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Review Article

Lipopeptide Biosurfactants from *Bacillus* spp.: Types, Production, Biological Activities, and Applications in Food

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Biosurfactants are a functionally and structurally heterogeneous group of biomolecules produced by multiple filamentous fungi, yeast, and bacteria, and characterized by their distinct surface and emulsifying ability. The genus *Bacillus* is well studied for biosurfactant production as it produces various types of lipopeptides, for example, lichenysins, bacillomycin, fengycins, and surfactins. *Bacillus* lipopeptides possess a broad spectrum of biological activities such as antimicrobial, antitumor, immunosuppressant, and antidiabetic, in addition to their use in skincare. Moreover, *Bacillus* lipopeptides are also involved in various food products to increase the antimicrobial, surfactant, and emulsification impact. From the previously published articles, it can be concluded that biosurfactants have strong potential to be used in food, healthcare, and agriculture. In this review article, we discuss the versatile functions of lipopeptide *Bacillus* species with particular emphasis on the biological activities and their applications in food.

1. Introduction

Biosurfactants (BSs) could be found on the surface of microbial cell and transferred into the extracellular space by multiple filamentous fungi, and yeast (*Starmerella, Candida, Ustilago, Saccharomyces, Trichosporon,* and *Pseudozyma*) and bacteria (*Nocardia, Rhodococcus, Acinetobacter, Arthrobacter,* and *Gordonia*) [1]. They are primarily classified according to their structural characteristics, associated microorganisms, and molecular weight (MW) [2].

BSs have a hydrophobic region and a hydrophilic end consisting of hydrocarbons acids, diverse fatty acids (saturated, unsaturated, linear, or branched long-chain) and carbohydrate cyclic peptide, alcohol, carboxylic acid, amino acid, and phosphate. This amphipathic framework provides an ability to reduce the surface tension at the interfaces of phases with divergent polarities, which includes emulsion (liquid-liquid) and suspension (liquid-solid), which is collectively named "dispersion" [3, 4]. BSs have also the capacity to produce molecular aggregates, for example, micelles, like the ones patented at the critical micelle concentration (CMC). The CMC of BSs is normally 1–200 mg/L, which is 10–40 times lower than that formed with chemical surfactants [5].

BSs are produced through microbial fermentation, which includes yeast, fungi, and bacterial strains (*Pseudomonas*, *Lactobacillus*, *Acinetobacter*, *Halomonas*, *Rhodococcus*, *Bacillus*, *Enterococcus*, and *Arthrobacter*). Among all microbes, genus *Bacillus* is well studied for its biosurfactant production as it produces various types of cyclic lipopeptides/lipoproteins such as lichenysins, bacillomycin, fengycins, and surfactins [6].

Lipopeptides and glycolipids are highly efficient and popular group of BSs such as surfactin and rhamnolipids, with low-MW [7–9], whereas the high-MW BSs are lipoprotein, phospholipids, and emulsion [10, 11]. Lipopeptide BSs are composed of two different regions: an acyl tail (s) and a short linear oligopeptide sequence, containing an amide bond. The hydrophobic tail contains a hydrocarbon chain, whereas the hydrophilic head contains the lipopeptide BSs peptide sequence. The peptide module includes cationic and anionic residues, as well as nonproteinaceous amino acids [12].

Taking into account the unique properties of *Bacillus* cyclic lipopeptides, and their applications in medicine, healthcare, environment, agriculture, and food industries, their biocompatibility, bioavailability, and structural diversity attracted further attention in the last decade [13–15]. The nonribosomal peptide synthetase (NRPS) enzyme is associated with the formation of cyclic lipopeptides. Lipopeptide surfactants are classified according to their structure, with isoforms comprising a variety of D and L amino acids [16, 17]. The demand for new lipopeptides is increasing in order to broaden their application. Earlier, various studies have been conducted to establish the biotechnological production, functional qualities, and physical properties of lipopeptide surfactants. In this review article, a comprehensive study is carried out to describe the contributions of *Bacillus* lipopeptides in the food industry and biological activities.

2. Classes of Lipopeptides Produced by *Bacillus spp*

Lipopeptides are a subgroup of microbial surfactants, for example, surfactin, fengycin, iturin, lichenysin, and kurstakin [18]. The types or classifications of lipopeptides surfactants are mainly based on the amino acid sequences and various strains of *Bacillus spp*. producing lipopeptides such as *B. subtilis*, *B. cereus*, *B. thuringiensis, B. globigii, B. amyloliquefaciens*, *B. megaterium*, *B. pumilus*, and *B. licheniformis*. [19–22] (Table 1 and Figure 1).

2.1. Surfactin. Surfactin belongs to the lipopeptides family, which was firstly isolated by Arima et al. in 1968 and produced by many *Bacillus* with surfactant activities [66]. Surfactin (1036 Da) is an amphipathic cyclic lipopeptide biosurfactant produced by many strains of the bacterial genus *Bacillus*. The surfactin molecule was firstly screened from the culture media of *B. subtilis* strains and applied as a clotting inhibitor [67, 68].

Surfactin is composed of a heptapeptide (ELLVDLL) along with chiral sequence LLDLLDL linked with β-hydroxy (fatty acid chain) of carbon chain (C12–C16) and forms a close cyclic lactone ring structure. The structure of surfactin consists of both hydrophobic (located at 2–4, 6, and 7) and hydrophilic (located at 1 and 5) part [69]. Surfactin displays a stable and conserved folding in aqueous solutions, and negatively charged amino acids, Glu and Asp, exhibit polar domain. Moreover, it is also soluble in organic solvents, for example, dichloromethane, ethanol, chloroform, butanol, and methanol [70].

The peptide part represents topology like "horse-saddle" and is called the β-sheet structure in the backbone folding, which believe that these structural traits contribute to the broad spectrum of biological properties of surfactin [71, 72].

Naturally, many isoforms of surfactin present, which only differ with their physicochemical properties such as (1) type of amino acid of peptide ring at 2nd, 4th, and 7th positions, and (2) branching of hydroxyl fatty acid moiety and chain length. What's more, isoforms also depend upon the *Bacillus* strain and other factors such as media, environmental, and nutritional conditions of substrate [73, 74]. Previously, studies reported that surfactin shows potent antitumoral, antiviral, anticoagulant, inhibitors of enzymes, and antimicoplasma activities [75].

2.2. Lichenysin. Lichenysin a lipopeptide produced most of *B. licheniformis* strains, and it has excellent surfactant and chelating agent for Ca^{2+} and Mg^{2+} [76–79]. Lichenysin was also reported to exert antimicrobial, anti-inflammatory, antitumor, and immunosuppressive properties. Besides good biological activities, it also has hemolytic activity [79]. These traits of lichenysin are caused by the amphiphilic nature of the lipopeptide. Structurally, lichenysin consists of amino acids (7) and a β-hydroxy fatty acid along with C12–C17 carbon atoms. Many isoforms of lichenysin are present in nature, for example, lichenysin A [80–82]. The structure of lichenysin is very similar to surfactin and differs with the substitution of glutamine with glutamic acid in the first amino acid position [82]. However, this small difference markedly increases the surfactant properties of lichenysin [79].

