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# Lipopeptides: A Distinct Class of Antibiotics with Diverse Applications

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**Abstract**

A number of novel microbial lipopeptides (LPs) have been reported over the last few years for their potential therapeutic applications for human welfare. Bacterial lipopeptides are of 1.1 to 1.2 kDa small lipidic peptides which have some specific/unique physicochemical and biochemical properties that make them successful for use by human beings. In the context of biological control, the three families of genus of *Bacillus* lipopeptides i.e. Surfactins, Iturins and Fengycins have been studied for their potent antagonistic activities against human as well as plant diseases. Iturins are composed of two major parts: a peptide part of 7 amino acid residues and a hydrophobic tail of 11-12 carbons. Surfactin (~1.036 kDa) is an amphipathic cyclic lipopeptide consisting of Glu-Leu-Leu-Val-Asp-Leu-Leu (ELLVDLL) interlinked with β-hydroxy fatty acid chain of the length of 12 to 16 carbon atoms to form a cyclic ring of lactone. The Surfactin molecule presents a high resistance to heat, cold and stearic influences. Fengycin is a bioactive lipopeptide produced by several strains of *Bacillus subtilis*. It has antifungal activity against filamentous fungi. The lipopeptide (LP) molecules are mainly considered as potent alternatives to the current problem of resistance of pathogens to the conventional antibiotics, microbial infections and life-threatening diseases. Besides antibiotic applications, the LPs may be used to enhance oil recovery, killing of cancer/ tumour cells and its possible application in loss of fat cells allowing anti-obesity treatment. Interestingly, the bacterial lipopeptides have lower toxicity for plants and animals, high biodegradability, low irritancy and good compatibility with human skin.

**Keywords:** Lipopeptides; Surfactins; Iturins; Fengycins; Structure; Applications

## Introduction

Environment pollution, food scarcity and health concern are serious problems in the today's scenario. Almost all the synthetic surfactants are toxic and not ecofriendly. They lead to adverse effects in the environment and also cause human skin health problems [1-3]. These chemical compounds extensively used in petroleum/oil industries are usually toxic, irritant and recalcitrant leading to disposal problems for oil field produced water, ground water contamination and ample health risks to humans [4]. Substantial use of chemicals to control plant/animal diseases has disturbed the ecological balance of microbes inhabiting soil leading to development of resistant strains of pathogens [5,6].

Cancer, a cell-proliferation disorder involving an obstruction to apoptosis, was one of the most frightened diseases of the 20th century and its continued spread with gradually increasing incidence has entered into the 21st century [7]. Apoptosis, which is a major method of programmed cell death, plays an important role in the regulation of tissue development and homeostasis [8].

The constant increasing drug resistance in the bacteria has elicited an urgent need to find out some other alternative lipopeptide-like molecules to be used for clinical and therapeutic applications as well as in food preservation and dairy products [9]. Demand of LPs is also surging by leaps and bounds due to their utility for the human welfare [6]. The published literature indicates that members of the genus *Bacillus* are considered as efficient natural microbial factories for the large scale production of such bioactive antibiotic molecules [10]. Due to diverse applications of lipopeptides, these antibiotics are considered as versatile weapon(s) to combat disease causing pathogenic organisms of the human beings. The three families of *Bacillus* lipopeptides i.e. Surfactins, Iturins and Fengycins have been studied for their vigorous antagonistic activities against various phytopathogens, too [11]. Polymyxin lipopeptide binds to lipopolysaccharides by electrostatic interaction through its N-terminal fatty acryl tail and exhibits potent antibacterial activity [12]. Multiple applications of Surfactin make it an effective candidate drug for the resolution of a number of global issues in the field of medicine [13], industry [14] and in environmental protection [15]. Interestingly, the bacterial lipopeptides are also getting more attraction due to their lower toxicity for plants and animals, high biodegradability, low irritancy and compatibility with human skin [16,17].

