



REVIEW ARTICLE

Cyclic and non-ribosomal microbial metabolites in the biological control of plant pathogens

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Abstract

Cyclic and non-ribosomal microbial metabolites are important bioactive secondary metabolites with significant potential in sustainable plant disease management. These metabolites are primarily produced by beneficial microorganisms including *Bacillus*, *Pseudomonas* and *Streptomyces* through non-ribosomal peptide synthetase (NRPS)-mediated biosynthetic pathways. This narrative review summarises the structural diversity, biosynthesis, mechanisms of action, detection methods and agricultural applications of cyclic and non-ribosomal microbial metabolites in the biological control of plant pathogens. Among these metabolites, surfactins, iturins, fengycins, bacillomycins and amphisins are the most extensively studied compounds due to their broad-spectrum antimicrobial activities. These metabolites exhibit strong inhibitory effects against major phytopathogens including *Fusarium*, *Alternaria*, *Rhizoctonia* and *Magnaporthe oryzae*, with disease suppression efficiencies ranging from 40 to 90 % under *in-vitro* and in-planta conditions. Iturin and fengycin have demonstrated 65 to 90 % inhibition against *Fusarium* species, whereas surfactin- and fengycin-producing strains have been reported to reduce rice blast severity by 40 to 70 %. Their amphiphilic structures enable membrane permeabilisation, pore formation, inhibition of spore germination and disruption of pathogen growth. In addition to direct antimicrobial activity, these metabolites promote biofilm formation, rhizosphere colonisation and induced systemic resistance mediated through jasmonic acid, ethylene and salicylic acid dependent pathways. Despite promising biocontrol potential, challenges related to large-scale production, formulation stability and field-level consistency remain major limitations for commercialisation.

Keywords: biological control; cyclic lipopeptides; induced systemic resistance; non-ribosomal peptides; plant microbe interactions

Introduction

The rise in global population continues, leading to an increased demand for food and agricultural produce. As per the Food and Agriculture Organization, food production should be increased nearly 70 % by 2050 to support a population projected to reach about 9.6 billion (1). Consequently, modern agriculture faces the significant challenge of achieving higher yield while ensuring sustainability and ecological safety. Additionally, the crop plants are repeatedly exposed to both biotic and abiotic stresses that can adversely affect productivity (2). The widespread use of fungicides to manage plant pathogens has proven effective in the short term, however, prolonged reliance has led to several adverse consequences, including the development of fungicide-resistant pathogen populations due to selection pressure, interruption of beneficial microbiota and negative environmental impacts (2, 3). In recent years, researchers have increasingly focused on cyclic lipopeptides produced by beneficial microorganisms like *Bacillus*,

Paenibacillus, *Pseudomonas*, *Streptomyces* and *Burkholderia*. The unique structural features of surfactin, iturin and fengycin compounds exhibit antimicrobial activity against a vast array of pathogens, including fungi, bacteria and viruses (3–6). Their low phytotoxicity, biodegradability and strong antimicrobial properties have made lipopeptides a promising environmentally benign alternative to conventional chemical pesticides in sustainable agriculture (6–9). Moreover, they provide a sustainable alternative approach to crop protection by reducing dependence on synthetic agrochemicals.

Methodology

This review follows a narrative review approach to summarise current knowledge on cyclic and non-ribosomal microbial metabolites involved in the biological control of plant pathogens. Relevant literature was collected from major scientific databases including PubMed, ScienceDirect, SpringerLink and Google Scholar. The literature search primarily focused on peer-reviewed articles

between 2019 to 2026 to capture the most recent advances and emerging trends in the field. The literature search was performed using combinations of keywords such as “cyclic lipopeptides”, “non-ribosomal peptides”, “*Bacillus* lipopeptides”, “microbial biosurfactants”, “non-ribosomal peptide synthetase (NRPS) biosynthetic pathway”, “biological control” and “plant pathogen suppression”. In addition to recent publications, approximately twenty foundational and highly cited studies were included to provide essential background information on microbial metabolites.

Peer-reviewed research articles, review papers and relevant book chapters published in English were considered for inclusion. Studies focusing on the biosynthesis, structure, mechanisms of action, antimicrobial activity, induced systemic resistance, detection methods and agricultural applications of microbial cyclic metabolites were prioritised. Duplicate, non-peer-reviewed and unrelated studies were excluded to ensure scientific reliability and relevance. Microbial nomenclature and taxonomic classifications were verified using NCBI Taxonomy, while metabolite information was cross-checked using PubChem databases. The collected information was critically analysed and organised into thematic sections to provide a comprehensive overview of cyclic and non-ribosomal microbial metabolites in sustainable plant disease management.

Cyclic lipopeptide: Structure and classification

Beneficial microorganisms including the genera *Bacillus*, *Paenibacillus* and *Pseudomonas*, are known to produce cyclic lipopeptides (CLPs) (4, 10). These lipopeptides embody a cyclic peptide moiety associated with a hydrophobic fatty acid chain, which imparts strong antimicrobial properties (4, 6). Their amphipathic nature enables them to interact with biological membranes and alter membrane permeability, making them effective against a wide range of plant pathogenic microorganisms (4, 11). Typically, CLPs are composed of 7–10 amino acid residues arranged in a cyclic peptide ring, linked to a β -amino fatty acid chain containing approximately 13 to 19 carbon atoms (4, 6, 12). The peptide and lipid components are joined through a lactone linkage, resulting in a stable cyclic nature (13). This cyclic configuration enhances resistance to enzymatic degradation and often exhibits greater biological activity compared to linear forms of peptides (6, 13).

Cyclic lipopeptides are synthesised via NRPS pathways, in which large, multi-enzyme complexes assembled as amino acids and fatty acid components into complex cyclic structures (12). These NRPS systems comprise functional domains viz., adenylation (A), condensation (C) and thiolation (T), which sequentially activate and incorporate amino acids into a growing peptide chain, followed by cyclisation (12, 14). Structural variations within lipopeptide families arise from variations in fatty acid chain length, amino acid composition, stereochemistry (L- or D-forms) and peptide ring size (4, 7, 11, 12). As a result, multiple homologues can exist within a single lipopeptide family, each exhibiting different biological activities (6). For instance, differences in lipid tail length can influence membrane interaction, inhibition of spore germination, antimicrobial property and molecular stability (5, 15, 16). Furthermore, the amphiphilic nature of cyclic lipopeptides enables them to form membrane-disrupting complexes, leading to microbial cell damage, suppression of spore formation and inhibition of pathogen growth (16, 17). These properties are collectively responsible for their broad-spectrum antifungal, antibacterial and antiviral activities (17, 18).

Surfactin

Surfactin is a well characterised biosurfactant belonging to the class of cyclic lipopeptides (19, 20). It was first isolated in 1968 by previous researchers from the culture filtrate of *Bacillus subtilis* and identified as a main inhibitor of fibrin clot formation (4). Surfactins are amphiphilic secondary metabolites of commercial and ecological importance that are synthesised through non-ribosomal peptide synthetase (NRPS) pathways (5, 6, 19, 20). The surfactin biosynthesis is governed by the *srfA* operon (*srfAA*–*srfAD*), which encodes NRPS enzymes responsible for assembling both lipid and peptide components. The surfactin synthetase complex, which has a molecular weight of 400–500 kDa, operates via an ATP-dependent thiotemplate mechanism, enabling peptide assembly without the involvement of ribosomes (19, 21). Surfactin structure is constituted of a cyclic heptapeptide linked to a β -hydroxy fatty acid chain containing 12–17 carbon atoms, forming a stable lactone ring structure (19, 20). The cyclic peptide portion of surfactin consists of amino acid sequence L-Glu-L-Leu-D-Leu-L-Val-L-Asp-D-Leu-L-Leu (Fig. 1), in which the cyclisation occurs via the formation of an ester linkage between the C-terminal carboxyl group and the β -hydroxy fatty acid chain, producing a stable cyclic lactone ring structure (20). The fatty acid component consists of linear, iso-branched, or anteiso-branched chains, contributing to the diversity of surfactin homologues (6, 22). The variations present in the amino acid sequence, particularly at the seventh position, along with differences in fatty acid chain length, give rise to distinct surfactin isoforms such as surfactin A, B and C. These isoforms showed variation primarily in the terminal amino acid residue (leucine, valine, or isoleucine, respectively) (20–22).

Iturin

Iturin is a CLP compound produced by beneficial microorganisms through non-ribosomal peptide synthetase (NRPS) pathways (5, 6, 23, 24). It is structurally characterised as a cyclic heptapeptide linked to an aliphatic carboxylic acid chain containing approximately 14–17 carbon atoms (6, 13, 25). The presence of a hydrophobic fatty acid tail and a hydrophilic peptide ring give an amphiphilic nature, enabling effective interaction with biological membranes (5, 18). The iturin family comprises several homologues, including iturin A, bacillomycin D, bacillomycin L, bacillomycin F and mycosubtilin (26, 27). These metabolites are typically produced during the stationary phase and are regulated by complex networks involving quorum sensing and global transcriptional regulators (4, 13, 26, 27). The iturin structure belongs to the cyclic lipopeptides, consisting of a heptapeptide ring linked to a β -amino fatty acid chain (13, 28). The characterised peptide sequence is reported as L-Asn-D-Tyr-D-Asn-L-Gln-L-Pro-D-Asn-L-Ser (13) (Fig. 2), which forms a lactone linkage with the fatty acid tail (29, 30). Structural variations in fatty acid chain length (C14–C17) result in different homologues such as C14-, C15-, C16- and C17-iturin A, influencing membrane affinity and antimicrobial activity (25, 29, 31).