2.3. Kurstakin. Kurstakin is a low-molecular-weight lipopeptide mainly produced and isolated from *Bacillus thuringiensis kurstakin HD-1*. The amino acid sequence of kurstakin was reported as follows: Thr-Gly-Ala-Ser-His-Gln-Gln. The fatty acyl chain of kurstakin is linked with N-terminal amino acid residue by amide bond, and every lipopeptide consists of lactone linkage among carboxyl terminal amino acid and hydroxyl group in the side chain of the serine residue [83, 84].

2.4. Iturin. Iturin are an important class of lipopeptides with a molecular mass of ~1.1 kDa. Iturin A consists of two parts: (a) C14–C17 (amino fatty acids) and (b) seven amino acid residues (heptapeptides; Asn-Tyr-Asn-Gln-Pro-Asn-Ser). Iturin (D and E) varies from iturin A due to the presence of a free carboxyl group in iturin D and carboxymethyl group in iturin E. The structure of iturin shows that it has an amphiphilic character [85, 86]. Iturin molecule is of great interest because of their biological activities and physicochemical traits and used in oil, pharmaceutical, and food industries. Almost all strains of *Bacillus subtilis* produce iturin lipopeptide, and its operon ranges from 38 to 40 kb in size and contains four open reading frames such as *ItuA*,

Table 1: Lipopeptide-producing strains and their applications.

Lipopeptides	LP-producing bacterial strain	Biological application	Ref.
Surfactin	*B. methylotrophicus* DCS1	Antioxidant, antimicrobial, and antiadhesive activities	[23]
	B. mojavensis A21	Diesel biodegradation	[24]
	B. mojavensis PRC101	Antagonism against *Fusarium verticillioides* (fungal species infecting maize)	[25]
	B. subtilis	Inhibitory activity against phytopathogenic *Fusarium sp.*	[26]
	B. atrophaeus L193	Aphicidal activity against the aphid Rhopalosiphum padi (pest in cereal crops)	[27]
	B. subtilis SAS-1 *B. amyloliquefaciens* BR-15	Engine oil degradation efficiently augmented (75–94%)	[28]
	B. subtilis SPB1	Antioxidant activity, chelating activity, histological study proved effective treatment of complicated wound healing and skin diseases	[29]
	B. subtilis strain ATCC6633	Microbial enhanced oil recovery	[30]
	B. subtilis 573	Decreased viability of breast cancer cell lines, T47D and MDA-MB-231 and nontumor fibroblast cell line (MC-3 T3-E1)	[31]
	B. natto TK-1	Therapeutic agent, anti-inflammation	[32]
	B. subtilis ANR 88	Effective in the synthesis of silver as well as gold nanoparticles	[33]
	B. pumilus	Silver nanoparticles produced as antimicrobial and nematicide	[34]
	B. subtilis LSFM-05	Nontoxic dispersion in biotechnology and nanotoxicology.	[35]
	B. (SPB) NH-100 and NH-217	Biocontrol agent against bakanae diseases in rice	[36]
Surfactin A	*B. stratosphericus sp.* A15	Antioxidant and antibacterial activity, wound healing activity by connective tissue regeneration, thickened epidermal layer, and keratinocyte formation	[37]
Pumilacidin	*B. stratosphericus* FLU5	Hydrocarbon removal from contaminated soil, negligible cytotoxic effect against the mammalian cells HEK293	[38]
Lipopeptide	*B. subtilis* SPB1	Anti-obesity effect through the inhibition of lipid digestive and liver dysfunction enzymes	[39]
Iturin A, fengycin	*B. amyloliquefaciens* DSM 23117	Biocontrol agent against a common fungal phytopathogen botrytis cinerea	[40]
Bacillomycin D	*B. amyloliquefaciens* fiply 3A	Killing human cancer cell line viz. A549 (alveolar adenocarcinoma), A498 (renal carcinoma) and HCT-15 (colon adenocarcinoma) while not effecting the normal cell line L-132 (pulmonary epithelial cells)	[41]
Iturin A	B. subtilis	Inhibiting chronic myelogenous leukemia in vitro via paraptosis, apoptosis, and inhibition of autophagy	[42]
Lipopeptide	*B. mojavensis* ifo 15718	Pharmaceutical applications as it possesses antibacterial activity against pathogen *S. aureus* and lack of toxicity to PC12 and PBMC cells	[43]
Iturin A	*B. amyloliquefaciens* PPCB004	Activity against postharvest fungal pathogens on stored fruits	[44]
Fengycin	*B. amyloliquefaciens* FZB42	Antifungal activity against fusarium moniliforme (rice bakanae disease), fusarium oxysporum (root rot) and trichoderma atroviride (ear rot and root rot)	[45]
Surfactin homologs	*B. amyloliquefaciens* MD4-12	Synergistic Antimicrobial effects against various gram-positive and Gram-negative bacteria	[46]
	B. subtilis NH 217, *B. amyloliquefaciens* FZB42	Excellent biofilm formation, antifungal activity against various phytopathogen and their associated diseases	[47]
Bacillomycin, Fengycin	*B. methylotrophicus* XT1 CECT 8661	Effective biocontrol agent against *B. cinerea* infection, antioxidant triggerer in different fruits	[48]
Iturin A, Fengycin C	*B. Subtilis* EA-CBOO15	Iturin A inhibited *M. fijiensis* mycelial growth, and fengycin C displayed strong inhibitory activity on ascospore germination	[49]
Iturin A, surfactin	*B. Subtilis*	Broad hypocholesterolemic activities, immune-modulators, toxins, and enzyme inhibitors	[50]
Surfactin, Fengycin	*B. subtilis* fmbj (CGMCC no. 0934)	Effective against Newcastle disease virus (NDV) and infectious bursal disease virus (IBDV)	[51]
Lichenysin	*B. licheniformis* VS16	Biofilm inhibition, removal of heavy metals	[52]
	B. licheniformis Ali5	Enhanced oil recovery and motor oil removal from contaminated sand	[53]
	B. licheniformis W16	Excellent emulsification and microbial enhanced oil recovery	[54]
Surfactin	B. subtilis C9	Effective biocontrol agent controlling cladoceran grazers in algal cultivation system	[55]
Lipopeptide biosurfactant	*B. pseudomycoides* OR 1	Biocontrol agent against food-borne pathogens *E. coli* (MTTC 43), Klebsiella pneumoniae (MTVV 530) and staphylococcus aureus (MTCC 96)	[56]
Novel cyclic lipopeptide C18	*B. pseudomycoides* BS6	Bioremediation and recycling waste cooking oil	[57]

Table 1: Continued.