## Types of microbial lipopeptides

Lipopeptides are a unique class of relatively low molecular weight compounds, which lower the surface and interfacial tension more efficiently than other bio surfactants. Lipopeptides which are predominantly synthesized by *Bacillus* spp. have good heterogeneity in the type and sequence of the amino acid moieties as well as in the nature, length and branching of attached fatty acid chain and their moieties [18]. Lipopeptides are mainly classified into: Iturins, Surfactins and Fengycins bio surfactants. Broadly there are four types of LPs namely Surfactins, Iturins and Fengycins and Kurstakins produces by various organisms.

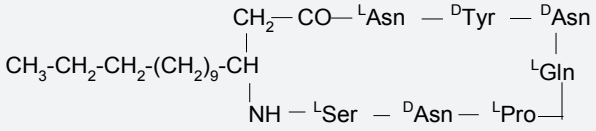


**Figure 1:** Cyclic structure of the lipopeptide Iturin A, containing 7 amino acids as well as 13-carbon long chain that indicate its amphipathic nature. The amino acids involved in this structure are three D-amino acids (Tyr, Asn, and Asn) and four L-amino acids (Pro, Ser, Asn and Gln).

**Iturins:** Amongst the three types of lipopeptides, Iturins has a molecular mass of ~1.080 kDa [19]. Iturin is composed of two major parts: a peptide part of 7 amino acid residues and a hydrophobic tail of 11-12 carbons (Figure 1). This structure of Iturin A clearly indicates an amphiphilic character of this compound, thus pointing towards the cellular membranes as the most probable site of its action [20]. Iturin lipopeptide is a cyclic peptide of 7 amino acids (heptapeptide) linked to a fatty acid (β-amino) chain that can vary from $C_{14}$ to $C_{17}$ carbon molecules, exhibits strong *in vitro* antifungal activity through the formation of ion-conducting pores on fungal membranes [11]. They exhibit structural heterogeneity at the amino acid residues as well as in fatty acid chain length and branching.

Some examples of these amphiphilic compounds include Iturins A, C, D and E, Bacillomycins D, F and L, Bacillopeptin and Mycosubtilin, all of which are arranged in an amino acid configurational sequence of LDDLLDL. Especially, Iturin A is composed of up to eight isomers (Iturin A1-A8) with different lengths (10-14 carbons) and branching (n, iso or anteiso configurations) of the fatty acid chain. These lipopeptide molecules are of appreciable interest because of their biological as well as physico-chemical properties, which can be exploited in food, oil and pharmaceutical industries. All strains of *Bacillus subtilis* produce lipopeptides of Iturin family. Iturin operon has a size of 38-40 kb and made up of four open reading frames namely ItuA, ItuB, ItuC and ItuD [21].