Fengycin

Fengycin is a cyclic lipopeptide antibiotic that is mainly produced by several species belonging to the genus *B. subtilis*, *B. velezensis* and *B. amyloliquefaciens* (4, 32). These *Bacillus* species are Gram-positive, endospore-forming bacteria commonly found in soil and plant rhizospheres and are significant in anti-pathogenic effects on plants and rhizosphere microbial interaction (3, 4). Among the three families of lipopeptides that are produced by *Bacillus* is fengycin,

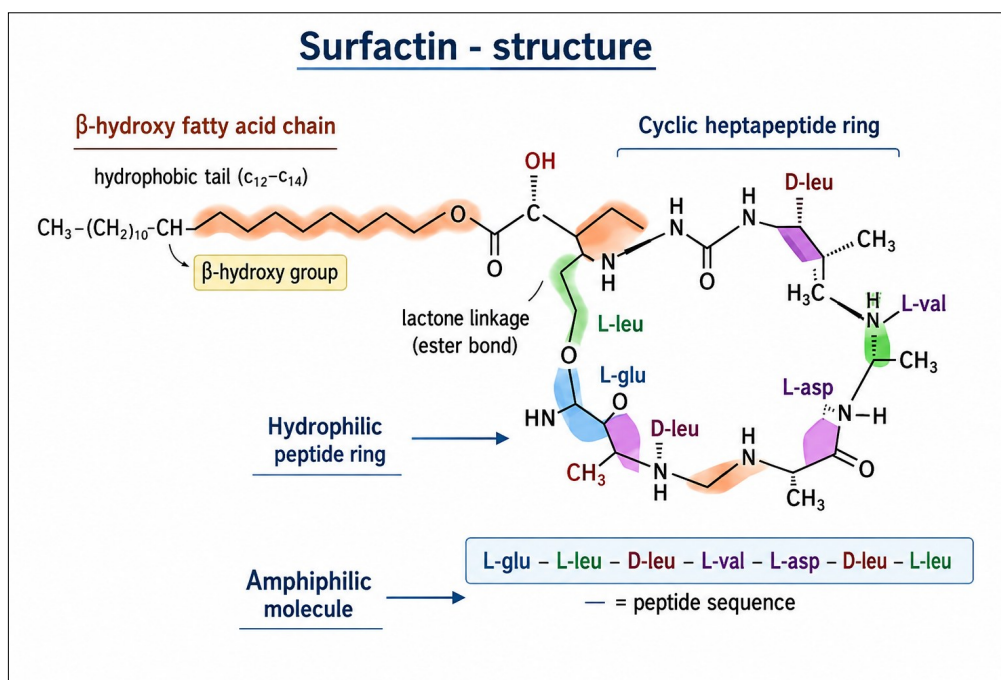


Fig. 1. Chemical structure of surfactin.

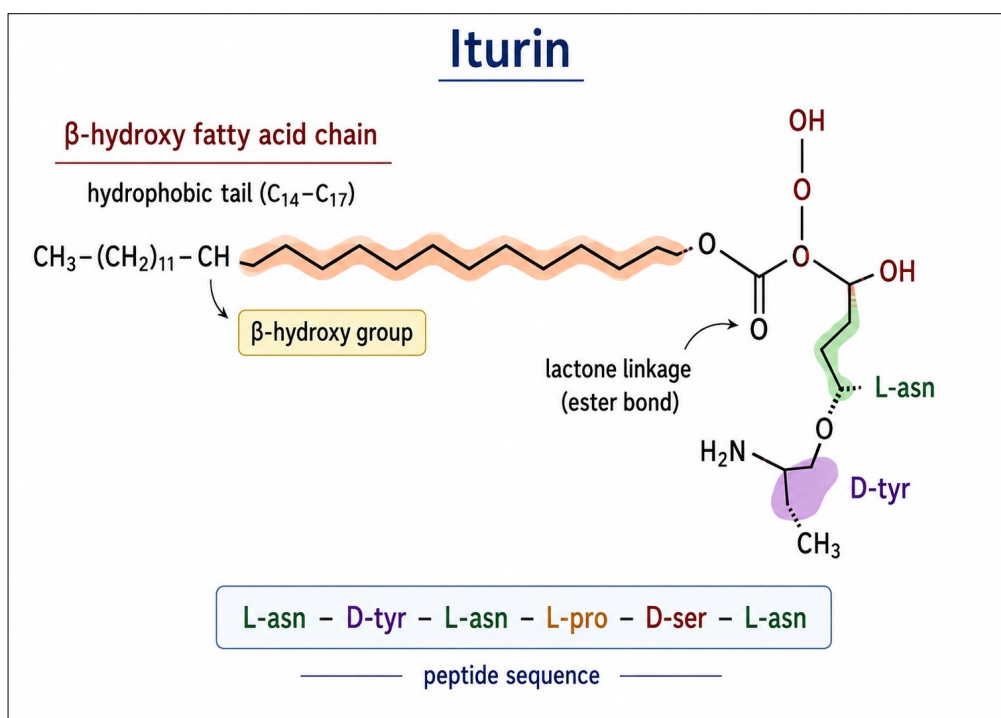


Fig. 2. Chemical structure of iturin.

surfactin and iturin are the most effective in relation to filamentous fungal pathogens (4, 5, 32). Fengycin is a non-cationic cyclic lipopeptide that consists of fengycin and plipastatin (30). Discoveries of fengycin and plipastatin as novel lipopeptides were made in 1986 in *B. subtilis* F-29-3 and *B. cereus* BMG302-F67 respectively (23, 24, 30, 33). The fengycin lipopeptide is composed of 10 amino acids attached to a 2-hydroxy fatty acid tail (30). The fatty acid chain is usually between C_{14} and C_{18} and this produces various homologues and structural variations of the molecule (30, 31, 33). Depending on the variation of amino acid at position 6, there are two major isoforms of fengycin like Fengycin A which has alanine at position 6 and fengycin B which has valine at position 6 (22, 30). The lipopeptide sequence was well characterised as Glu- Orn- Tyr- Thr- Glu- Ala- Val- Pro- Glu- Tyr- Ile (6, 33) (Fig. 3). The fungal cell membranes interact strongly with the amphiphilic molecule

fengycin because its amphiphilic nature disrupts membrane integrity and leads to the leakage of cellular content (32,34–37).

Bacillomycin

Bacillomycin is a secondary metabolite synthesised primarily by *Bacillus* spp. including *B. subtilis*, *B. velezensis* and *B. amyloliquefaciens* (4, 6). These bacteria are widely distributed in soil and plant rhizospheres, where they contribute to the biological control of plant pathogens (4, 13, 38). This compound is a part of a family of cyclic lipopeptides that include Iturin A, Bacillomycin D, bacillomycin L, mycosubtilin and bacillipeptin, that are structurally similar and act as antifungal agents (4–6). Genomic studies of plant-associated *Bacillus* strains indicated that genes of Bacillomycin biosynthesis are generally found in dedicated secondary metabolite gene clusters. These groups are highly preserved in the representatives of the *B. amyloliquefaciens* group and play the role

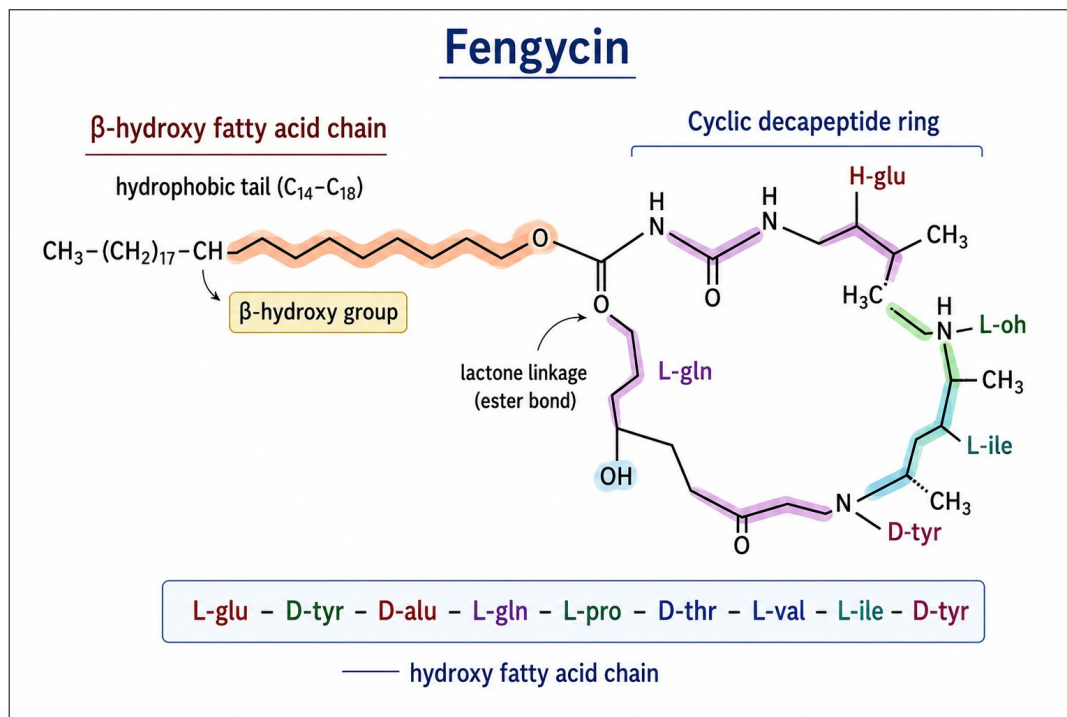


Fig. 3. Chemical structure of fengycin.

of contributing to their biocontrol potential in the agricultural ecosystems (26, 39). Other cyclic lipopeptides like surfactin and fengycin are typically produced by bacillomycin-producing strains and they constitute an antimicrobial system that is more effective against plant pathogens (39).

Bacillomycin is described as a cyclic heptapeptide that is attached to a chain of 14–18 carbon fatty acid, usually a 14 to 18 fatty acid chain (4, 15, 16). It has a general structure with 7 amino acids forming a lactone ring due to intramolecular cyclisation with the fatty acid tail (39). The L-Asn, D-Tyr, D-Asn, L-Pro/Ser, L-Glu, D-Ser and L-Thr (Fig. 4) are some of the primary residues present in the peptide core, yet bacillomycin homologues vary in these (6, 26). The consequences of this interaction include the formation of pores

and destabilisation of the membrane that eventually leads to the leakage of intracellular contents and cellular death (15, 16). The structural variability of the bacillomycin analogues is mainly due to the difference in fatty acid chain length and replacement of amino acids in the peptide ring. These differences affect the antifungal activity and spectrum of action (26). The production of bacillomycin is regulated through a non-ribosomal peptide synthetase gene cluster, also known as the *bmy* operon, that produces the enzymatic machinery needed to assemble the cyclic lipopeptide structure. Recent genomic and metabolomic analyses have shown that the bacillomycin biosynthetic gene cluster (BGC) usually covers about 37 kb and has 4 genes at its center: *bmyD*, *bmyA*, *bmyB* and *bmyC* (14, 26).

