Bacterial Cyclic Lipopeptides: Nature's Tiny Warriors Boosting Plant Health and Soil Life

Vicky Rajadurai[1], Sreegayathri Elango*[2], Durgadevi Dhakshinamoorthy[2], Kalaivannan Ravichandran[2]

III B.Sc., (Hons.) Agriculture, Vanavarayar Institute of Agriculture, Pollachi – 642103, Coimbatore, Tamil Nadu, India.

Assistant Professor, Department of Plant Pathology, Vanavarayar Institute of Agriculture, Pollachi – 642103, Coimbatore, Tamil Nadu, India.

Corresponding Author: prakrudhi99@gmail.com, vickyrajadurai1@gmail.com

Abstract

Modern agriculture often relies heavily on synthetic chemicals to control plant diseases and ensure high productivity, but this approach has serious downsides Excessive use of these chemicals can disrupt soil microbial communities, contaminate water and foster more resilient plant pathogens. As a result, there is a growing need for safer, environmentally friendly solutions, making lipopeptides increasingly important in sustainable agriculture. Cyclic lipopeptides (CLPs) are potent bioactive molecules produced by beneficial bacteria such as *Bacillus* and *Pseudomonas* species, playing vital roles in plant disease management. They function through multiple mechanisms, including direct antimicrobial activity by disrupting pathogen membranes and indirect stimulation of plant defence via induced systemic resistance (ISR). CLPs are synthesized by non-ribosomal peptide synthetases, resulting in diverse structures that determine their specific activities. Surfactin, iturin, and fengycin are prominent CLP families known for their antimicrobial and immune-priming properties. These molecules modulate plant immunity by interacting with plasma membrane components, triggering signaling cascades without causing cellular damage. The effectiveness of ISR induction varies with CLP type, plant species, and pathogen, highlighting the complexity of plant–microbe interactions. Beyond pathogen control, CLPs promote beneficial microbial interactions, enhance bacterial colonization, motility and biofilm formation, contributing to a healthy rhizosphere. While CLPs offer promising eco-friendly alternatives to chemical pesticides, challenges such as low natural production, extraction difficulties, field efficacy in complex environments and regulatory considerations remain. Advances in biotechnology and molecular understanding of CLP mechanisms will be crucial to develop efficient, scalable and sustainable CLP-based biocontrol agents.

Introduction

Plants face constant threats from diseases caused by fungi, bacteria and other pathogens. Unlike animals, plants cannot move to escape danger. Instead, they rely on natural partnerships with beneficial bacteria living around their roots in the "rhizosphere" to protect themselves. A remarkable group of molecules called cyclic lipopeptides (CLPs), produced by these helpful soil bacteria, play a crucial role in this protection and in shaping the bustling life beneath the soil surface. Lipopeptides (LPs) are small molecules made by fungi and bacteria like *Bacillus, Pseudomonas, Streptomyces* and other bacteria. They are synthesized via non ribosomal peptide synthetases (NRPSs) and feature a cyclic or short linear peptide linked to a lipid tail. LPs act as antimicrobials, surfactants, immunosuppressants and more. Their main function in disease management is forming pores in pathogen membranes, which disrupts vital cell processes and leads to cell death. Beyond this, lipopeptides can also play roles in microbe surface attachment, motility and triggering plant immune responses.

Cyclic Lipopeptides (CLPs) and its biosynthesis

CLPs are small molecules made by bacteria that combine a short chain of amino acids (the building blocks of proteins) arranged in a closed loop (cyclic peptide) linked to a fatty acid chain. This combination gives them a unique nature where one part is watery (hydrophilic) and one part is oily (hydrophobic). This amphiphilic design allows CLPs to interact strongly with cell membranes, which are made of lipids. CLPs are made by specialized bacterial enzymes called non ribosomal peptide synthetases (NRPSs), which assemble amino acids and fatty acids with great precision. Different bacteria produce many types of CLPs that vary in their amino acid sequence and fatty acid chains, resulting in diverse forms with distinct biological activities. These enzymes first build the peptide ring, then attach a fatty acid chain in different ways depending on the specific CLP being produced. In *Bacillus* species, there are three main CLP families are surfactins, iturins and fengycins each differing in peptide sequence and fatty acid type. Surfactins are heptapeptides linked to β-hydroxy fatty acids (13-15 carbons), mainly known for their surfactant properties and some antiviral and antibacterial effects, but weak antifungal activity (Chen *et al.*, 2022). Iturins are also heptapeptides but linked to β-amino fatty acids (14-17 carbons) and have strong antifungal effects, along with hemolytic activity. Fengycins consist of a decapeptide linked to β-hydroxy fatty acids (14-18 carbons), and are powerful against filamentous fungi but less hemolytic than surfactins or iturins. Other bacteria like *Paenibacillus, Burkholderia*, *Serratia*, and *Streptomyces* also produce specialized CLPs but are less studied in the context of plant health.