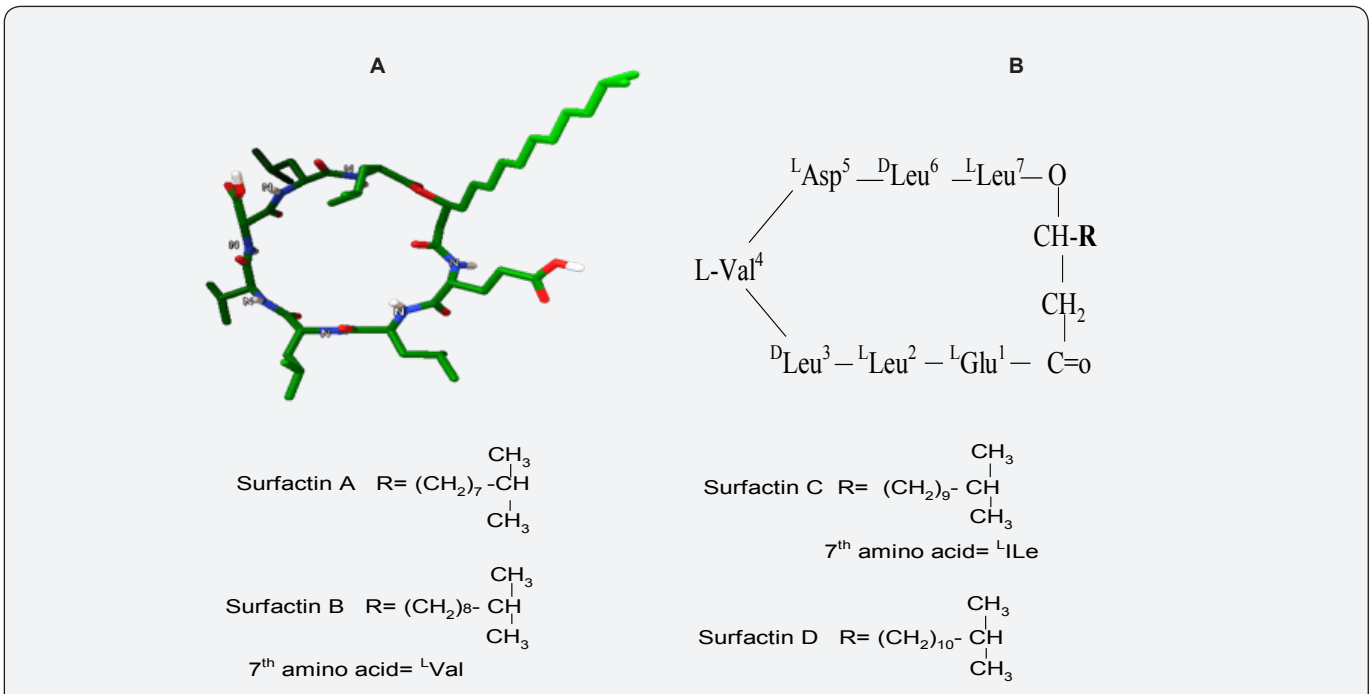


**Figure 2:** (A) Surfactin structure generated by PyMOL viewer.
(B) Heptapeptide cyclic structures of different isomers of surfactins, containing both hydrophobic and hydrophilic amino acids. This lipopeptide contains two D-amino acids (Leu and Leu) and five L-amino acids (Val, Asp, Leu, Glu and Leu) thus indicating its amphipathic nature.

**Surfactins:** Surfactin (~1.036 kDa), an amphipathic cyclic lipopeptide consists of Glu-Leu-Leu-Val-Asp-Leu-Leu (ELLVDLL) interlinked with β-hydroxy fatty acid chain of the length of 12 to 16 carbon atoms (Figure 2) to form a cyclic ring of lactone [22]. Same sequence of amino acids is also found in AMS-$H_2O$-1, a strain of *Bacillus* spp. well known for the lipopeptide


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production. The type of Surfactin varies according to the order of amino acids and the size of lipid portion present in the molecule [23]. Hydrophobic amino acids of the Surfactin molecule are located at 2, 3, 4, 6 and 7 positions from right below in the cyclic structure while the Glu and Asp residues located at 1 and 5 positions, respectively introduce two negative charges to the molecule. Usually, Surfactin isoforms coexist in the cell of a bacterium as a mixture of several peptidic variants with a different aliphatic fatty acid chain length. The pattern of amino acids and β-hydroxy fatty acids in the Surfactin molecule depends not only on the producer bacterial strain but also on the type of bacterial culture conditions [22]. The β-turn may be formed by an intramolecular hydrogen bond, whereas the β-sheet may depend on an intermolecular hydrogen bond [24]. Under natural conditions, the Surfactin is produced with a mixture of its isomers. Composition of this mixture depends on the external factors like growth medium and physico-chemical factors and type of culture conditions.

This Surfactin lipopeptide molecule presents high resistance to heat, cold and stearic influences. The amino acid chain of the Surfactin can vary in its sequence, whereas the Surfactin molecules can be classified into 4 isoforms namely Surfactin A, Surfactin B, Surfactin C and Surfactin D (Figure 2). In Surfactin molecule, residues number 2 and 6 face each other in the vicinity of the acidic Glu-1 and Asp-5 side chains, which define a minor polar nature of the molecule. Residue 4 faces the connection of a long lipid chain consisting a major hydrophobic domain, which includes the side-chains of residues 3 and 7 to a lesser extent, giving it amphiphilic nature and strong surfactant properties [25].