Lipopeptides	LP-producing bacterial strain	Biological application	Ref.
Pumilacidin	*B. safensis* CCMA-560	Thermal stable and microbial enhanced oil recovery	[58]
Lipopeptide	*B. sp*. H20-1	Antagonistic effect against sulfate-reducing bacteria	[59]
Lipopeptide	*B. cereus* UCP1615	Bioremediation of petroleum derivative in soil and water with above 90% removal	[60]
Paenibacterin	*Paenibacillus elgii* HOA73	Effective bio-pesticide against diamondback moth Plutella xylostella (destructive insect pest)	[61]
Paenibacterin	*Paenibacillus thiaminolyticus*OSY-SE	Minimized endotoxemia showed low toxicity against human kidney sell line (ATCC CRL-2190)	[62]
Lipopeptide	*B. altitudinis* MS16	Promising emulsification and antifungal activity	[63]
Lipopeptide	*B. brevis*	Excellent emulsifier and antibacterial effects	[64]
Lipopeptide	*B. subtilis* SPB1	Toothpaste formulation	[65]

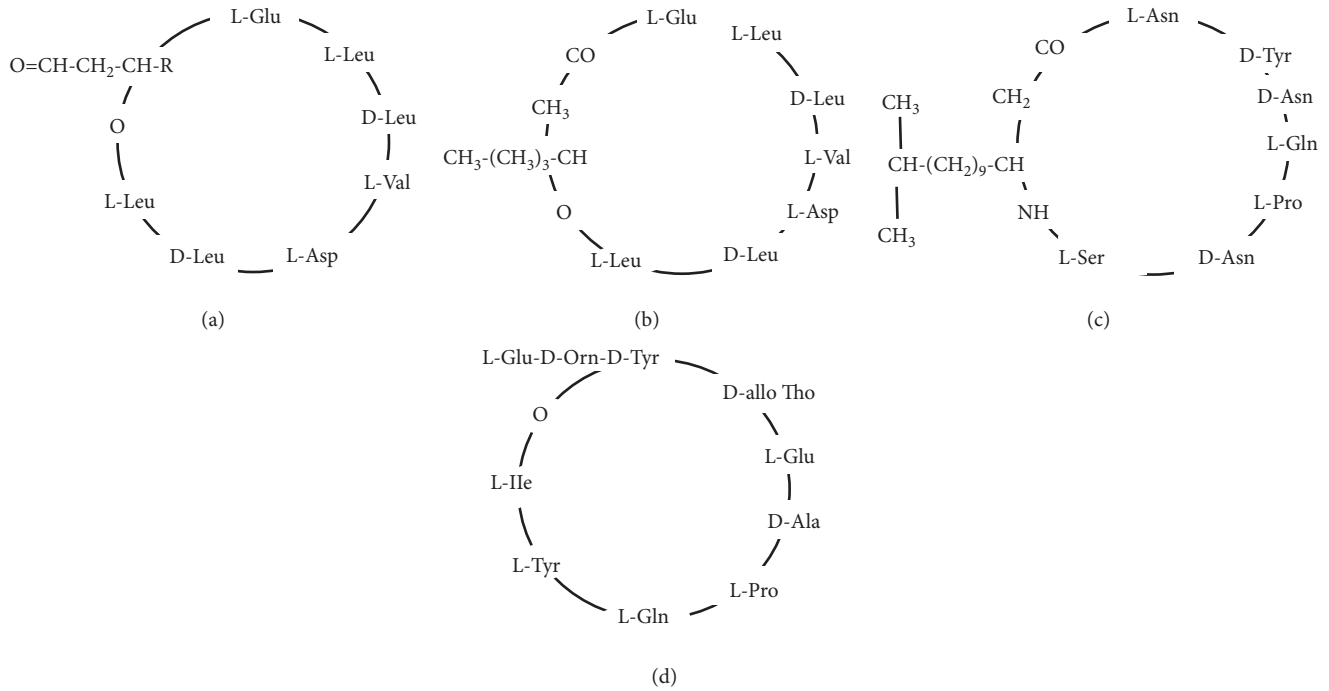

Figure 1: Chemical structures of some lipopeptides: (a) surfactin, (b) lichenysin, (c) iturin, (d) fengycin.

ItuB, ItuC, and *ItuD* [87]. Iturin lipopeptide also contains mojavensin, mycosubtilin, bacillomycin D, bacillomycin F, and bacillomycin L, which differ in amino acid sequences of the heptapeptides [88]. Iturin was reported to exert potent antifungal activity against, *Botrytis cinerea*, *Alternaria alternate*, and *Penicillium expansum*. Moreover, it also has strong surface activity and destabilizing effect [89].

2.5. Fengycins. Fengycins are lipopeptides mainly produced by the genera of *Bacillus* and *Paenibacillus*. Fengycins have strong antifungal activity and markedly affect filamentous fungi [90]. Fengycins are decapeptides and C14–C19 to β-hydroxy fatty acid chain, which showed potent antifungal activity [91, 92]. There are two subclasses of Fengycins, namely, Fengycin A and Fengycin B, that only differ from each by the amino acid attached at position 6. Fengycin B contains Val at position 6, whereas Fengycin A contains Ala. Fengycins (A and B) were firstly reported in *B. subtilis* strain by Vanittanakom et al. [93]. The closely related fengycin type was reported and named plipastatin due to the position of amino acids L- Tyr and D- Tyr [94].

3. Production, Isolation, and Characterization of *Bacillus* Lipopeptides

Lipopeptide surfactants are produced by many microbes including bacteria, fungi, and yeast. However, herein, we mainly focus on the production of *Bacillus* lipopeptides. The biosurfactants are synthesized from the extracellular or intracellular part of microbes. Notably, biosurfactants are produced during the stationary and exponential phase, whereas the biosurfactant production is predominate in the death phase. Reduction in surface tension to 8 mJm^{-2} is the minimum value to be considered when producing the biosurfactant. The various strains of *Bacillus spp*. produced

novel lipopeptides such as *B. licheniformis,* and *B. circulans*. Furthermore, details of lipopeptide production from various *Bacillus* along with fermentation conditions are presented in Tables 1 and 2.

3.1. Substrates. Many substrates mainly consist of hydrophobic mixtures, vegetable oils, waste products, dairy products, etc. and are used for the production of lipopeptide-based surfactants. To minimize the production cost of lipopeptide-based surfactants, renewable and low-cost substrates were applied as presented in Tables 1 and 2. Moreover, it is also necessary to select substrates with a high nutritional value for the growth of microbes. One of the best methods used is to apply organic matter such as industrial waste, oil substrate, and agro-based materials. Interestingly, these waste materials provide distinct energy source for microbes with effective surfactants production.

3.2. Production of Biosurfactants by Using Agro-Industrial Waste. Agro-industrial waste is an ideal choice for the production of lipopeptide and helps in the industrial waste management. Agro-industrial wastes contain both carbon and lipids along with other necessary nutrients, which are the major requirement for the growth of biosurfactant-producing microbes. Previously, many researchers successfully utilized various agro-industrial wastes such as sugarcane molasses, date molasses, cassava flour, rice straw, corn, fruits and vegetable wastes, bran, and others for the production of biosurfactant [115, 140–146].