Lipopetides produced by plant beneficial bacteria and its functions

Bacillus and *Pseudomonas* species are major producers of lipopeptides (LPs), natural compounds key to their survival and antimicrobial abilities. Both bacteria thrive in diverse habitats and include beneficial and pathogenic strains. LPs from these genera exhibit vast structural diversity due to variations in the length and composition of their lipid tails and amino acid sequences. *Pseudomonas* cyclic LPs were initially grouped into four types: viscosin (9 amino acids), amphisin (11 amino acids), tolaasin (19–25 amino acids with unusual residues), and syringomycin (9 amino acids with unique amino acids including chlorinated residues). Newer *Pseudomonas* LPs like putisolvins and orfamides show distinct structural features and cyclization patterns, with some LPs being linear rather than cyclic. *Bacillus* LPs also vary structurally, and single strains can produce multiple analogs differing in peptide and lipid components, impacting their antimicrobial properties and biological functions. Surfactins (e.g., pumilacidin, lichenysin) have heptapeptide rings linked to β-hydroxy fatty acids and act as powerful biosurfactants. Fengycins (including plipastatin) are decapeptides connected to β-hydroxy fatty acids, showing strong antifungal activity. Iturins (such as bacillomycin, mycosubtilin) are heptapeptides with β-amino fatty acids, known for potent antifungal and membrane-disrupting effects. Additional *Bacillus* CLPs like kurstakin and locillomycin differ in fatty acid types and peptide structure, with ester bonds dominating β-hydroxy types (e.g., surfactin) and amide bonds common in β-amino types (e.g., iturin). *Serratia* species produce unique cyclic lipopeptides (CLPs), mainly from the Serrawettin family, which includes serratamolide A to G and serrawettins W2 and W3. Serratamolide A (also called serrawettin W1) has a symmetric dilactone structure with two β-hydroxy fatty acids linked to two serine amino acids and shows antitumor, antimicrobial, and plant-protective effects. *Actinomycetia* bacteria also produce diverse bioactive CLPs (Balleux *et al.*, 2025). *Streptomyces* species are prolific producers of CLPs, including the clinically important antibiotic daptomycin and others like calcium-dependent antibiotics and amphomycin, contributing valuable drugs and bioactive compounds (Wang *et al.*, 2023). *Paenibacillus* produces diverse cyclic lipopeptides (CLPs) with broad antimicrobial activity. Fusaricidins have a hexapeptide ring and exhibit antifungal and antibacterial effects, with structural variations affecting their potency. Cationic CLPs include polymyxins (such as colistin), octapeptins with broad-spectrum activity and lower toxicity and other peptides like paenibacterin and pelgipeptin. Notably, octapeptins act against both Gram-negative and Gram-positive bacteria through unique mechanisms.

Identification and characterization of these LPs use chemical analyses such as chromatography and spectroscopy, alongside immunological assays that offer sensitive in situ detection, especially in plant-associated environments. Various molecular tools like PCR primers help detect LP-producing strains by targeting genes linked to LP biosynthesis. Overall, the structural diversity and advanced detection methods highlight *Bacillus* and *Pseudomonas* LPs' complexity and their important role in microbial ecology and potential agricultural applications.