**Fengycins:** Fengycin is a bioactive lipopeptide produced by several strains of *Bacillus subtilis*. It has antifungal activity against filamentous fungi [26]. This represents the third family of LPs after the Surfactin and Iturin and is also called Plipastatin (Figure 3).

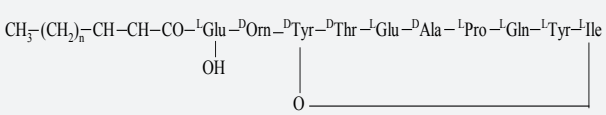


**Figure 3:** Primary cyclic structure of Fengycins A. This structure usually contains a peptide chain of 10 amino acids and a β-hydroxy fatty acid chain that can vary according to fengycins isomer from C-14 to C-17 carbons. This lipopeptide contains 6 moieties of L-amino acids (Glu, Glu, Pro, Gln, Tyr and Ile) and 4 moieties of D-amino acids (Tyr, Orn, Thr and Ala).

These bioactive molecules are lipopeptides containing lactone ring in the β-hydroxy fatty acid chain that may be saturated or unsaturated. The structure of Fengycin contains a peptide chain of 10 amino acids linked to a fatty acid chain [27]. The length of the fatty acid chain can vary from $C_{14}$ to $C_{17}$ carbon atoms for Fengycin thus giving different homologous compounds and isomers. Fengycins are cyclic decapeptide formed by lactonization. The peptide portion of Fengycin lipopeptide consists of a decapeptide chain (Figure 3), which is made up of 8 amino acids (Tyr, Thr, Glu, Ala, Pro, Gln, Tyr and Ile) that are involved in the formation of a peptide ring via lactone linkage between side chain phenolic -OH group of $Tyr_3$ and C-terminal -COOH group of $Ile_{10}$ [28]. Members of Fengycin family exhibit heterogeneity at 6th position in peptide moiety as well as in chain length of ß-hydroxy fatty acid, which varies from $C_{14}$ to $C_{17}$ carbons. On the basis of variation at single amino acid at 6th position in peptide ring, Fengycins have been classified in two classes' *viz*. Fengycin A and Fengycin B. Fengycin A contains Ala at position 6 which is replaced by Val in case of Fengycin B.

**Polymyxins:** Polymyxin family of lipopeptides contains 10 amino acids with a content of the non-proteinogenic amino acid 2,4-diamino butyric acid. Usually, seven amino acids form a peptide cycle and a fatty acid is fused to the C-terminus of the three exocyclic amino acids. Six-methyl-octanoic acid or 6-methyl-heptanoic acid can be found as lipid side chain moiety. Two representatives, Polymyxin B (i.e. a mix of Polymyxin B1 and B2) and Polymyxin E (i.e. a mix of Polymyxin E1 and E2 ) obtained from *B. polymyxa* and *B. colistinus*) respectively, are already in clinical use. Polymyxins show little activity against Gram-positive and anaerobic bacteria but have potent bactericidal activity towards many Gram-negative bacteria including clinically relevant *Pseudomonads, Enterobacteria* and *Acinetobacter* species [29]. This can be explained by their mode of action, which involves a specific interaction of the penta-cationic peptide ring with lipopolysaccharide (LPS) of the anionic outer membrane, a target structure which exists solely in Gram-negative bacteria. By binding to LPS, Polymyxins competitively displace calcium and magnesium bridges which stabilize the outer leaflet of the outer membrane [30].

## Applications of LPs

Amongst the lipopeptides, Surfactin has been preferentially accepted as a potent antimicrobial and anticancer candidate drug for various commercial applications (Figure 4).