Molasses is the key waste product of sugar and date industries, and it has gained a lot of attention for the production of biosurfactant. This popularity to use as a substrate for biosurfactant production is mainly due to its low cost and rich source of dry matter (75%), protein (2.5%), nonsugar organic matter (9–12%), minerals (potassium, calcium, phosphorus, and magnesium), and other components (thiamine, biotin, inositol, and pantothenic acid). The sugar content in the molasses ranges from 48 to 56%, making it ideal for the growth of various microorganisms [147–149].

Makkar and Cameotra [150], Saimmai et al. [142], and Joshi et al. [151] reported the biosurfactant production from *Bacillus subtilis* strains (MTTCC 2423, MTCC1427, and SA9) and *Bacillus licheniformis* TR7) by using molasses as carbon source. In another study, Joshi et al. [54] documented that cane molasses and date molasses used as a carbon source enhance the production of lichenysin-A-like lipopeptide by using *Bacillus licheniformis* W16. Rane et al. [33] conducted a study to utilized agro-industrial wastes (molasses, banana peels, orange peels, whey, potato peels, and bagasse) as a substrate for the production of biosurfactant by *Bacillus subtilis* ANR 88. Their study results revealed that biosurfactant production in the molasses substrate as a carbon source was higher (0.24 g/L) compared to other agro-industrial wastes. Moreover, they also found that by optimizing the conditions (ammonium ferric citrate 0.25%, molasses 4%, and pH 7), the yield of biosurfactant significantly increases to 2-fold (0.513 g/L).

Recently, Al-Dhabi et al. [141] used date molasses as a carbon source for the production of biosurfactant from *Bacillus subtilis* strain Al-Dhabi-130. They found that using date molasses as a carbon source yields the biosurfactant to 74 mg/g substrate and can be used for the large-scale production of biosurfactant .

Peanut oil cake is a novel agro-waste, which can be used for the production of lipopeptide. Nalini et al. [152] reported that maximum lipopeptide production was obtained (8.18 g) from peanut oil cake as a substrate by using *B. cereus* strain SNAU01. Paraszkiewicz et al. [153] also observed that lipopeptide surfactants such as surfactin and iturin can be produced by *Bacillus* strains using carrot peel as substrate.

3.3. Production of Lipopeptides by Using Oil Waste. Wastes from oil processing industries represent one of the best and readily available renewable substrates for microbial biosurfactant production. The hydrophobic substrate containing media such as oil helps microbes to produce lipopeptide surfactant. Sunflower, olive oil, coconut oil, and canola are the main oil made from oil industries and considered the best carbon source for biosurfactant production [22, 38, 143, 154].

Ostendorf et al. [143] reported the excellent production of lipopeptide biosurfactants by *Bacillus stratosphericus* strain FLU5 using waste vegetable oils (olive oil, corn oil, and residual frying oil). In another study, Md Badrul Hisham et al. [155] observed the excellent yield of surfactin by *Bacillus* sp. HIP3 when using used cook oil as a substrate (2%).

4. Isolation, Purification, and Characterization of Lipopeptides

Lipopeptides are mostly synthesized by bacterial genus *Bacillus*. The bacterial cells are grown in their respective media with specific conditions (varied from strains to strains) to produce lipopeptides prior to their separation by centrifugation. Malfanova et al. [156] grew bacterial cells (60 h at 28°C) subjected to centrifugation (13,000 rpm for 10 min) to obtain crude lipopeptides. The obtained supernatant was acidified by using HCl acid, while the precipitate was extracted with methanol and further concentrated by vacuum evaporation [156, 157]. The crude extract was purified by many methods such as gel filtration in Sephadex column and high-performance liquid chromatography, and the collected eluent was further subjected to MALDI-TOF-MS/LC-MS/MS-MS/NMR/FTIR [53].

5. Pharmacological Activities

5.1. Anticancer. Bacillus lipopeptides are considered versatile bioactive compounds with potent antitumor activity. For example, surfactin has been documented to exert antitumor activity towards human colon carcinoma cell lines (HCT15 and HT29), Ehrlich's ascites carcinoma cells, and breast cancer cell lines (T47D and MDA-MB-231) [31, 104, 158]. Surfactin inhibits the growth of transformed

Table 2: Strategies and mechanisms used to enhance lipopeptide production by *Bacillus sp*.