Role of CLPs in Shaping Key Developmental Traits

Surface motility is vital for plant-associated *Bacillus* to compete and colonize roots. Surfactin, by lowering surface tension, enhances sliding motility and flagella-driven swarming, helping *Bacillus* spread and colonize new root sites. It also triggers biofilm formation by signalling potassium leakage, which activates genes for matrix production. Biofilms support bacterial fitness, protect cells from competitors and are critical for stable root colonization. While surfactin plays a key role, other cyclic lipopeptides like iturins also aid in biofilm formation, with effects varying by strain. *Pseudomonas* CLPs similarly regulate biofilms, promoting or dispersing them depending on type. Additionally, surfactin can increase genetic transformation by enhancing cell membrane permeability, facilitating horizontal gene transfer important in bacterial evolution and adaptation. These functions make surfactin essential for *Bacillus* survival and competitiveness in the rhizosphere. They support symbiotic relationships, such as with arbuscular mycorrhizal fungi, enhancing plant nutrient uptake. CLPs additionally act as chemical signals or "public goods" within microbial communities. This signalling helps bacteria organize cooperative actions, improving their survival and colonization in complex environments like the rhizosphere. CLPs serve as both microbial weapons and communication tools, enabling *Bacillus* and related bacteria to thrive and protect plants in competitive soil ecosystems.

Beneficial CLPs: Dual Role in Defense Against Pathogens and ISR Induction

Bacillus subtilis and *Pseudomonas* strains can stimulate plant defense through cyclic lipopeptides (CLPs), with surfactin playing a key role in triggering induced systemic resistance (ISR). In tobacco cells, micromolar levels of surfactin but not fengycin or iturin induce early defense responses like medium alkalinization, ion fluxes, and reactive oxygen species production. Surfactin also activates defense enzymes and changes phenolic compound production without harming the plant cells. Its perception seems based on the structure of both the fatty acid and peptide parts, interacting with the plasma membrane to trigger a signaling cascade. This activation leads to enhanced plant immune responses, showing how beneficial bacteria communicate with plants to boost their defenses. Fengycin and iturin family cyclic lipopeptides (CLPs) also trigger induced systemic resistance (ISR) in various plants (Ding *et al.*, 2025). Fengycin induces ISR in tomato against *Botrytis cinerea*, *Arabidopsis* against *Pseudomonas syringae*, and Chinese cabbage against *Plasmodiophora brassicae*. Iturin protects strawberry, chili pepper and *Arabidopsis* against several pathogens. In rice, fengycin and iturin work synergistically to induce ISR regardless of soil type. ISR efficacy is plant and pathogen-dependent; for example, surfactin induces resistance in beans and peanuts but not in tomatoes, while fengycin primes tomato defenses but not beans. Surfactin uniquely triggers ISR against certain pathogens like *Podosphaera fusca* in melon. These findings highlight the complex relationship between CLP type, plant species, and pathogen in determining ISR effectiveness. Combining mycosubtilin (an iturin variant) with fengycin and surfactin enhances control of *Fusarium oxysporum* (Al-Mutar *et al.*, 2023). *Bacillus subtilis* inhibits *Botrytis cinerea* using both surfactin and plipastatin (a fengycin variant). Surfactin and fengycin also show synergistic antifungal effects against a tebuconazole-resistant *Venturia inaequalis* strain. Additionally, cyclic lipopeptides from *Streptomyces*, *Pseudomonas*, *Brevibacillus*, and *Serratia* exhibit direct antibiotic activity, though their toxicity toward other soil microbes requires further study.

CLP Perception and Signaling in Plants

Plants recognize microbes through plasma membrane pattern recognition receptors (PRRs) that detect conserved microbial molecules called microbe-associated molecular patterns (MAMPs), triggering pattern-triggered immunity (PTI). Unlike PTI's immediate and energy-intensive defense, beneficial bacteria-triggered induced systemic resistance (ISR) primes plants to respond more efficiently upon future pathogen attacks without significant metabolic cost. For example, surfactin from *Bacillus* does not strongly activate early PTI responses like reactive oxygen species but primes plants for enhanced defense when challenged. CLPs interact specifically with membrane components, causing subtle perturbations to trigger signaling cascades leading to ISR (Figure 1). The effectiveness of CLPs depends on their precise structural features, such as fatty acid chain length and peptide configuration, which influence their membrane affinity and biological activity. Unlike classical receptor-ligand binding, surfactin likely triggers lipid-driven signaling, including modulation of jasmonic acid pathways. Though structure-activity relationships provide insight into CLP function, plant molecular sensors and detailed signaling networks remain largely unknown, highlighting the need for further study to fully understand CLP-mediated plant immunity.