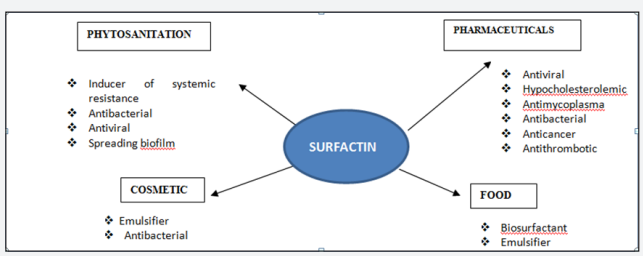


**Figure 4:** Broader applications of Surfactin [5].

**Antitumor activity and induction of apoptosis by ROS/JNK pathway by the Surfactin:** Surfactin is an important bacterial lipopeptide considered as a versatile molecule with wider applications. Surfactins have been reported to show anticancer activity against Ehrlich's ascites carcinoma cells. The effect of Surfactin as cytotoxic agent on to the proliferation of a human colon cancer cell lines such as HCT-15 and HT29 [31] has


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also been reported. The transformed cells inhibition by Surfactin was due to the cell-cycle arrest and apoptosis induction via the suppression of cell survival signalling proteins such as ERK and PI3K/Akt [32]. The percentage of viable cells decreased with increasing concentrations and exposure time of Surfactins that indicated its cytostatic/cytotoxic effect against breast cancer cell lines like T47D and MDA-MB-231 [33].

Another study revealed that Surfactin lipopeptide inhibits proliferation and induces apoptosis of human breast MCF-7 cancer cells trough a ROS/JNK-mediated caspase pathway (Figure 5) in a dose-dependent manner [34]. Surfactin generates the reactive oxygen species (ROS), which further activate the mediator of survival and JNK and ERK1/2, which are the key regulating elements in the apoptosis process. This showed that the action of Surfactin seems to be realized *via* two independent signalling mechanisms. The induction of apoptotic cell death is an emerging strategy for the prevention as well as treatment of cancer.

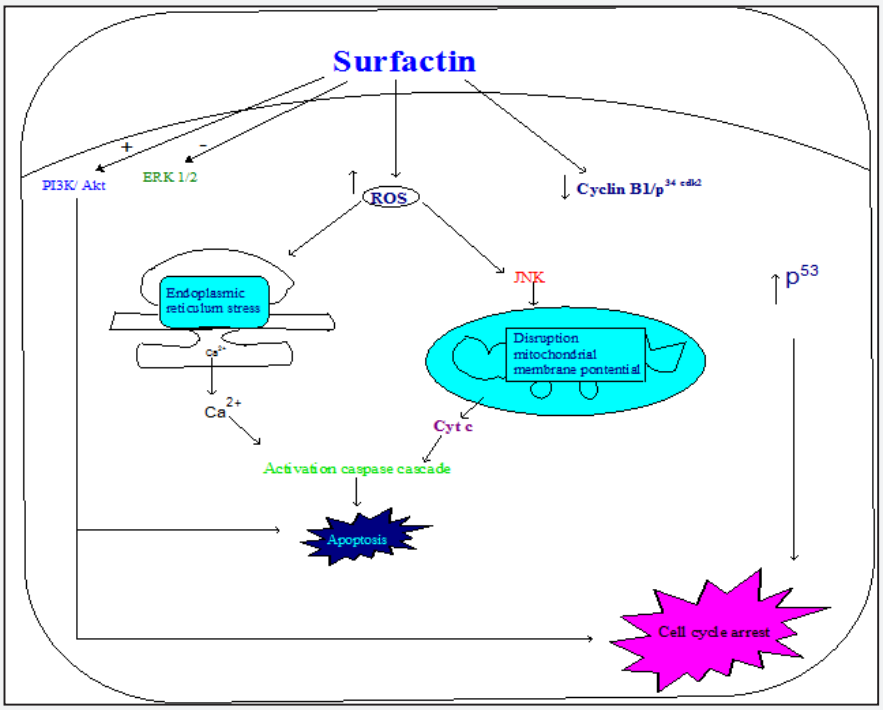


**Figure 5 :** Proposed mechanisms involved in the antitumor activity of Surfactin. Abbreviations: AIF: Apoptosis Inducing Factor; Cyt- c: Cytochrome c; ERK: Extracellular signal Regulated protein Kinase; JNK: c-Jun N-terminal Kinase; PI3K: Phosphoinositide 3-Kinase; ROS: Reactive Oxygen Species.