Strategy used	Factors evaluated	Strain	Results	BS nature	Ref.
RSM, CCD	Brewery waste and (carbon, nitrogen, agitation speed, temperature, pH)	*B. subtilis* N3–1P	657 $g.l^{-1}$	Surfactin	[95]
RSM, BBD	(d-glucose, sucrose, xylose), hydrocarbons (hexadecane, diesel, benzene, heptane), nitrogen source ($NaNO_3$, NH_4NO_3, $(NH_4)_2SO_4$, $NaHCO_3$, urea)	*Bacillus sp*. SS105	2.65 $g.l^{-1}$	Surfactin	[96]
CCD, PBD	Sucrose, glucose, starch, peanut oil, potato), nitrogen source (peptone, beef extract, trypsin, yeast extract), other variables ($MgSO_4$, KCl, KH_2PO_4, $FeSO_4.6H_2O$, NH_4Cl, $MnSO_4$, $CuSO_4$, sodium glutamate)	*B. subtilis* N7	0.706 $g.l^{-1}$	Surfactin	[97]
RSM, PBD, (TFAT) two factors at time	Nitrogen source ($(NH_4)_2SO_4$, KNO_3, $NaNO_3$, NH_4Cl, beef extract, yeast extract)	*B. subtilis* KLP2015	0.98 $g.l^{-1}$	Surfactin	[98]
RSM, OFAT one factor at a time	Carbon source (glucose, fructose, sucrose, xylose, rhamnose, soluble starch), nitrogen source (NH_4Cl, $C_6H_{17}N_3O_7$, urea, peptone, soybean meal), metal ions (ZN^{2+}, Fe^{3+}, Mg^{2+}, Mn^{2+}, Ca^{2+}, K^+)	*Bacillus sp. BH072*	0.027 $g.l^{-1}$	IturinA A	[99]
OFAT	Single and multidose Fe^{2+}	*B. megaterium*	4.2 $g.l^{-1}$	Surfactin	[100]
2^2 factorial design, RSM	Glucose and yeast extract	*B. subtilis* EA-CB0015	0.78, 0.355 $g.l^{-1}$	Fengycin, Iturin A	[101]
PBD, CCD	Carbon source (glucose, maltose, dextrose, mannitol, sorbitol, galactose, xylose, starch), nitrogen source (KNO_3, $(NH_4)_2SO_4$, $NaNO_3$, soy flour, peptone, casein hydrolysate, yeast extract urea)	*B. amyloliquefaciens* MD4-12	1.25 $g.l^{-1}$	Surfactin	[102]
CCD, Fed-batch strategy	Fed-batch strategy (pH-stat, DO-stat, constant rate feeding, combined feeding), Sunflower oil, $NaNO_3$, $MgSO_4.7H_2O$, yeast extract	*Aneurinibacillus thermoaerophilus* HAKO1	11.2 $g.l^{-1}$	Surfactin	[103]
ANN-GA	Glucose, urea, $SrCl_2$, and $MgSo_4$	*B. circulans* MTCC 8281	4.38 $g.l^{-1}$	Unidentified	[104]
ANN-GA	Lp concentration, Ca^{2+}, pH	*B. licheniformis*, *B. megaterium*	45% oil recovery	Lipopeptide	[105]
BBD	Glucose, glutamic acid, temperature, NaCl	*B. mojavensis* 14	4.12 $g.l^{-1}$	Lipopeptide	[106]
BBD	Optimization of non-nutritional factors (inoculum age and size, pH, agitation, aeration, temperature)	*B. subtilis* SPB1	3.3 $g.l^{-1}$	Lipopeptide	[107]
	Nitrogen source ($(NH_4)_2SO_4$, KNO_3, NH_4NO_3, NH_4Cl, peptone, beef extract, yeast extract), carbon source (glucose, sucrose, fructose, maltose, sorbitol, starch)	*B. velezensis* KLP2016	2.5 $g.l^{-1}$	Lipopeptide	[108]
Media composition and characteristics	n-paraffin, n-dodecane, n-hexadecane, sunflower oil, canola oil, sucrose, glycerol, diesel fuel, n-tetradecane, nitrogen source ($(NH_4)_2SO_4$, $NaNO_3$, KNO_3, urea, peptone, yeast extract, beef extract), metal and sulfur source ($FeSO_4$, $MnSO_4$, $MgSO_4$), and C/N ratio, pH	*Paenibacillus sp*. D9	4.11 $g.l^{-1}$	New lipopeptide	[109]
	Different culture media, shaking speed of shaker, liquid and solid fermentation, attapulgite powder	*B. natto* NT-6	1.94-fold increased	Iturin A, surfactin	[110]
	Different culture media, vine-trimming shoots, glucose, hemicellulosic hydrolysate, and cellulosic hydrolysate	*B. tequilensis* ZSB10	1.52 $g.l^{-1}$	Lipopeptide	[111]
Taguchi method	Carbon source (sucrose, whey, crude oil)), NaCl, Na_2HPO_4, NaH_2PO_4, and $(NH_4)_2SO_4$	*B. cereus*	1.8 $g.l^{-1}$	Lipopeptide	[112]

Table 2: Continued.

Strategy used	Factors evaluated	Strain	Results	BS nature	Ref.
Use of cheap substrate/raw material	Carbon source (orange peel, citrus medica peels, banana peels, and potato peels), inoculum size, incubation time, temperature, substrate concentration	*B. licheniformis KC710973*	1.796 g.l^{-1}	Lichenysin	[113]
	(Butter milk, poultry-transforming waste flour, inoculum size), submerged fermentation	*B. subtilis SPB1*	12.61 g.l^{-1}	Lipopeptide	[114]
	Corn steep liquor (CSL), iron, manganese, and magnesium	*B. subtilis #573*	4.8 g.l^{-1}	Surfactin	[115]
	Potato peels, temperature, pH, saline conditions	*B. pumilus* DSVP18	3.2 g.l^{-1}	Iturin A	[116]
Solid state fermentation (SSF)	Grape seed flour	*B. amyloliquefaciens C5*	0.80 g.l^{-1}	Bacillomycin D	[117]
	Distiller grains (DGS, coculture fermentation with B. B. amyloliquefaciens X82	*B. amyloliquefaciens MT45*	3.4 g.l^{-1}	Surfactin	[118]
	Palm oil, waste glycerol, immobilized on chitosan	*Bacillus Sp. GY 19*	9.8 g.l^{-1}	Lipopeptide	[119]
	Soybean flour, rice straw, starch, yeast extract, kinetic parameters (iso- and nonisothermal process, isothermal and nonisothermal process in fermenter)	*B. amyloliquefaciens XZ-173*	(55.83 mg/gds)	Lipopeptide	[120]
	Soybean flour, rice straw, glycerol, maltose, pH, water content, inoculum size, fermentation time, temperature	*B. amyloliquefaciens XZ-173*	15.03 mg/gds	Surfactin	[121]
	Wheat bran, rice straw, soybean flour, temperature, pH, water content, inoculum size	*B. subtilis CCTCCM207209*	70.90 mg/gds	Lipopeptide	[122]
	Rice bran husk, sunflower oil, coconut oil cake, cotton oil cake, corn cob, orange peel, jackfruit peel, sugarcane leaf, pineapple peel, banana leaf, cheese whey, dry yeast cells, pongamia seed cake, jatropha seed cake ground oil cake, glucose with MSM	*B. amyloliquefaciens*	3-fold increased	Iturin A	[123]
	Olive leaf residue flour, olive cake flour	*B. subtilis SPB1*	0.3067 g.l^{-1}	Lipopeptide	[124]
Mutagenesis induced enhanced yield	UV and gamma ray-induced mutagenesis	*B. subtilis HS0121*	2-fold increased	Surfactin	[125]
	Random mutagenesis using gamma irradiation	*B. subtilis UTB1*	1.8-fold increased	Iturin A	[126]
	UV irradiation, nitrosoguanidine, and ion beam mutagenesis	*B. amyloliquefaciens* ES-2-4	10.3-fold increased	Lipopeptide	[127]
	Combination of UV irradiation and nitrous acid treatment	*B. subtilis SPB1*	2-fold increased	Lipopeptide	[51]
Genome shuffling	Genome shuffling	*B. amyloliquefaciens FMB38*	2-fold increased	Surfactin	[128]
	Genome shuffling and gene (fenA) expression	*B. amyloliquefaciens ES-2-4*	8.30-fold increased	Fengycin	[129]
	Mutagenesis (UV, nitrosoguanidine, atmospheric, and room temperature plasma)	*B. amyloliquefaciens LZ-5*	2.03-fold increased	Iturin A	[130]
	Protoplast fusion	*B. mojavensis JF-2*	0.382 g.l^{-1}	Lipopeptide	[131]

Table 2: Continued.