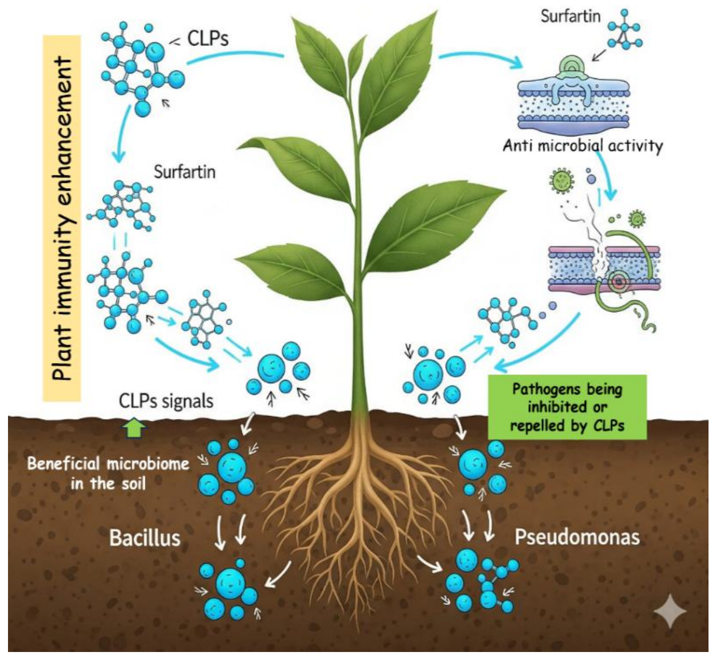

Fig. 1 Cyclic lipopeptides produced by beneficial soil microbes enhance plant immunity and suppress pathogens, promoting sustainable agriculture

CLPs as Mediators of Mutualism

Bacillus subtilis produces surfactin, a key molecule that aids its survival and competitiveness within microbial communities. Surfactin enhances bacterial motility, biofilm formation, and sporulation helping *Bacillus* colonize and persist in complex soil environments. It also acts as a signaling molecule, promoting coexistence and cooperation with other beneficial microbes like *Paenibacillus dendritiformis* and *Pseudomonas chlororaphis*, while boosting fungal partners such as arbuscular mycorrhizal fungi. Surfactin facilitates horizontal gene transfer by inducing cell lysis and DNA release within *Bacillus* populations, contributing to genetic diversity and adaptation. Its role extends to eliciting plant immune responses, stimulating induced systemic resistance in various dicot plants. Overall, surfactin is a versatile molecule central to *Bacillus* ecology, microbial interactions, and plant health. Iturin functions as an ISR elicitor in wheat as well as in rice.

Challenges and Opportunities for Agricultural Application

Cyclic lipopeptides (CLPs) from bacteria like *Bacillus* and *Pseudomonas* show great promise as eco-friendly alternatives to chemical pesticides due to their antimicrobial and plant immunity-boosting properties. However, challenges remain for their commercial use. Natural bacterial production of CLPs is low, so improving yield requires advanced metabolic engineering and optimized fermentation processes. Extracting and stabilizing CLPs efficiently and cost-effectively for field application also poses difficulties. While CLPs are effective in lab settings with controlled soils, their performance under complex natural environmental stresses needs more validation. Additionally, regulatory frameworks demand thorough ecological safety assessments to confirm that CLPs do not harm non-target organisms or disrupt soil ecosystems. Continued advances in synthetic biology, improved bioprocessing techniques, and deeper understanding of CLP mechanisms of action are expected to overcome these challenges and enable wider use of CLP-based biocontrol products in sustainable agriculture.

Conclusion

Cyclic lipopeptides (CLPs) are multifunctional bioactive molecules produced mainly by *Bacillus* and related bacterial species. Their unique cyclic structure confers high stability and diverse biological activities, including potent antimicrobial effects against fungi and bacteria, as well as immune-boosting properties in plants. CLPs act not only by directly disrupting pathogen membranes but also by signalling to both microbial communities and host plants, enhancing plant defences and promoting beneficial microbe interactions. Their amphiphilic nature facilitates motility, biofilm formation and environmental adaptation for the producing bacteria. Despite promising roles in sustainable agriculture and potential medical applications, challenges such as production scale-up, purification, and understanding precise mechanisms in complex ecosystems remain. Continued research and technological advances are crucial to fully harness CLPs as eco-friendly biocontrol agents and therapeutic molecules, supporting integrated pest and disease management and reducing reliance on chemical pesticides.

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