E. coli*.

7.2 | Food safety of microbial lipopeptides

Lipopeptides may also have potential toxic effects, which need to be assessed before being used in food products. The safety of these valuable compounds should be guaranteed before being commercialized. Cytotoxicity, nephrotoxicity, and hemolytic activity are major factors affecting the safety of the lipopeptide's evaluation. However, there are limited publications strictly devoted to toxicity of lipopeptides, and they are commonly considered as low or non-toxic (Zhang et al., 2022). According to an in vitro study (Kourmentza et al., 2021) conducted on Caco and Vero cells using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay, surfactin and fengycin were found to have low toxicity, with an IC50 value above 0.1 g/L. On the other hand, iturin A and mycosubtilin were classified as having moderate cytotoxicity, with an IC50 value ranging from 0.01 to 0.1 g/L.

Another study tested the safety of lipopeptides by estimating their hemolytic activity. Brevibacillin V or brevibacillin exhibited lower toxicity than fengycin, iturin and surfactin, which might be due to their lipid shorter carbon chain length (Wu, Zhi, et al., 2019). Moreover, findings (Zhao et al., 2018), of an investigation of oral toxicity of *B. subtilis* CCTCCM207209 iturin conducted in Kunming mice, indicated no negative effect on body weight and organ weight as well as hematological (e.g., red blood cell count and neutrophil count) and biochemical (e.g., aspartate aminotransferase [AST], alanine transaminase [ALT], urea, and triglycerides) parameters of the mice treated with iturin (2000 mg/kg/day) (Zhao et al., 2018). Furthermore, Dey et al. (2016) reported that the administration of iturin A at either low or high doses (10–20 mg/kg) caused no substantial changes in hematological profile (e.g., neutrophil and lymphocyte), and biochemical parameters (albumin, AST, ALT, and alkaline phosphatase [ALP]). Another toxicological study on surfactin was carried out using a zebrafish model and the results demonstrated that the concentration of this lipopeptide below 1 mg/mL was safe for experimental research (Wang et al., 2021).

8 | CONCLUSIONS AND FUTURE PERSPECTIVES

Microbial lipopeptides predominantly extracted from *Bacillus* spp. and *Pseudomonas* spp., possess multifunctional properties, mainly antimicrobial, antioxidant, anti-inflammatory, and anticancer effects. Therefore, lipopeptides have great potential for use in the food sector as a food preservative and nutraceutical. In particular, the application of lipopeptides in food systems (Hoffmann et al., 2021; Jemil et al., 2020; Mnif et al., 2013; Wu, Zhou, et al., 2019), as natural inhibitors/biopreservative and antioxidants, has currently drawn growing attention because of consumer concerns toward synthetic preservatives. However, the impact of food processing, such as thermal treatments and storage, on lipopeptides in food formulation, needs further study. Therefore, the influence of adding these antimicrobials and antioxidants into food systems, with respect to the relationships between food processing conditions and lipopeptide potency, especially under realistic food product production conditions, requires further attention.

Although several studies have confirmed the beneficial biological effects of lipopeptides, their commercial utilization remains restricted. This may be due to the lack of preclinical and clinical data to verify their effectiveness, safety, and organoleptic properties. Most previous studies have focused on demonstration of either the low toxicity or apparent lack of toxicity of some lipopeptides in in vitro models. In addition, there is lack of information on the biological mechanisms of lipopeptides at the molecular level.

More importantly, the main obstacle to industrialization of lipopeptide production, currently, is the relatively high cost. As previously mentioned, using waste as a raw material to produce value-added products has opened new horizons for contributing to environmental sustainability and reducing the total cost of production. However, few studies have been conducted on producing lipopeptides using alternative materials, such as frying oils and agricultural waste. Moreover, some strategies to potentially enhance lipopeptide production are ultrasonication and genetic engineering. There is a lack of information concerning the influence of ultrasound irradiation on the productivity of these fermentative products.

Recent studies reveal a lack of in-depth data on the relationships between the structure and functional activities of lipopeptides. Different methods, such as in silico approach genetic methodology and molecular analysis, can be used

to determine their structural activities. Furthermore, food technology applications and the performance of lipopeptides in food systems, and their absorption from the digestive system, can be enhanced through encapsulation technologies. Designing formulated lipopeptide containing products will likely be a major focus of future research.

The use of PMB and other lipopeptides, such as daptomycin, are considered as a last resort against multi/pan-resistant bacteria (Gray & Wenzel, 2020; Roberts et al., 2022). This is indeed a critical aspect of modern medicine. These antibiotics play a crucial role in treating infections that are unresponsive to other available treatments. However, the widespread use of these peptides, particularly in large-scale applications such as food production, or their presence of fermented foods that are regularly consumed, raises concerns about the potential development of bacterial resistance. The risk of selecting for bacteria resistant to these peptides, whether in the intestinal microbiota or the environment, is a substantial consideration. Antibiotic resistance can emerge when bacteria are exposed to compounds over time, leading to the survival and proliferation of resistant strains. If lipopeptides are extensively used in food processing, there is a chance that bacteria in these settings could develop resistance, compromising the effectiveness of these antibiotics in medical treatments. However, knowledge about the ability to form lipopeptide resistance and the fate of these lipopeptides during processing and subsequent storage and consumption of foods is limited, and hence further research is required to fill this gap of knowledge.

AUTHOR CONTRIBUTIONS

Salome Dini: Writing—original draft; investigation; software; methodology. **Fatih Oz**: Writing—review and editing; investigation. **Alaa El-Din A. Bekhit**: Conceptualization; supervision; writing—review and editing; project administration. **Alan Carne**: Writing—review and editing. **Dominic Agyei**: Conceptualization; supervision; writing—review and editing; project administration.

ACKNOWLEDGMENTS

Open access publishing facilitated by University of Otago, as part of the Wiley - University of Otago agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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How to cite this article: Dini, S., Oz, F., Bekhit, A. E.-D. A., Carne, A., & Agyei, D. (2024). Production, characterization, and potential applications of lipopeptides in food systems: A comprehensive review. *Comprehensive Reviews in Food Science and Food Safety*, *23*, e13394. https://doi.org/10.1111/1541-4337.13394