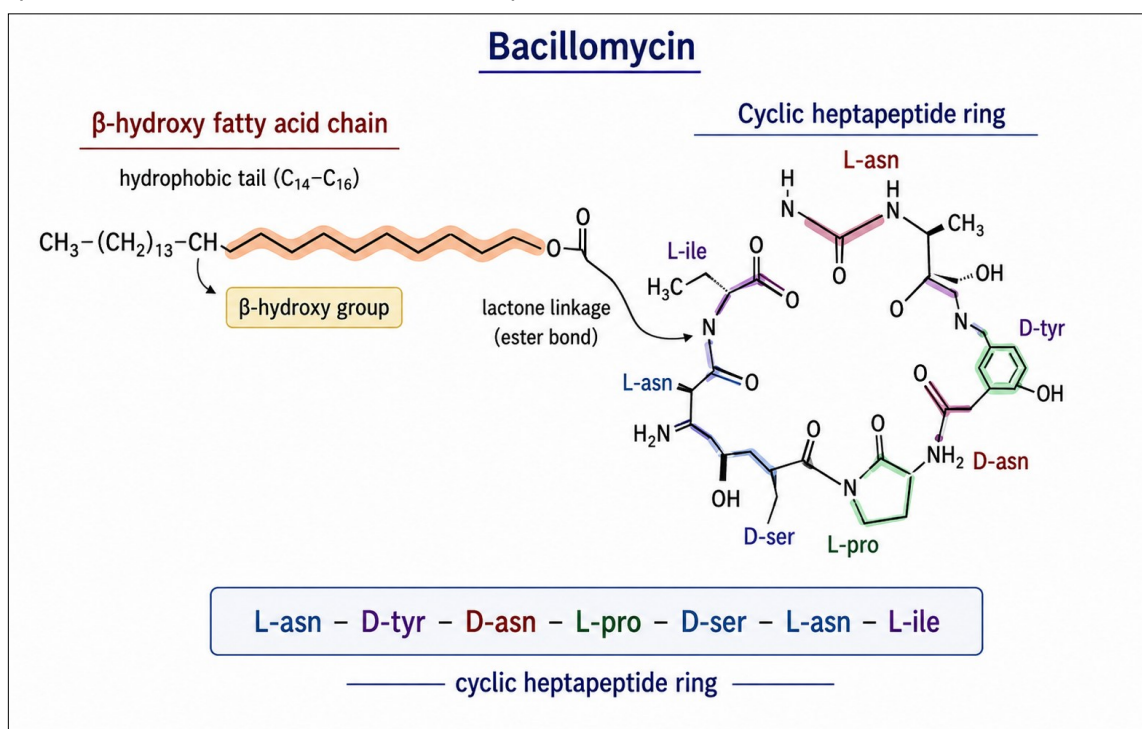


Fig. 4. Chemical structure of bacillomycin.

The *bmy* operon constitutes the main genetic determinant of bacillomycin production. The bacillomycin cluster was found to be highly conserved between the *Bacillus amyloliquefaciens* and is frequently found in conjunction with other secondary metabolite clusters like surfactin (*srf*) and fengycin (*fen*) through genome mining studies with the help of tools like antiSMASH (14, 26). The four essential genes code for multifunctional NRPS enzymes that are large and catalyse the sequential addition of amino acids to the bacillomycin peptide backbone. The *bmyD* gene codes malonyl-CoA transacylase (MCAT) or fatty-acid activation enzyme which is critical to triggering the synthesis of bacillomycin. This is an enzyme that is involved in the construction and contribution of the 2 amino fatty acid group, which is the lipid tail of the molecule of bacillomycin. The chain of fatty acid helps to make bacillomycin amphiphilic and binds to the fungal cell membranes (14, 32). The first major NRPS enzyme is encoded by the *bmyA* gene which encodes the enzyme carrying out the initial phase of assembling a peptide. This enzyme has various catalytic domains such as adenylation (A), condensation (C) and thiolation or peptidyl carrier protein (PCP) domains, which activate and attach the first amino acid residues to the growing peptide chain. The synthetase encoded by *bmyA* is also capable of incorporating the fatty acid moiety in the peptide backbone during earlier stages of bacillomycin assembly (14, 32). The *bmyB* gene expresses a large NRPS protein that has multiple modules that sequentially add multiple amino acids of the bacillomycin heptapeptide core. The enzyme is made up of each module having catalytic domains including adenylation, condensation and epimerisation domains that define the stereochemistry and sequence of incorporation of amino acids. These domains guarantee the correct assembly of the cyclic peptide backbone of bacillomycin molecules (32). The *bmyC* gene is the gene that codes the terminal NRPS module that involves the final steps of the peptide elongation and cyclisation. The enzyme has a thioesterase (TE) domain that facilitates the release and cyclization of the peptide chain leading to the production of the mature cyclic lipopeptide structural form. This is a vital step in

biological activity and stability of bacillomycin molecules which undergo a cyclisation process (32, 38).

Amphisin

Amphisin was first identified from *Pseudomonas fluorescens* strain DSS73 isolated from the sugar beet rhizosphere. The substance also contributes to ecological fitness of the bacterium because it suppresses the development of other microorganisms and enhances the settlement of the plant roots (40, 41). Amphisin is a structurally amphipathic lipid-binding cation made of 11 amino acids and a fatty acid tail to create a cyclic lipoundecapeptide with a stable amphipathic fold that can interact with the lipid bilayers. The antimicrobial and surface-active properties of the molecule are characteristic of the peptide sequence that includes such residues as leucine, aspartic acid, serine, threonine, glutamine and isoleucine (Fig. 5) (41–43).

Amphisin is synthesised via NRPS pathway, whereby the large multiplex enzyme complexes synthesise the lipopeptide, without the aid of ribosome. The amino acid activation, condensation and cyclisation of the assembly of enzymatic peptide modules are coded by specific amphisin synthetase genes. In *Pseudomonas* strains, the synthesis of amphisins is well-coordinated with the global regulatory systems, in particular, GacA/GacS two-component regulatory system that reacts to the environmental cues such as plant root exudates and regulates the expression of the NRPS gene groups (42).

Amphisin-producing strains of *Pseudomonas* prevent several economically important phytopathogenic fungi including *Rhizoctonia solani*, *Pythium ultimum*, *Phytophthora*, *Botrytis cinerea*, *Fusarium culmorum*, *Colletotrichum coccodes*, *Monilinia fructigena*, *Penicillium expansum* and *Aspergillus species*. These pathogens cause severe diseases such as rotting fruits, damping off as well as post-harvest spoilage of crops. Several studies have demonstrated that amphisin has a significant anti-fungal effect and can inhibit the germination of spores in culture but has prospects of protecting crops in a sustainable manner (42, 44, 45).

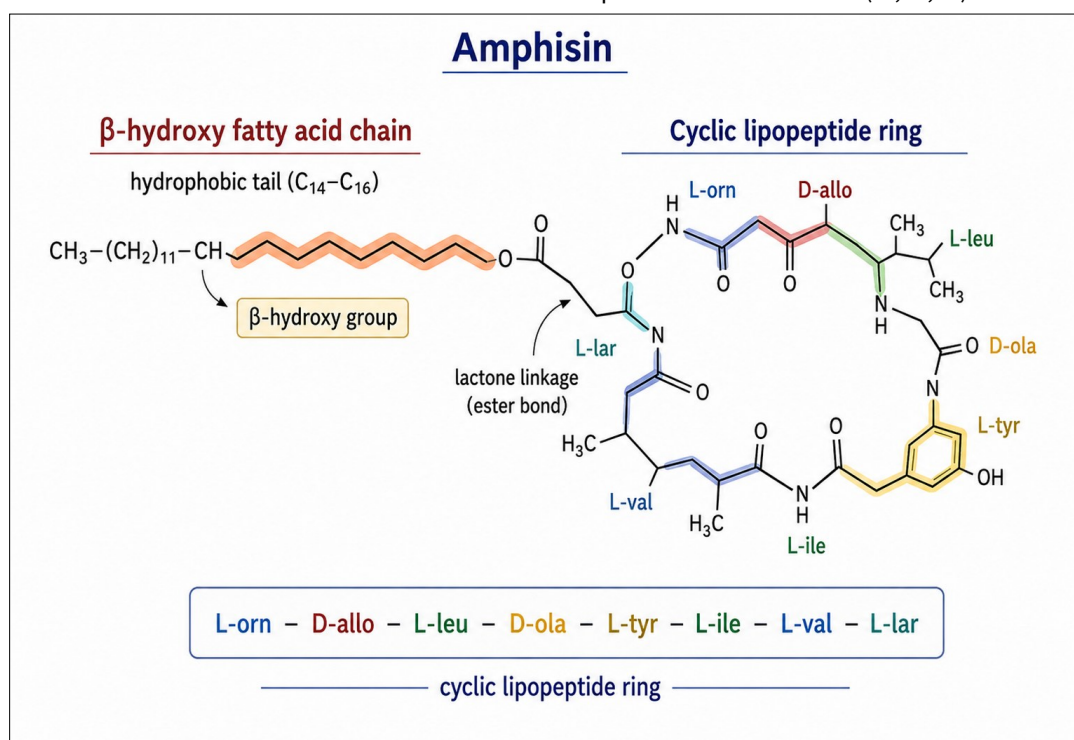


Fig. 5. Chemical structure of amphisin.