Strategy used	Factors evaluated	Strain	Results	BS nature	Ref.
Recombinant strains for higher yield	Surfactin promoter THY-15 was replaced to THY-15/pg3-srfA. Then introduced a Vitreoscilla hemoglobin (VHb) gene into engineered strain to obtain a novel THY-15/pg3-srfA (VHb)	*B. subtilis THY-15*	10.02 $g.l^{-1}$	Surfactin C15	[132]
	Loc gene expressed, the fosmid N13 with whole *Loc* gene screened from B. velezensis 916 genomic library, the cassette fused with IPTG inducible promoter Pspac induced in the fosmid N13 resulted N13+spec and N13+PSSpec transformed to obtained derivative strains FZBNPLOC and FZBPSLOC	*B. velezensis FZB42*	15-fold increased	Locillomycins	[133]
	Enhanced transcription of iturin A biosynthetic genes was implemented by inserting a strong promoter C2up into upstream of the *itu* operon, fermentation optimization using RSM and furthermore, overexpression of pleiotropic regulator DegQ	*B. amyloliquefaciens LL3*	8-fold increased	Iturin A	[134]
	Cloning of the biosurfactant genes sfp, sfp0, sfpA into BioS a, BioS b, BioS c, recombinant strains after cloning of biosurfactant genes in to *E. coli*. (*E. coli* DH5ά)	*B. subtilis* SK320	2-fold increased	Lipopeptide	[135]
	Wild type, overexpression of THY-7-P_{grac}-*ycxA*, overexpression of THY-7-P_{grac}-*krsE*, overexpression of THY-7-P_{grac}-*yerP*	*B. subtilis 168*	0.55, 1.15, 0.93, 1.67 $g.l^{-1}$	Surfactin	[136]
	Using CRISPRi 20 genes were repressed, *yrpC, racE, murC* genes were inhibited individually. Furthermore, combination inhibition of *bkdAA* and *bkdA*B genes	*B. subtilis*	4.69-fold increased	Surfactin	[137]
	Replacement of PsrfA with P_{g3}	B. subtilis	0.55–9.74 $g\,l^{-1}$	Surfactin	[138]
	Insertion of *sfp* gene from Paenibacillus sp. D9 into *E. coli*	Paenibacillus sp. D9	3-fold increased	Paenibacterin	[139]

cells via cell cycle arrest and induction of apoptosis and suppresses ERK (extracellular-signal-regulated kinase) and PI3 K/Akt pathway [158]. In another study, Liu et al. [159] reported that surfactin-like lipopeptides purified from *B. subtilis* Hs0121 exert cytotoxicity towards Bcap-37 breast cancer cells (IC_{50}: $29 \pm 2.4\,\mu M$). Surfactin was also documented to inhibit the LoVo colon cancer cells (IC_{50}: $26\,\mu M$) [158] (Figure 2). What's more, Wang et al. [160] observed that *B. subtilis* natto T-2 with crude cyclic lipopeptides (CLPs) showed a cytotoxic effect against human K562 leukemia cells. Surfactin was also reported to exhibit the cytotoxic effect on hepatocellular carcinoma [159, 160]. Recently, Hong et al. [161] have reported that five Surfactin isomers produced by *B. pumilus* HY1 during Cheonggukjang fermentation markedly inhibited the growth of two cancer cell lines (MCF-7 and Caco-2).

Fengycin, a lipopeptide produced by various strains of *B. subtilis*, was reported to exert strong anticancer activity on colon cancer cell line HT29 and human lung cancer cell line 95D [162, 163]. Similarly, *Bacillus* lipopeptide (iturin) was also reported to possess a broad spectrum of anticancer activity on several cell lines (e.g., HepG2, Caco-2, BT474, MDA-MB-231, MCF-7, HUVEC, BIU-87, BRL-3A, A549, and K562 cells [42, 164–171].

5.2. Hemolytic Activity. The lipopeptide surfactants induce the hemolysis of human erythrocytes due to their detergent effect and membrane forming ability. Therefore, lipopeptide surfactants are used as potent inhibitors of fibrin clot formation. Arima et al. [172] reported for the first time that the surfactin potently inhibits the fibrin clot formation via abrogating the conversion of fibrin monomer into fibrin polymer. Bernheimer and Avigad studied the inhibition of fibrin clot formation and hemolysis of erythrocyte by subtilysin derived from *B. subtilis* since 1970 [173] (Figure 2).

The hemolytic activity of lipopeptide iturin A was studied by Aranda et al. They documented that iturin dependently exerts hemolytic activity on human erythrocytes. The underlying mechanism of action was that iturin A induced hemolysis via colloid-osmotic mechanism and K^+ leakage followed by hemoglobin release [85]. In another study, Dehghan-Noudeh et al. [174] documented that *B. subtilis* ATCC 6633-derived lipopeptide surfactant attenuated potent hemolytic effect in comparison with chemical surfactants such as hexadecyl trimethyl ammonium bromide, sodium dodecyl sulfate, tetradecyl trimethyl ammonium bromide, and benzalkonium chloride.

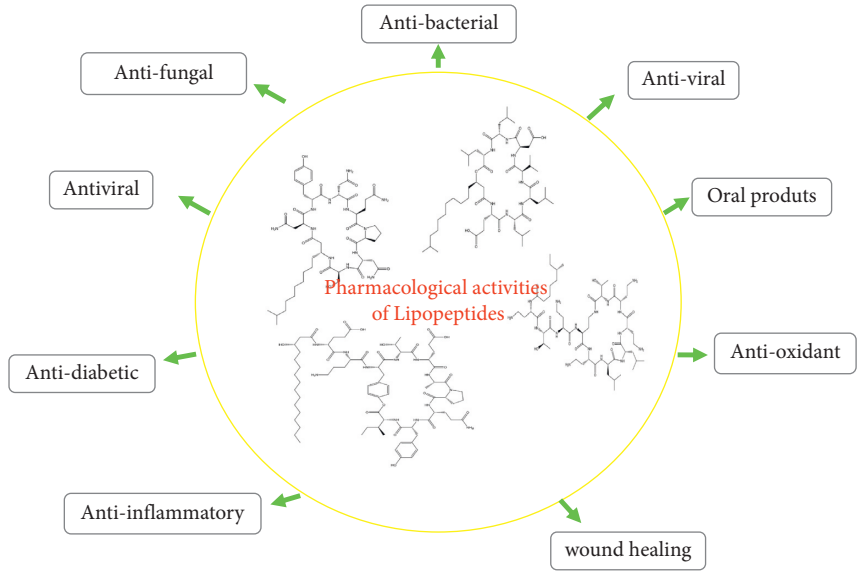

Figure 2: Pharmacological activities of lipopeptides.

5.3. Anti-Inflammatory. Previously, it was reported that lipopeptides exert anti-inflammatory activities via several pathways such as modulation of the TLR4 (Toll-like receptor 4), inhibition of lipoteichoic acid (LTA)-induced NF-κB, activator of transcription-1 (STAT-1), interaction with cytosolic phospholipase A2 (PLA2), and increase in the phosphorylation of STAT-3 [88] (Figure 3).

Moreover, it also impairs the antigen-presenting function of macrophages, suppresses the LPS-induced expression of cluster of differentiations (CD40, CD54, CD80), and inhibits the activation of $CD4^+$ T-cells [32, 88].