**LPs induced apoptosis pathway:** Oxidative stress induced by the LPs leads to the production of ROS in LPs-treated cancer cells. This oxidative stress in the cells further resulted in induction of apoptotic pathway in the cell, as evident by the fragmentation/ condensation of nuclei. Another marker for apoptotic cell death is DNA nicking, which is indicated by FACS-based TUNEL assay. Ample nicking of DNA depends on the concentration of the lipopeptide(s). However, surprisingly, caspase-3 band could not be detected using biotin-conjugated polyclonal rabbit anti active human caspase-3 antibody. PARP-1 is a key nuclear enzyme that regulates transcription under homeostatic conditions while during in stress conditions, it responds to DNA damage and facilitates DNA repair [35]. In caspase independent death processes, some scientists have shown that PARP-1 plays an important role of initiator, activation of which is caused by DNA damage [36]. Many agents that cause DNA damage lead to PARP-1 activation.

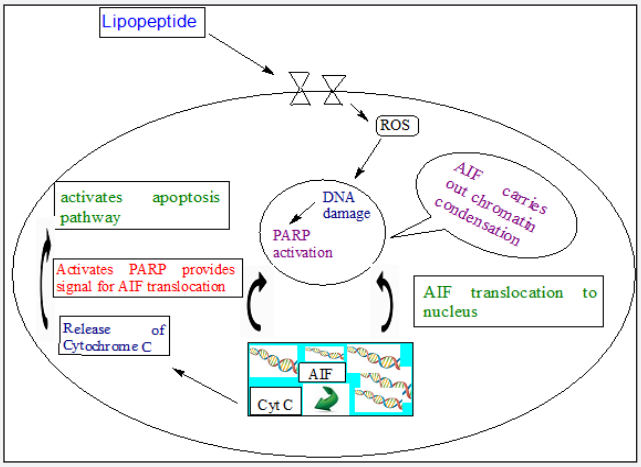


**Figure 6 :** Lipopeptide(s) induced apoptosis pathway.


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Some of these agents include $H_2O_2$, DNA alkylation agent N-methyl-N O-nitro-N-nitrosoguanidine (MNNG) and a neurotoxin 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP). Most of these agents generate ROS that lead to DNA damage. It is reported that oxidative stress/ROS lead to activation of both PARP-1 and AIF. In one of the pathways researchers have shown that imprudent activation of PARP-1 leads to an intrinsic caspase independent cell death program, in which PAR polymer appears to be a signaling molecule of death (Figure 6) that acts as a nuclear/mitochondrial signal to release AIF from the mitochondria of the cell [37].

Once released, AIF molecule translocates to the cytoplasm followed by nucleus, where it induces chromatin condensation. Subsequent to its own expulsion from mitochondria, AIF also triggers release of mitochondrial cytochrome c and caspase activation. In one of the experiments with cell-free systems, incubation of isolated HeLa nuclei with recombinant AIF resulted in peripheral chromatin condensation and DNA loss associated with high molecular weight (50 kb) DNA fragmentation. AIF released from mitochondria and subsequent cell death was shown to be triggered by excessive calcium influx resulting in over activation of poly (ADP-ribose) polymerase-1. The normal cell division may be altered by some mutagenic event leading to onset of cancer/ tumor growth and proliferation (Figure 7).