Biosynthesis of microbial lipopeptides

Microbial lipopeptides are a vast variety of amphiphilic secondary metabolites primarily produced by the genera *Bacillus*, *Pseudomonas* and *Streptomyces*. These molecules generally consist of cyclic or linear peptide moieties that are attached to a β -hydroxy fatty acid chain and possess high antimicrobial, antifungal, antiviral and biosurfactant properties. Most microbial lipopeptides are synthesised via NRPS systems and enable the use of typical amino acids and structural alterations unlike ribosomally synthesised peptides. Lipopeptide biosynthesis involves coordinated interactions among NRPS enzymes, biosynthetic gene clusters and regulatory networks (4, 10, 21).

Non-ribosomal peptide synthesis pathway

Biosynthesis of lipopeptides in microbes is mainly mediated by the NRPS pathway which provides a modular assembly line of enzymes. The NRPS enzymes are huge multi-domain proteins that consist of sequential modules, which incorporate a particular amino acid into the growing peptide chain. A standard NRPS module comprises three catalytic domains: adenylation (A), thiolation or peptidyl carrier protein (PCP) and condensation (C) domains (Fig. 6) (10). The biosynthetic mechanism starts with the activation of one of the 2-hydroxy fatty acids and becomes the lipid tail of the lipopeptide molecule. Activation of fatty acids takes place via the ATP-dependent phosphorylation reactions, resulting in acyl-adenylate intermediate and transferred to the first NRPS module (46, 47). The adenylation domain then identifies and activates certain amino acids to give aminoacyl-AMP intermediates which are then transferred to the PCP domain through a phosphopantetheine arm. This is followed by the condensation domain, which accelerates the formation of peptide bonds joining the adjacent amino acids bound to adjacent PCP domains and the elongation of the peptide. These catalytic domains can also mediate structural changes, such as

domains of epimerisation (E) that make the conversion of L-amino acids into D-amino acids, or domains of modification of the residues of peptides (Fig. 6) (4). The last stage of NRPS mediated synthesis is the thioesterase (TE) domain that catalyses the discharge of the peptide out of the complex of enzymes. This reaction usually leads to intramolecular cyclisation in cyclic lipopeptides, which include surfactin, iturin and fengycin to generate the stable macrolactone or lactam ring structure (Fig. 6) (24).

Gene clusters involved in lipopeptide synthesis

The genes of lipopeptides biosynthesis are typically clustered as biosynthetic gene clusters (BGCs) which encode NRPS enzymes and accessory proteins that mediate metabolite assembly, modification and transport. These groups usually have an area of 30 to 50 kb and several genes with NRPS modules packed in the order of incorporation of amino acids in the product (15, 26). In *Bacillus* species, three large families of lipopeptide are generally produced, including surfactin, iturin and fengycin that are synthesised by three different NRPS gene clusters. Surfactin biosynthetic cluster (*srfA* operon) includes the genes *srfAA*, *srfAB*, *srfAC* and *srfAD* that encode NRPS modules involved in the assembly of surfactin heptapeptide backbone (19). Likewise, the iturin gene cluster (*itu* or *bmy* operon) has NRPS enzymes that produce cyclic heptapeptides which have high antifungal activity. The fengycin operon (fengycin gene cluster) contains various NRPS enzymes, which help to assemble the decapeptide fengycin structure (4, 31). Gram negative bacteria such as *Pseudomonas* make lipopeptides such as viscosin, amphisin and syringomycin using similar NRPS gene clusters with several modules dictating peptide sequence and fatty acid composition. Genome sequencing and bioinformatic studies have also demonstrated that numerous bacterial genomes have several NRPS clusters, allowing the generation of multiple lipopeptide families concurrently (10).

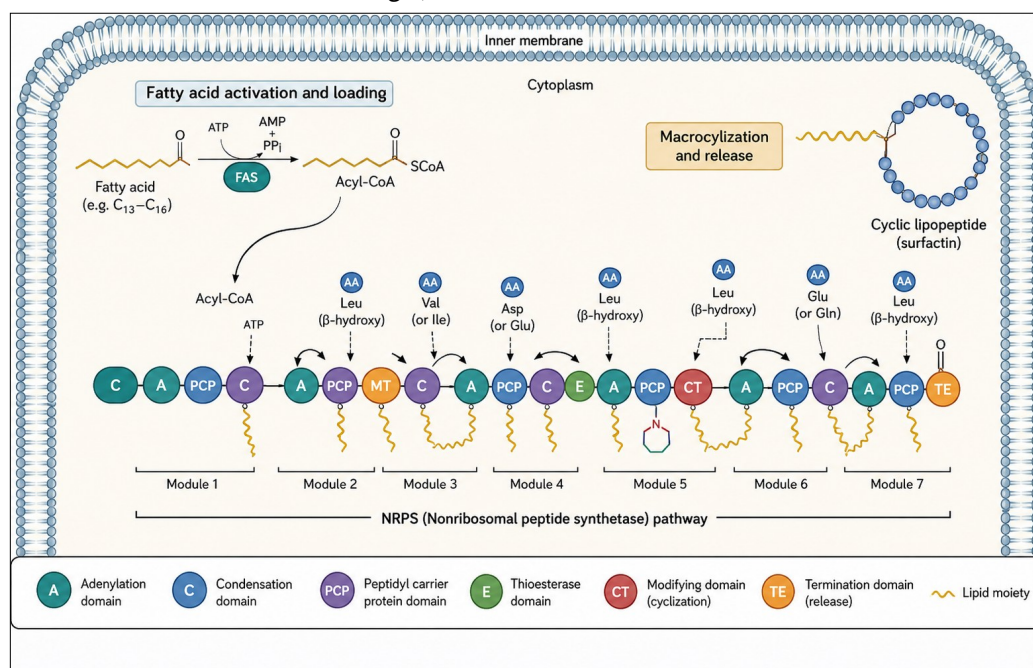


Fig. 6. Lipopeptide biosynthesis.

Fatty acids are activated by acyl-CoA synthetase (ACS) to form acyl-CoA, which is loaded onto the starter module of the NRPS complex. Adenylation (A) domains activate and load amino acids onto peptidyl carrier protein (PCP) domains, while condensation (C) domains catalyse peptide bond formation. Optional modifying domains (MT, E and Cy) introduce structural modifications during peptide elongation. Finally, the thioesterase (TE) domain catalyses macrocyclisation and releases the mature cyclic lipopeptide product. Biosynthesis occurs in the cytoplasm adjacent to the inner membrane.

Source: Gemini AI and Biorender.

Regulation of lipopeptide production

Microbial lipopeptides biosynthesis is impacted by both genetic and environmental factors that regulate gene cluster NRPS expression. In most bacteria, lipopeptide production is regulated by quorum sensing systems, two-component regulatory systems and global transcription factors (11, 46, 47). The ComQXPA quorum sensing system is the most critical regulatory systems in *Bacillus* species and it controls the production of surfactins. The signalling peptide ComX is concentrated in the extracellular space as the cell density increases. At a predetermined concentration, ComX activates the histidine kinase ComP that phosphorylates the response regulator ComA (Fig. 7). Transcription of *srfA* operon is also triggered by activated ComA and results in surfactin biosynthesis (19). The other important regulatory pathway is the

GacS/GacA (Fig. 7) two-component that regulates secondary metabolites production in various bacteria such as *Pseudomonas*. The system controls the expression of small RNA that has the effect of regulating the transcription of NRPS genes that are associated with lipopeptide biosynthesis (4). The list of genes involved in cyclic lipopeptide synthesis is shown in Table 1. Other global transcription regulators, including Spo0A, DegU, CodY and AbrB, (Fig. 7) also take roles in regulating the production of lipopeptides through the response to nutrition availability, stress conditions and transitions in the growth phase (28). The other environmental factors such like temperature, pH, oxygen and carbon sources (Fig. 7) affect the process of lipopeptide synthesis by modulating the expressions of genes and enzyme activity (26).

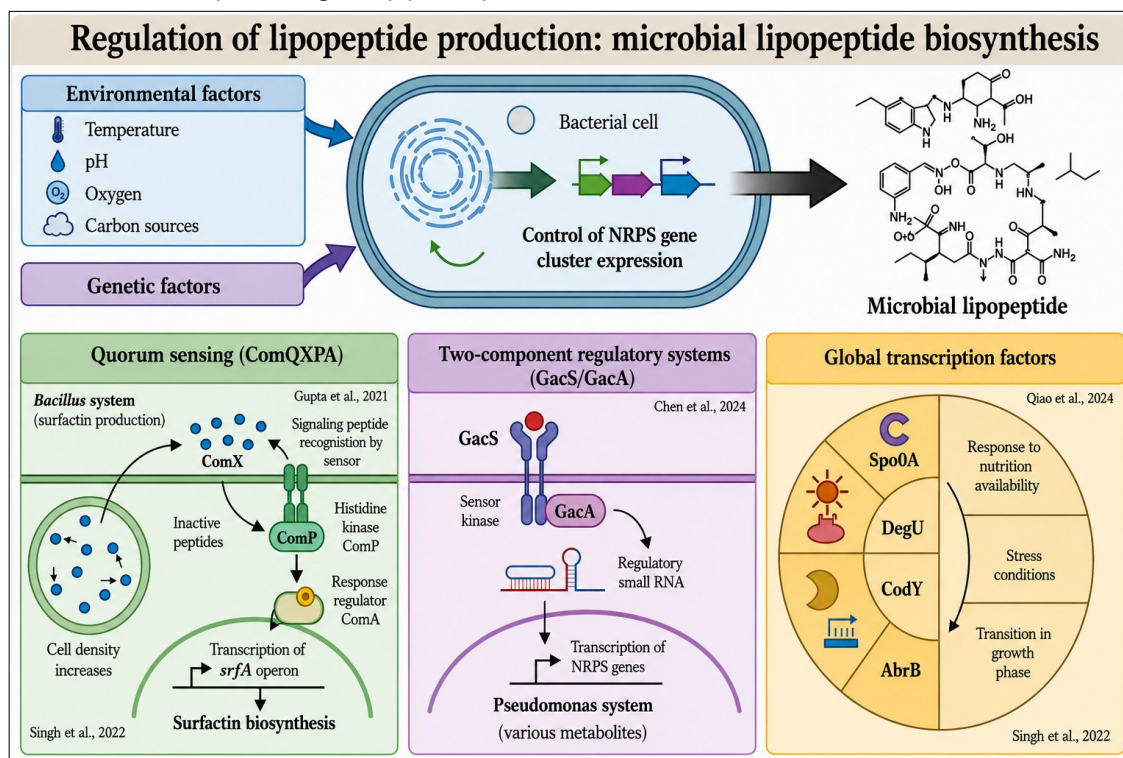


Fig. 7. Regulation of lipopeptide production. Environmental and genetic factors regulate lipopeptide production by controlling the expression of non-ribosomal peptide synthetase (NRPS) genes. Quorum sensing, two-component regulatory systems and global transcription factors control this process in response to changes in cell density, environmental conditions, nutrient availability, stress and different growth.