It was also documented that surfactin markedly inhibits the overproduction pro-inflammatory mediators (IL-6, tumor necrosis factor alpha or TNF-alpha, and interleukin beta or IL-1β), prostaglandin E2, monocyte chemoattractant protein-1, NO, and reactive oxygen species (ROS), and suppresses the expression of MMP-9 (matrix metallopeptidase 9), COX-2 (cyclooxygenase-2), and iNOS (inducible nitric oxide synthase) [175].

5.4. Antibacterial Activity. The demand for new antimicrobial agents significantly increases due to the resistance of pathogenic microorganisms towards already present antimicrobial drugs. Surfactin, a lipopeptide, was reported to exert antibacterial activity against various pathogenic bacteria. Beside surfactin, other *Bacillus*-related lipopeptides were also reported to possess well-known inhibitory activity towards the growth of pathogenic bacteria [176–179].

Huang et al. [178] reported that surfactin and fengycin produced by the strain *B. subtilis* fmbj effectively inactivate endospores of *B. cereus*. The lipopeptide mainly damages the surface structure of the spores. *B. velezensis* strain H3-isolated surfactin isoforms were reported to active against *P. aeruginosa*, *St. aureus*, *Klebsiella pneumoniae,* and *Mycobacterium* [179].

In another study, fengycin isoforms isolated from marine *Bacillus* strain markedly inhibited the growth of various bacteria such as *K. aerogenes*, *Citrobacter fruendii, Micrococcus flavus*, *Proteus vulgaris*, *Alcaligenes faecalis*, *E. coli*, and *Serratia marcescens* [180].

Lipopeptide antibiotic subtulene A isolated from the culture filtrate of *B. subtilis* SSE4 was reported to inhibit the growth of Gram-positive and Gram-negative bacterial strains such as *Stenotrophomonas maltophilia*, *Enterobacter cloacae*, and *Xanthomonas campestris* [181]. Fengycin and surfactin lipopeptides containing culture filtrate of the endophytic B. amyloliquefaciens was reported to potently inhibited the growth of all tested Gram-negative ones except *Ochrobactrum anthropi* and all Gram-positive bacteria tested except *B.* [157].

Recently, a study conducted by Lv et al. [177] has also reported that *B. amyloliquefaciens* C-1 fermentation supernatant contains a mixture containing surfactin and fengycin, which inactivate the growth of *Clostridium difficile* (bacteria that can infect the bowel and cause diarrhoea). Iturin analog isolated from *Bacillus* strain was reported to inactivate the growth of *Xanthomonas arboricola* and *Pseudomonas syringae* [176].

5.5. Antifungal and Biocontrol. It has been documented that *Bacillus* lipopeptides exert a wide array of antifungal activities. Briefly, iturin markedly inhibits the growth of nematophagous fungi, wood-staining fungi, *Aspergillus flavus*, *Penicillium roqueforti*, and *Colletotrichum demiatium* [19, 182–186], whereas fengycin was reported to inhibit the *Fusarium graminearum*, *Botrytis cinerea*, and *Podosphaera fusca* [187, 188].

More detailed investigations conducted by various researchers reported that lipopeptides exert morphological changes such as hyphal swellings, changed organization of mitochondria, decreased intracellular pH, esterases, and mitochondria activities, and decreased hydrophobicity of the hyphae [48, 189].

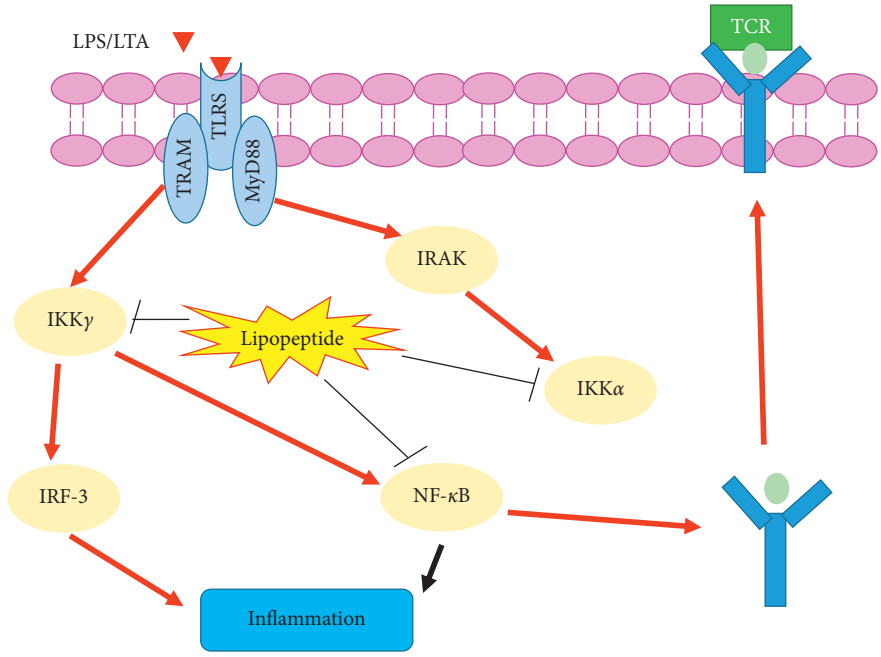

Figure 3: The proposed anti-inflammatory mechanism of *Bacillus subtilis* lipopeptides.

Desmyttere et al. [190] conducted a study to explore the antifungal activities of lipopeptides isolated from *B. subtilis* against apple scab disease causing *Venturia inaequalis* strains. Their study results revealed that *Bacillus subtilis* lipopeptide mixtures containing (fengycin, surfactin, and mycosubtilin) markedly inhibited the growth of *V. inaequalis* S755 and *V. inaequalis* rs552.

Han et al. [191] documented that *B. amyloliquefaciens* L-H15-derived peptides (iturin A with C15*β*-amino fatty acid and cyclic peptide with a molecular weight of 852.4 Da) exhibited strong antagonism against *Fusarium oxysporum*, *Rhizoctonia solani*, and *Phytophthora capsici*.

Dimkić et al. [176] studied five different lipopeptide-producing strains of *Bacillus* (SS-10.7, SS-12.6, SS-13.1, SS-27.2, and SS-38.4), and their extracts were further tested against *Pseudomonas syringae* pv. *aptata* (P16) and *Xanthomonas arboricola* pv. *juglandis* (301, 311, and 320). The results revealed that *Bacillus* strains mostly produced kurstakins, iturins, surfactins, and fengycins lipopeptides. Moreover, they reported that ethyl acetate extracts exert more favorable effect on phytopathogens.

Botrytis cinerea is a necrotrophic fungi, which infects more than 200 plant species including fruits and vegetables. Toral et al. [48] conducted a study to determine anti-*B. cinerea* activity of lipopeptides isolated from *Bacillus* XT1 CECT 8661. They observed that lipopeptide-rich extract mainly containing surfactin, bacillomycin, and fengycin potently inhibits the growth of *B. cinerea*. What's more, SEM (scanning electron microscope) and TEM (transmission electron microscope) analysis revealed that lipopeptides alter the morphology of the phytopathogen.