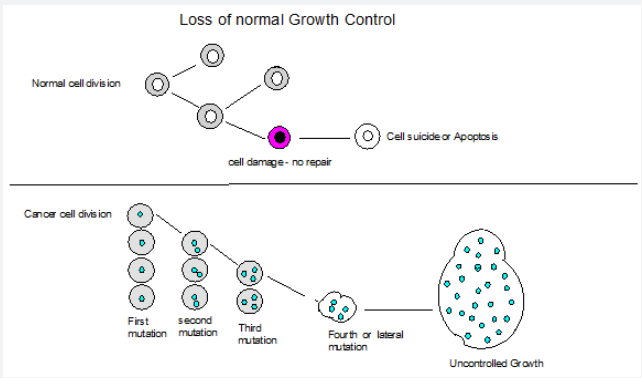


**Figure 7 :** Normal and cancer cell division.

**Lipopeptides in laundry and enhanced oil recovery:** Cyclic LPs are stable and compatible for use as laundry detergents. Kiran et al. [38] found a new LP biosurfactant produced from strain *B. aureum* [2]. The biosurfactant produced can be employed successfully in enhanced oil recovery process in marine environments. LP from *E. fergusonii* KLU01 that was not sensitive to manganese, irons, lead, nickel, copper and zinc [38]. So, this bio surfactant possessed a potential in hydrocarbon degradation and heavy metal bioremediation. The extracellular LP produced from entophytic *B. subtilis* K1 was taken from aerial parts of the banyan tree. The strain had high heterogeneity with secreted mixtures of Surfactins, Iturins and Fengycins. The lipopeptide resulted in about 43% enhanced oil recovery on a laboratory scale in the sand-packed column with four stroke engine oil. Soonglerdsongpha isolated a LP biosurfactant from *Bacillus* sp. GY19 [39]. The result implied that ~1-3% lipopeptide solutions had 80-100% efficiency of oil displacement with Oman light oil, heavy oil, diesel oil and Arabian light oil. In addition, the LP preparations were stable at extreme salinity, pH and temperature. Consequently, formate and powder containing LPs could be used directly as dispersants for oil spill remediation. LP biosurfactant was produced from, a propitious bacterial *E. fergusonii* KLU01strain isolated from oil contaminated soil [40]. The strain emerges as a new class of biosurfactant lipopeptide producer with potential environmental and industrial applications, especially in hydrocarbon degradation and heavy metal bioremediation.

**Antiobesity activity of the lipopeptides:** Obesity is considered as a life style disorder especially in developing countries. It is prevailing mainly in new world countries due to fast food intake, including high fructose corn syrup added products consumption and lack of physical activity [41]. Pancreatic lipase inhibitory activity of the bioactive molecules has been largely used for the exploration of potential effectiveness of natural products. Lipopeptides biosurfactant have recently emerged as key molecules owing to their structural novelty, versatility and diverse properties that are potentially useful for advanced therapeutic applications [42]. *Bacillus* subtilis SPB1 lipopeptide can be a major drug of future to treat the obesity related metabolic disorders. *B. subtilis* lipopeptides can be administered orally, in order to achieve an effective control on body weight [43]. *Bacillus* subtilis SPB1 crude lipopeptide biosurfactant has a protective and a curative action on obese persons and it reduces the body weight of obese rats and treats hyperlipidemia without apparent side effects. *Bacillus* subtilis LPs reduced the body weight of mouse by reducing the serum pancreatic lipase activity [43].

## Conclusion

The lipopeptides are relatively small sized lipidic-peptides of 1.1 to 1.2 kDa size mainly synthesized by many *Bacillus* species. Being of bacterial origin, they also fulfil the criteria of an antibiotic. The LPs are categorised in three main types, i.e. Surfactins, Iturins and Fengycins besides Polymyxins. The Surfactin has strong surfactant properties besides high resistance to heat, cold and stearic influences. Iturin A is an amphiphilic cyclic peptide which also exhibits antifungal activity. It is produced by several strains of *Bacillus subtilis* and is being exploited in food, oil and pharmaceutical industries. The Fengycin has strong antifungal activity against filamentous fungi. Besides antibiotic applications, the LPs may be used in enhanced oil recovery, killing of cancer/tumour cells and their possible application in loss of fat cells allowing anti-obesity treatment. Interestingly, the bacterial lipopeptides have lower toxicity for plants and animals, high biodegradability, tissue compatibility and low irritancy.


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