Source: Gemini AI and Biorender.

Table 1. Major genes involved in cyclic lipopeptide synthesis

Lipopeptide	Producing organisms	Gene clusters	Major genes	References
Surfactin	<i>B. subtilis</i> , <i>B. velezensis</i>	<i>srfA</i> operon	<i>srfAA</i> , <i>srfAB</i> , <i>srfAC</i> , <i>srfAD</i>	(4, 20)
Iturin / Bacillomycin	<i>B. amyloliquefaciens</i> , <i>B. subtilis</i>	<i>itu/bmy</i> operon	<i>ituA</i> , <i>ituB</i> , <i>ituC</i> , <i>ituD</i>	(28, 48)
Fengycin	<i>B. velezensis</i> , <i>B. amyloliquefaciens</i> , <i>B. halotolerans</i>	<i>fen</i> operon	<i>fenA</i> , <i>fenB</i> , <i>fenC</i> , <i>fenD</i> , <i>fenE</i>	(49, 50)
Lichenysin	<i>B. licheniformis</i>	<i>lch</i> operon	<i>lchAA</i> , <i>lchAB</i> , <i>lchAC</i> , <i>lchAD</i>	(51, 52)
Mycosubtilin	<i>B. subtilis</i>	<i>myc</i> operon	<i>mycA</i> , <i>mycB</i> , <i>mycC</i>	(27, 53)
Amphisin	<i>P. fluorescens</i>	<i>ams</i> cluster	<i>amsA</i> , <i>amsB</i> , <i>amsC</i>	(54)
Viscosin	<i>P. fluorescens</i>	<i>visc</i> operon	<i>viscA</i> , <i>viscB</i> , <i>viscC</i>	(55, 43)
Putisolvin	<i>P. putida</i>	<i>pso</i> operon	<i>psoA</i> , <i>psoB</i> , <i>psoC</i>	(56, 12)
Syringomycin	<i>P. syringae</i>	<i>syr</i> operon	<i>syrA</i> , <i>syrB</i> , <i>syrC</i> , <i>syrD</i>	(57, 58)

Methods for detection and characterisation of cyclic lipopeptide metabolites

Cyclic lipopeptides are important microbial metabolites exhibiting antimicrobial, biosurfactant and biocontrol activities and include well-characterised compounds as surfactin, iturin, fengycin and amphisin. The CLPs are complex molecules in structure which consist of a cyclic peptide and a fatty acid chain and hence they cannot be detected and characterised without the application of some analytical techniques. In the past few years, chromatographic separation, mass spectrometry and spectroscopic techniques were used to identify and structurally explain cyclic lipopeptides in a far more effective manner (46, 47). Detection of cyclic lipopeptides typically begins with the extraction and purification of microbial cultures. In most cases, CLPs particularly those derived from marine fermentation are extracted using organic solvents such as methanol, acetone, or ethyl acetate. Standard procedures often involve solvent extraction followed by acid precipitation and subsequent analytical characterisation. Furthermore, chromatographic techniques are widely employed for purification, where methods like solid-phase extraction (SPE) and ultrafiltration are used to concentrate lipopeptide fractions prior to instrumental analysis (8).

Thin-layer chromatography (TLC) and agar diffusion bioassays are widely employed as preliminary screening tools to detect antimicrobial lipopeptides. These techniques are simple and cost-effective; however, they provide only limited structural information and therefore must be followed by more advanced confirmatory analyses. Chromatography forms the backbone of both separation and analytical workflows for cyclic lipopeptides. High-performance liquid chromatography (HPLC) is frequently used to detect and quantify CLPs in microbial extracts, as it efficiently separates lipopeptide homologues that vary in fatty acid chain length and amino acid composition. Typically, reverse-phase C18 columns are used, where separation is governed by hydrophobic interactions between the lipopeptides and the stationary phase. Ultra high performance liquid chromatography (UHPLC) has gained significant attention in recent years due to its higher resolution, faster analysis time and improved sensitivity compared to conventional HPLC methods (26).

These chromatographic approaches are often coupled with spectroscopic or mass spectrometric techniques to obtain detailed structural information. Mass spectrometry is now considered a powerful tool for the identification and characterisation of cyclic lipopeptides. Techniques such as LC-MS and LC-MS/MS allow precise determination of molecular mass, structural variants and peptide sequences. Tandem MS further enables fragmentation of the peptide ring, producing diagnostic ions that help elucidate amino acid composition and fatty acid chain length (22). High-resolution methods like liquid chromatography-high-resolution mass spectrometry (LC-HRMS) enhance the detection of minor lipopeptide congeners in complex microbial extracts and assist in deducing peptide sequence order and structural analogues based on fragmentation patterns (49). Another widely used technique is matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS), which allows rapid screening of cyclic lipopeptide families directly from bacterial colonies or crude extracts. This method has been effectively applied to identify variants of surfactin, iturin and fengycin produced by *Bacillus* species (33).

While mass spectrometry provides accurate mass determination, detailed structural elucidation is achieved through nuclear magnetic resonance (NMR) spectroscopy. Techniques such as ^1H -NMR, ^{13}C -NMR, COSY, HSQC and HMBC offer insights into peptide sequence, stereochemistry and functional groups within the molecule (59).

Mechanisms of action against fungal plant pathogens

Iturins are heptapeptide lipopeptides that bind sterols and phospholipids to fungal membranes, insert their hydrophobic acyl chain and create pores, leading to leakage, oxidative stress, mitochondrial dysfunction and subsequent apoptosis (5–7, 18, 25, 29). Recent studies have identified other targets: iturin A can activate fungal voltage-gated K^+ channels (Fig. 8), which causes an enormous K^+ efflux and cell death, regardless of ergosterol levels (18). Omics studies on *Fusarium graminearum* indicate that a combination of iturin and fengycin treatment disintegrates the membrane ergosterol, phospholipids and GPI-anchored proteins to cause cell wall reorganisation and osmotic imbalance (11, 17). On its own, fengycin destabilises cell wall and membrane structure, disrupts metabolism and triggers programmed cell death and autophagy in a variety of phytopathogens (5, 30–32, 35, 36, 60). Surfactin is a less potent antifungal agent, but capable of working in a synergistic relationship with iturin to create mixed micelles which increase permeabilisation of the membrane (4–6, 19, 20). Kurstakin is an iturin like cyclic lipopeptide produced by beneficial microorganisms that exhibits antifungal activity by disrupting fungal cell membranes and increasing membrane permeability, leading to cell death (33). On a larger scale, *Bacillus* lipopeptides (iturin, fengycin, surfactin, mycosubtilin/plipastatin, kurstakin-like molecules) and daptomycin like NRPS antibiotics are similar in a general amphiphilic, pore-forming membrane mechanism of action, which vary in specific targets of plant pathogens (4–6, 17, 27, 33).

Inhibition of spore germination

In clubroot disease, *B. subtilis* XF-1 mutants lacking fengycin production are less lethal to the germination of the spores of *Plasmodiophora brassicae* due to reduced lysis of the resting spores and reduced protection of Chinese cabbage (35). Surfactin and fengycin product of *B. subtilis* JN005 that deforms *Magnaporthe oryzae* and conidia and drastically decreases the blast count in preventive and curative tests in rice (Fig. 9) (60). Transcriptomic profiling of *Fusarium* and *Plectosphaerella* subjected to iturin depicts colossal restructuring of genes which are related to energy metabolism (17, 61), cell wall formation and stress signalling, which are in line with inhibited germination and initial growth. Several studies have identified inhibition of spore germination as an early and critical event in lipopeptide-mediated biocontrol.

ISR in plants

Recently cyclic lipopeptides have become well established as ISR elicitors. Surfactin is one of the best-characterised ISR elicitors, capable of inducing systemic resistance at nanomolar to micromolar concentrations. (4–6, 19, 62). In various plant–pathogen systems, surfactin has been shown to induce systemic resistance (ISR), whereas fengycin and iturin/plipastatin do not, indicating functional specialisation among different lipopeptide families (4, 5, 62). In wheat, combinations of iturin and fengycin can trigger ISR against *Fusarium* head blight, leading to reduced disease severity and lower deoxynivalenol (DON) accumulation, while also influencing plant hormone pathways such as auxin, cytokinin,