5.6. Antiviral Activity. It has been well documented that lipopeptides such as surfactin possess a broad spectrum of antiviral activity against SARS-CoV-2, herpes simplex virus (HSV-1 and HSV-2), Newcastle disease virus, Semliki Forest virus, murine encephalomyocarditis virus, Simian immunodeficiency virus, vesicular stomatitis virus, transmissible gastroenteritis virus, porcine parvovirus feline calicivirus, pseudorabies virus, and bursal disease virus, porcine epidemic diarrhoea virus, and viral hemorrhagic septicemia virus. The chemical structure of surfactin lipopeptide, for example, length of the carbon chain, makes it fit for the inactivation of various viruses [51, 192–194]. Moreover, it was also observed that surfactin more significantly inactivates the enveloped viruses such as herpes viruses and retroviruses compared with nonenveloped viruses [195]. This may be due to the physicochemical interaction among membrane active property of surfactin and the virus lipid membrane [196]. Surfactin permeates into the lipid bilayer and results in the complete disintegration of the envelope containing the viral proteins involved in virus adsorption and penetration to the target cells [195].

5.7. Antiadhesion and Antibiofilm. Surface adhesion and biofilm formation are the mechanisms by which most of bacteria are used for their survival. Lipopeptides have the potential to decrease the interfacial tension and surface of biofilms. In numerous ways, lipopeptides disrupt the membrane structure. For example, surfactin gets inserted into the lipid bilayers, chelates monovalent and divalent cations, solubilizes the fluid phospholipid phase, and modifies the membrane permeability [197]. Surfactin may form voltage-independent channels in biofilms, and these channels disturb the membrane integrity and permeability, leading to membrane disruption [13, 198]. Iturin isoform (mycosubtilin) produced by *B. subtilis* interacts with membranes via its sterol alcohol group and exhibits resistance to fungi [199]. *B. circulans* strain showed

antiadhesive property towards many bacteria species [200]. Similarly, various *Bacillus* strains inhibit biofilm formation [6, 78–80].

5.8. Others. Bacillus lipopeptides were also reported in wound healing and oral care products [65]. Zouari et al. [29] documented how the *B. subtilis* SPB1 biosurfactant supplementation improves the liver function, hyperlipidemia, and hypertriglyceridemia in high-fat-high-fructose (HFHF) diet-fed rats. In another study, the same research group also observed that *B. subtilis* SPB1 biosurfactant treatment improves the renal functions and inhibits angiotensin I-converting enzyme (ACE) in HFHF diet-fed rats [39]. Moreover, *B. subtilis* strain containing surfactin was shown to effectively kill the larval and pupal stages of mosquito species, for example, *Aedes aegypti*, *Culex quinquefasciatus,* and *Anopheles stephensi* [195].

6. Lipopeptide Applications in Food

Lipopeptides have well-defined antiadhesive, antibacterial, antiviral, and anticancer properties, ensuring their role in the cosmetics, pharmaceutical, and even food industries. Lipopeptides are mainly employed as surfactants in the food industry. Moreover, rhamnolipids and surfactins are positively exploited in the baking industry, providing good texture, volume, and product stability. They are also used to promote the emulsification process in the fat tissue to regulate fat globule agglomeration. Certain lipopeptides derived from *Enterobacter cloacae* have recently been presented into the food market with their high emulsifying characteristics owing to the potential to improve viscosity even at extreme acidic conditions. In terms of economic growth, the most significant increases in food additives have been seen in emulsifiers and hydrocolloids that were up to 10.5% and 6.0%, respectively.

The vulnerability of biologically active peptides as an antimicrobial agent in the food preservation is rare due to their limits to proteases. The usage of ring-structured peptides like lipopeptides, on the other hand, can prevent this susceptibility. There are two types of lipopeptides: a cyclic heptapeptide acylated with β-amino fatty acids that have a chain length of C14–C16, and the fengycin group containing a β-hydroxy fatty acid with uncommon amino acids including allo-threonine and ornithine. They also consisted of cyclic heptapeptide that makes a lactone linkage with β-hydroxy fatty acids. They are enzyme-insensitive (particular protease), suppressing the development of a broad variety of pathogenic fungi (*Fusarium graminearum, Rhizoctonia solani,* and *Aspergillus flavus*) as well as postharvest pathogens such as *Botrytis cinerea* and *Penicillium expansum*.

Gandhi and his coworkers revealed that the rhamnolipid emulsifier with a concentration of 0.10% significantly improved the texture, moisture content, and appearance of muffins for longer periods. Surfactin inclusion in many fermented food products, like natto, a Japanese soybean meal, is extremely favorable for acceptance as an ingredient or addition. Juola et al. [201] determined the surfactin content of various natto types. Notably, the greatest concentrations discovered were close to 2.2 mg/g, which corresponds to 80–100 mg surfactin per 50 g natto. Additional research is required to establish the surfactant's recommended daily intake (RDI) to pronounce it harmless and is usually considered to be a generally recognized as safe (GRAS) organism. Therefore, surfactin has strong potential to be used in the food sector.

Zouari et al. [202] prepared the cookies using sesame peel flour partially replaced with white wheat flour. When additional sesame peel flour was employed, the characteristics such as toughness, water content, and spread factor had been degraded. Interestingly, adding 0.1% *B. subtilis* SPB1 biosurfactant significantly enhanced the textural profile, even when compared to the standard surfactant glycerol monostearate [202]. In another research, the possible lipopeptides from *Bacillus spp*. reduced the *Ochratoxin* and *A. carbonarius* that were found in the processing of wine-making [203]. In the wine-making process, the concentration of *Ochratoxin* should not surpass 2.0 μg/L as it is a carcinogenic mycotoxin. Additionally, this compound has a detrimental effect on yeast fermentation behaviour. Lipopeptides also had higher antifungal capabilities than SO_2 and stimulated yeast growth as well as the generation of esters and acids that are involved in the olfactory profile [203].

7. Conclusion

Lipopeptides are very useful molecules due to their multiple applications. Most *Bacillus* lipopeptides have been applied in food, cosmetic, biotechnology, pharmaceutical industries, where emulsifying, antimicrobial, and surfactant properties are used. The application and production of lipopeptides are very promising trend; however, the high cost of production makes them unfit for large-scale synthesis. Furthermore, even though there are many reports displaying the thrombolytic, antitumor, and anti-inflammatory activity of lipopeptides, the few numbers of clinical trials warrant more significant efforts. In future, extensive studies should be carried out to verify previously published author findings, which further help with the utilization of these miracle compounds. In summary, *Bacillus* lipopeptides have strong potential application in various fields and a lot of work will be needed to formulate strategies for improved large-scale biosynthesis of lipopeptides.

Data Availability

No data were used in this article.

Conflicts of Interest

The authors declare no conflicts of interest.

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