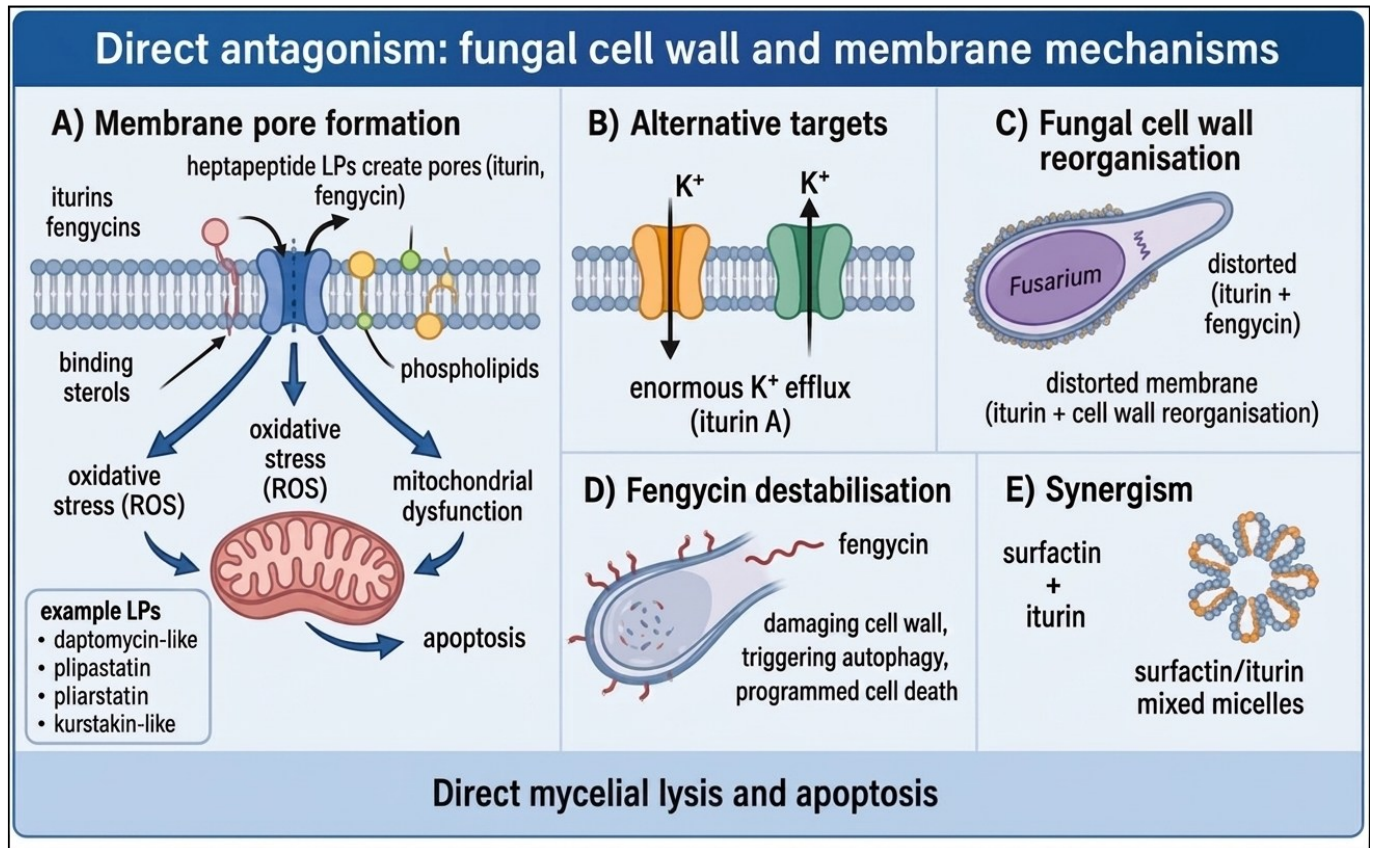


Fig. 8. Fungal cell wall disruption. (A) Membrane pore formation: Lipopeptides (Fengycin) interact with fungal membrane sterols, resulting in pore formation, reactive oxygen species (ROS) generation, mitochondrial dysfunction and apoptosis. (B) Alternative antifungal targets: Lipopeptides (Iturin) inhibit β -(1,3) glucan synthesis, disrupt fungal cell wall integrity and interfere with multidrug efflux pumps. (C) Cell wall regulation: Fengycin and Iturin distort membrane structure, while Surfactin enhances antifungal activity through synergistic interactions with Iturin, leading to fungal cell death.

Source: Gemini AI and Biorender.

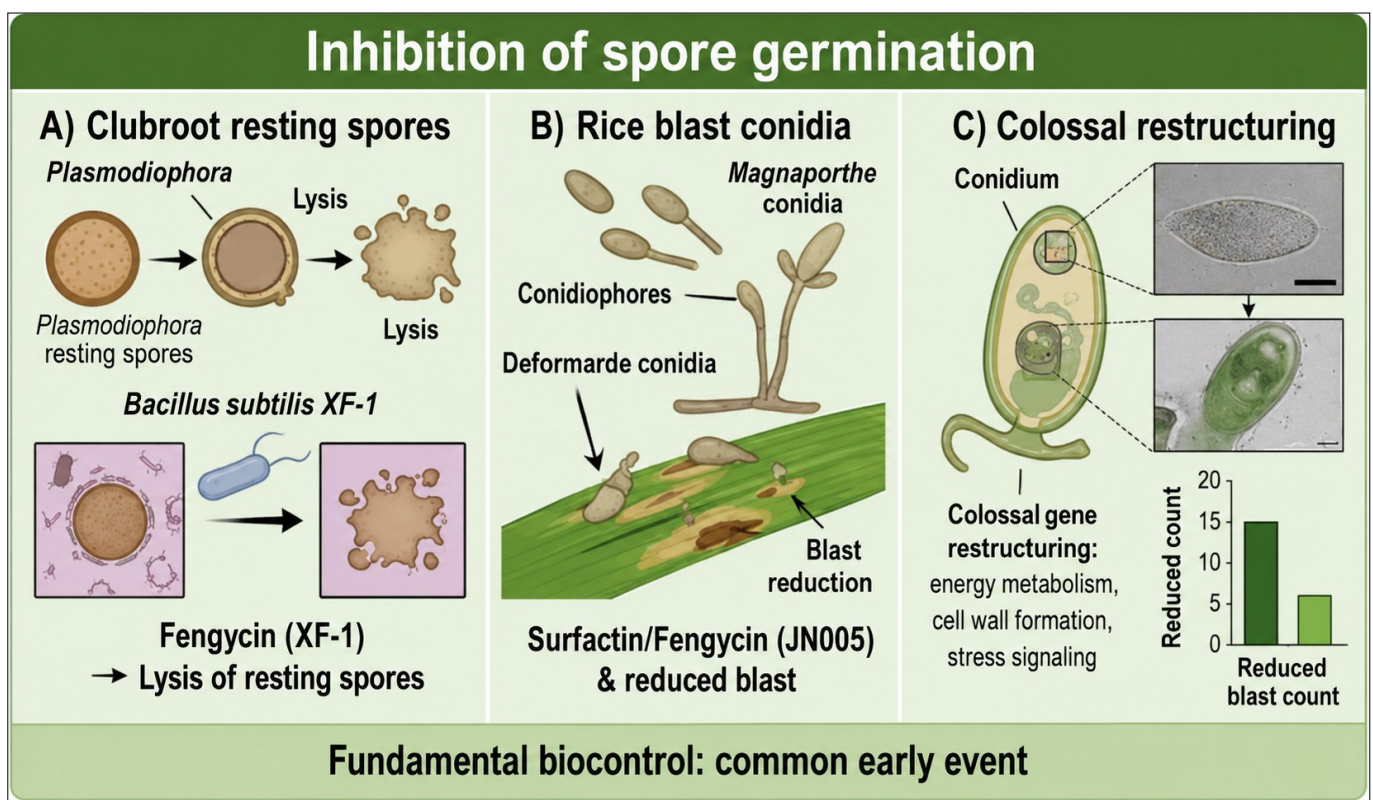


Fig. 9. Inhibition of spore germination. (A) Fengycin produced by *Bacillus subtilis* lyses the resting spores of *Plasmodiophora brassicae*, thereby preventing spore germination. (B) Surfactin and Fengycin produced by *Bacillus* strain JN005 deform and inhibit the germination of *Magnaporthe oryzae* conidia. (C) Cyclic lipopeptides inhibit fungal conidial germination by disrupting energy metabolism, impairing cell wall biosynthesis and inducing extensive intracellular structural changes.

gibberellin, abscisic acid (ABA) and ethylene (17). Similarly, cotton plants treated with *Bacillus* antagonists that produce iturins, surfactins, fengycins and mixirins exhibit enhanced defence responses, including increased activity of enzymes like phenylalanine ammonia-lyase (PAL), polyphenol oxidase (PPO), peroxidase, catalase and superoxide dismutase (SOD). These plants also accumulate higher levels of phenolics and osmolytes, consistent with jasmonic acid (JA) and ethylene (ET)-mediated ISR against pathogens such as *Fusarium* and *Macrophomina* (3, 38, 63). More broadly, ISR studies emphasise the importance of cyclic lipopeptides produced by *Bacillus* and *Pseudomonas*, along with other non-ribosomal peptide metabolites (including daptomycin-like and taromycin-like compounds), as key signalling molecules that coordinate systemic plant defenses mediated by salicylic acid (SA), jasmonic acid (JA) and ethylene (ET) pathways (2, 4, 5, 10, 11, 47, 62, 64).

biofilm formation and root colonisation

Many cyclic lipopeptides act as biosurfactants that shape microbial biofilms and root colonisation. Surfactin is central for surface motility, biofilm architecture and rhizosphere colonisation in *Bacillus* facilitating persistent delivery of other antifungal lipopeptides at the root surface. While fengycin is essential for spore lysis and defence activation in clubroot diseases affected roots, it is dispensable for leaf internalisation and root colonisation of *B. subtilis* XF-1 (35), illustrating division of labor among CLPs. Lipopeptide-producing *Bacillus velezensis* DMW1 (iturin) effectively colonises tomato roots and reshapes rhizosphere microbial communities, enriching beneficial taxa that contribute to long-term suppression of *Plectosphaerella cucumerina* and other pathogens (61). More generally, LPs from *Bacillus* and *Pseudomonas* (including viscosin, amphisin, putisolvin and tolaasin type NRPS products) modulate biofilm formation, surface wettability and competitive exclusion on roots and in the spermosphere, thereby reinforcing both direct antagonism and plant ISR (3, 10, 11, 12, 43, 55, 65).

Mechanisms of action against bacterial plant pathogens

Cyclic lipopeptides produced by beneficial microorganisms including iturins, fengycins, surfactin, bacillomycins, as well as synthetic analogues are amphiphilic molecules that integrate into bacterial membranes, leading to pore formation, leakage of cellular contents and ultimately cell death (4–6, 18). In phytopathogens including *Xanthomonas citri* pv. *malvacearum* and *Pseudomonas aeruginosa*, fengycins cause pronounced alterations in cell surface structure, increased membrane damage and significant potassium (K⁺) efflux, all of which are associated with membrane permeabilisation and lysis (63). At low micromolar concentrations, ultrashort synthetic lipopeptides act rapidly as membrane active agents, exhibiting strong lytic activity against a vast array of plant-pathogenic bacteria while maintaining low phytotoxicity. Similar lipopolysaccharide binding behaviour has been observed in newly developed cationic lipopeptides, where a direct correlation exists between LPS neutralisation and the killing of *Xylella fastidiosa* (6, 63). In addition to their direct antimicrobial effects, lipopeptides produced by *Bacillus* and *Pseudomonas* can induce systemic resistance in plants, activating pathogenesis-related (PR) proteins and hormone-mediated defence pathways that suppress bacterial pathogens such as *Pseudomonas syringae* (3, 11, 41, 43, 47, 55, 64, 65). They also enhance root and rhizosphere colonisation, promote

swarming motility and improve competitive ability, enabling beneficial microbes to outcompete pathogens for space and nutrients. Although the concentration of cyclic lipopeptides in the rhizosphere may be lower than the minimum inhibitory concentrations (MICs) observed under laboratory conditions, their overall effectiveness is achieved through a combination of mechanisms, including induced systemic resistance, inhibition of pathogen adhesion and community-level competition, alongside direct antimicrobial activity (3, 4, 5, 10, 11, 47, 55, 62, 65).

Mechanisms of action against viral plant pathogens

Direct disruption of viral particles represents a key antiviral mechanism of cyclic lipopeptides. Owing to their amphiphilic nature, CLPs can associate with lipid membranes as well as viral structural proteins. For instance, surfactin produced by *B. subtilis* exhibits strong virucidal activity by inserting its hydrophobic fatty acid chain into viral membranes, thereby compromising virion integrity and reducing infectivity (66). Even in the case of non-enveloped plant viruses, CLPs can interact with viral coat proteins, destabilising viral particles and limiting infection efficiency (4). The CLPs also interfere with early stages of viral infection by preventing virus attachment and entry into host cells. Compounds such as surfactin and viscosin alter the physicochemical properties of plant cell membranes, thereby disrupting host-virus interactions and reducing viral adsorption and penetration (11, 55, 66).

Another important antiviral mechanism involves the induction of plant defence responses. The CLPs act as microbial elicitors that activate signalling pathways associated with systemic resistance, leading to the expression of defence-related genes and the production of pathogenesis-related proteins, reactive oxygen species and antimicrobial metabolites (4). This enhanced defence state has been observed in crops such as tomato, tobacco and Arabidopsis, where CLPs like surfactin and fengycin produced by *Bacillus* reduce viral infection levels (34, 67, 68). Additionally, CLP-induced defence responses can suppress viral replication within host cells. Activation of plant immune pathways promotes RNA-based defence mechanisms such as RNA silencing, which targets and degrades viral RNA, thereby limiting genome replication and accumulation (4, 5, 62). Structural defences are also strengthened, as CLPs stimulate the deposition of callose and lignin in cell walls, restricting viral movement through plasmodesmata and reducing cell-to-cell spread (34, 62, 64, 67, 68).

Beyond direct and induced defences, CLPs enhance rhizosphere colonisation and biofilm formation by plant growth promoting rhizobacteria. Surfactin facilitates bacterial motility and biofilm development, allowing beneficial microbes to establish on plant roots and continuously produce antimicrobial and defence-inducing compounds (11). Marine actinomycetes also represent promising sources of antiviral metabolites. Extracts from *Streptomyces variantis*, *Pseudomonas putida* and *Bacillus licheniformis* have demonstrated significant inhibitory effects against Pepper mild mottle virus, reducing infection levels in chilli plants. Identified active compounds include cyclic dipeptides such as cyclo (L-Pro-L-Val), cyclo (Pro-Leu) and cyclo (Phe-Pro), which also trigger hypersensitive responses in *Nicotiana glutinosa*, indicating activation of plant defence mechanisms (4, 11, 19, 55, 62). The list of plant growth-promoting rhizobacteria (PGPR)-derived lipopeptides is presented in Table 2.

Table 2. Plant growth-promoting rhizobacteria (PGPR)-derived lipopeptides for the management of plant diseases

Bioactive compound	Producing organism	Target pathogen	In vitro efficacy	Mode of action	Commercial status	References
Surfactin	<i>B. subtilis</i> M51	<i>Fusarium oxysporum</i> VJ-2 <i>Botrytis cinerea</i> , <i>F. solani</i> , <i>F. graminearum</i> , <i>Bipolaris sorokiniana</i> , <i>Rhizoctonia cerealis</i> , <i>Alternaria alternata</i>	64.35, 44.44, 51.11, 34.07, 40.00, 69.63, 39.26 %	Membrane disruption, oxidative stress induction, ROS accumulation, reduction of peroxidase activity	Experimental stage	(69)
	<i>B. subtilis</i> T6	<i>Alternaria alternata</i>	85.88 %	Membrane disruption and antifungal lipopeptide activity	Experimental stage	(70)
	<i>Bacillus subtilis</i> SCB-1	<i>Alternaria</i> , <i>Cochliobolus</i> , <i>Curvularia</i> , <i>Fusarium</i> , <i>Neodeighthonia</i> , <i>Phomopsis</i> and <i>Saccharicola</i>	Not specifically reported	Volatile-mediated inhibition, membrane disruption	Experimental stage	(71)
	<i>Bacillus amyloliquefaciens</i> ETL2	<i>Xanthomonas citri</i> pv. <i>Malvacearum</i>	Strong inhibition area of 983.76 mm ²	Antibiotic-mediated inhibition of pathogen growth	Experimental stage	(63)
	Chitosan nanoparticles + <i>Bacillus subtilis</i>	Potato virus Y	Synergistic antiviral protection observed	Antiviral activity, induction of systemic resistance, antioxidant enhancement, reduction of oxidative stress	Experimental stage	(67)
Iturin	<i>Bacillus velezensis</i> LB002	<i>Botrytis cinerea</i>	70 %	Plasma membrane disruption, ROS accumulation, cytoplasmic leakage, inhibition of hyphal growth	Experimental stage	(39)
	<i>Bacillus velezensis</i> NRRLB-41580	<i>Phytophthora infestans</i>	80.7 %	Disruption of cell membrane and internal cell structure observed through SEM and TEM	Experimental stage	(29)
Iturin A	<i>Bacillus velezensis</i> HN-2	Pepper veinial mottle virus	60 %	Induced systemic resistance (ISR), activation of antioxidant enzymes, PR protein induction	Experimental stage	(34)
	<i>Bacillus amyloliquefaciens</i>	<i>Fusarium oxysporum</i>	Caused 65–90 % inhibition of fungal growth under <i>in-vitro</i> conditions	Potential application in seed and soil treatment	Experimental stage	(23, 25)
Fengycin	<i>Bacillus velezensis</i> Y19	<i>Ralstonia solanacearum</i>	75 %	Lipopeptide-mediated membrane disruption, biofilm formation, induced systemic resistance (ISR) and rhizosphere colonization	Experimental stage	(72)
	<i>B. amyloliquefaciens</i> A3	<i>Dickeya dadantii</i>	55 %	Membrane destabilisation, suppression of spore germination, mitochondrial dysfunction	Field stage	(73)
	<i>Bacillus velezensis</i>	<i>Fusarium graminearum</i>	60–85 %	Membrane disruption	Field application under investigation	(11, 17)
	<i>Bacillus velezensis</i>	<i>Fusarium verticillioides</i>	100 µg (L1) and 200 µg (L2) of lipopeptides required to control	Membrane disruption	Experimental stage	(74)
	<i>Bacillus subtilis</i> BS155	<i>Magnaporthe grisea</i>	Strong inhibition of <i>M. grisea</i> hyphal growth	Disruption of plasma membrane integrity and fungal cell wall structure	Experimental stage	(36)
Bacillomycin D/L	<i>Bacillus velezensis</i> GFB08	<i>Stemphylium vesicarium</i> , <i>Colletotrichum spaethianum</i> and <i>C. circinans</i>	70, 80, 90 %	Membrane disruption, pore formation, leakage of cytoplasmic contents, inhibition of fungal growth	Experimental stage	(75)
	<i>Bacillus amyloliquefaciens</i> MBI600	Tomato spotted wilt virus, Tomato yellow leaf curl virus, <i>Colletotrichum gloeosporioides</i>	30 %	ROS induction, ISR activation	Experimental stage	(68)
Amphisin	<i>Bacillus subtilis</i>	<i>Rhizoctonia solani</i>	55–80 %	Inhibition of mycelial growth and membrane damage	Experimental stage	(15, 16)
	<i>Pseudomonas fluorescens</i>	<i>Rhizoctonia solani</i>	50–75 %	Significantly inhibited fungal growth and reduced spore germination	Rhizosphere biocontrol application under study	(40)
	<i>Pseudomonas fluorescens</i> DSS73 and <i>Pseudomonas aeruginosa</i> #112	<i>Aspergillus amoebensis</i> DSM 1943, <i>Penicillium nordicum</i> DSM 12639 and <i>Monilinia fructigena</i> IOR 2138	5 mL CFS completely inhibited fungal growth; 2.5 mL partially inhibited growth	Mitochondrial hypertrophy, vacuole formation, membranous vesicle induction	Experimental stage	(44)
Putisolvlin	<i>Pseudomonas capeferrum</i>	<i>Phytophthora capsica</i>	89–99 %	Mycelium inhibition	Experimental stage	(42)
Viscosin	<i>Pseudomonas fluorescens</i>	<i>Rhizoctonia solani</i>	45–65 %	Antibiotic-mediated inhibition of pathogen growth	Under greenhouse evaluation	(45)
Fengycin + Surfactin	<i>Bacillus subtilis</i>	<i>Plasmadiophora brassicae</i>	50 µM shows 60–95 % inhibition	Hyphal swelling, increased septation, membrane destabilization and inhibition of mycelial growth	Experimental stage	(65)
			50–70 %	Inhibited resting spore germination	Integrated disease management potential	(53)

Applications of cyclic lipopeptides

Seed treatment

Seed treatment with cyclic lipopeptide-producing bacteria such as *B. subtilis*, *B. velezensis* and *B. amyloliquefaciens* is used to protect seeds against soil-borne and seed-borne pathogens during early plant development (4, 6, 26, 37). Cyclic lipopeptides including surfactin, iturin and fengycin disrupt fungal cell membranes, inhibit spore germination and prevent pathogen colonisation on germinating seeds (4, 6, 11, 30, 31, 32). Seed coating with CLP-producing *Bacillus* strains improves seed germination, enhances seedling vigour and provides early protection against plant pathogens such as *Fusarium*, *Rhizoctonia* and *Pythium* (3, 26, 76).

Soil applications

Soil application involves introducing CLPs producing microorganisms into the rhizosphere, allowing bacteria to establish and produce lipopeptides *in situ*. This priming strategy is effective for managing soil-borne pathogens like *Fusarium oxysporum*, *Rhizoctonia solani* and *Pythium ultimum* which cause significant losses in crops including cereals, vegetables and pulses (4, 6, 11). The production of iturin and fengycin in the rhizosphere directly inhibits fungal growth by targeting cell membranes, suppressing hyphal elongation and preventing spore germination. Surfactin enhances biofilm formation and motility of *Bacillus*, facilitating rhizosphere colonisation and competitive exclusion of pathogens (6, 49). Moreover, soil-applied CLPs can trigger induced systemic resistance in plants, priming defence mechanisms and enhancing production of pathogenesis-related proteins, phytoalexins and reactive oxygen species (4, 6, 19). These systemic effects not only protect roots but also improve overall plant health and stress tolerance. Soil application is especially valuable in integrated disease management, where combining microbial inoculants with organic amendments or reduced fungicide doses can sustainably suppress pathogens (24).

Foliar spray

Foliar application of CLP-producing bacteria or purified lipopeptides is effective against aerial pathogens affecting leaves, stems and fruits. Direct contact of CLPs with pathogens on the phyllosphere disrupts fungal membranes and inhibits spore germination, thereby preventing disease establishment (4, 6, 26). The CLPs also act as elicitors of plant immunity, activating ISR in leaves. Surfactin, for example, stimulates jasmonic acid- and ethylene-mediated defence pathways, enhancing resistance against leaf spot, blight and mildew diseases (4, 16). Field trials indicate that foliar spraying of *Bacillus*-based CLPs reduces disease severity by 30–60 %, improves photosynthetic efficiency and maintains yield under pathogen pressure (38, 77). Furthermore, CLPs suppress pathogen toxin production and enhance the antioxidant defence system in leaves, providing additional protection against oxidative stress caused by infections.

Commercial formulations

The CLPs are incorporated into commercial biocontrol products due to their broad-spectrum antimicrobial activity and environmental safety. Commercial formulations include wettable powders, granules, liquid suspensions and oil-based formulations containing *B. subtilis*, *B. amyloliquefaciens*, or *B. velezensis* strains that produce surfactin, iturin and fengycin (26, 78). Formulation strategies aim to maintain microbial viability, enhance shelf life and improve field performance under varying environmental conditions (9, 16). Liquid and oil-based formulations improve adhesion to leaf

surfaces during foliar application, whereas granules and powders are suitable for soil and seed treatments (6, 26). The adoption of CLP based biopesticides in integrated pest management (IPM) programs offers an eco-friendly alternative to chemical pesticides. These products not only reduce chemical residues in crops but also contribute to sustainable disease management, improve soil microbial diversity and enhance plant productivity (9).

Challenges and limitations

Despite cyclic lipopeptides having good potential to be used as an environmentally friendly biocontrol agent, there are several challenges that limit their application to large scale in an agricultural system. Surfactin, iturin, fengycin and bacillomycin are surfactants produced by beneficial microorganisms such as *Bacillus* and *Pseudomonas* species and are highly antimicrobial to a variety of plant pathogens. Nevertheless, the laboratory results of these metabolites in the field are still limited by several biological, environmental and technological reasons (7, 13, 19, 30, 79). Large-scale production is costly and intricate and this is one of the major constraints. Processes needed in fermentation to make CLP are frequently highly costly in their need of substrates like glucose, sucrose and yeast extract to make CLP, which form an obstacle to business activities. Besides, industrial-scale production does not yet have an efficient method to ensure that fermentation conditions result in the highest quantity of metabolites (80). The other issue is that the efficacy of biocontrols may vary in the field. The production and activity of cyclic lipopeptides can be heavily affected by environmental factors that include temperature, the content of soil, the availability of nutrients and competition by microorganisms. It has been established that alteration of the abiotic factors (composition of the culture medium and temperature) has a profound impact on CLP biosynthesis and the antagonistic capacity of the *Bacillus* strains against plant pathogens (26). The stability and successful concentration of CLPs in natural conditions is a significant limitation. Cyclic lipopeptides concentrations that exhibit a high level of antimicrobial activity *in vitro* are frequently challenging to obtain or sustain in soils and plants. In natural environments, CLPs necessarily antimicrobial compounds may serve as signaling molecules or plant defence elicitors, but not at higher concentrations and can result in lower pathogen suppressive activity.

The minimal knowledge on the molecular pathways of plant protection by CLP is a setback of their successful use. Even though it is well known that cyclic lipopeptides cause systemic resistance in plants, the specific signaling pathways, receptors and host responses of the process are not clearly understood. This is the inability to create rationalised biocontrol strategies due to the absence of mechanistic knowledge. Regulatory and formulation problems also constitute another limitation. Microbial metabolites used commercially must be in stable formulations to preserve the activity of the metabolites while they are kept in store or in the field. Nevertheless, most CLPs are prone to environmental damage and can need sophisticated formulation technologies like encapsulation or carrier-based delivery systems to remain stable and effective (9, 78). Moreover, the ecological relationships in the rhizosphere can alter the activity of CLP producing microorganisms. The production and activity of cyclic lipopeptides can be changed in response to competition with natural microbial communities, fluctuating root exudates and the presence of other soil organisms and result in negative disease control in various fields (23). Altogether, despite the fact the cyclic lipopeptides are the strong natural metabolites which

can be used in biological regulation, the problems connected with production efficiency, stable conditions in the environment, understanding of their mechanisms and field of operation are to be overcome to be effectively commercialised (3, 5, 6, 8, 66). Future research focusing on genetic engineering of producing strains (19, 26, 28), optimisation of fermentation processes (8, 52, 80) and development of improved formulations (8, 6, 21), along with a deeper understanding of plant-microbe interactions, will be crucial for maximising the effective and sustainable use of cyclic lipopeptides (CLPs) in plant disease management (3, 5, 6, 62).

Conclusion

Cyclic and non-ribosomal microbial metabolites constitute an important group of bioactive secondary metabolites involved in the biological control of plant pathogens. These molecules are synthesised via non-ribosomal peptide synthetase pathways and are predominantly produced by plant growth-promoting rhizobacteria (PGPR) such as *Bacillus*, *Pseudomonas* and *Streptomyces*. This biosynthetic system enables the generation of structurally diverse compounds with strong antimicrobial property. Among these, cyclic lipopeptides such as surfactin, iturin, fengycin and bacillomycin have received considerable attention due to their broad-spectrum antifungal and antibacterial activities, as well as their ability to induce systemic resistance in plants. The distinct structural characteristics of non-ribosomal peptides including cyclic peptide rings, uncommon amino acids and lipid moieties enhance their stability and facilitate strong interactions with microbial membranes. These interactions result in mechanisms such as membrane permeabilisation, pore formation, inhibition of cell wall synthesis and interference with pathogen signalling pathways. Beyond their direct antimicrobial effects, several of these metabolites also function as elicitors of plant defence responses. They activate induced systemic resistance (ISR), thereby strengthening the plant's innate immune system and improving its ability to withstand pathogen attack.

Recent advances in genomics, metabolomics and synthetic biology enhanced the discovery and characterisation of non-ribosomal peptide synthetase gene clusters involved in metabolite biosynthesis. Genome mining strategies revealed a wide array of previously unrecognised biosynthetic gene clusters, underscoring the potential of beneficial microorganisms as valuable sources of novel biocontrol agents. At the same time, improvements in fermentation processes and formulation technologies are enabling the efficient large-scale production and practical field application of microbial metabolites for sustainable crop protection. However, despite this improvement in developments, challenges remain in translating laboratory findings into field-level success. Still the factors such as environmental variability, reduced stability of metabolites under field conditions and regulatory limitations can restrict their widespread adoption in agriculture. The future research should be focused on strain improvement, metabolic engineering and the integration of these metabolites into holistic disease management strategies to enhance their reliability and performance. Overall, cyclic and non-ribosomal microbial metabolites offer a promising, environmentally friendly alternative to conventional chemical pesticides. The continuous exploration of microbial diversity, along with progress in molecular biology and biotechnology, is expected to further expand their application in sustainable plant disease management and eco-friendly agriculture.

Future prospects

Development of stable and cost-effective formulations for improving shelf life and field efficacy of cyclic lipopeptides. Genetic engineering and strain improvement approaches to enhance metabolite production and consistency under field conditions. Multi-location field trials to evaluate the long-term performance of cyclic lipopeptides under diverse environmental conditions. Advanced metabolomic and transcriptomic studies to better understand ISR signalling pathways and plant microbe interactions. Integration of cyclic lipopeptide-producing microorganisms into sustainable integrated disease management and eco-friendly agricultural practices.

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Authors' contributions

PS¹ and KK conceptualised the study and prepared the original draft. PS², OM, JI, RS, PR and SM revised the manuscript, incorporated the tables and figures and proofread the final version. All authors have read and approved the final manuscript [PS¹ stands for Punitha Shanmugam and PS² stands for Prabhu Somasundaram].

Compliance with ethical standards

Conflict of interest: Authors do not have any conflicts of interest to declare.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used Google Gemini to generate images, as some of the required illustrative images were like those available in the BioRender application and therefore alternative image generation was needed. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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