Antimicrobial Applications of Sophorolipid from *Candida bombicola*: a Promising Alternative to Conventional Drugs

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Abstract
Sophorolipids are extracellular glycolipids, produced mainly by yeast *Candida bombicola*, composed of a disaccharide sophorose (O β-D-glucopyranosyl-2-1-β-D-glucopyranose) linked by a glycosidic bond to the terminal or sub-terminal carbon of a fatty acid chain. Because of these structural characteristics, sophorolipids have been reported with several applications, which are directly related to the predominance of their acidic and lactonic forms. Sophorolipids are the most promising and attractive biosurfactant, highlighting its antimicrobial action against Gram-positive and negative bacteria. The antimicrobial activities of sophorolipids is due the mechanism of changes or rupture in the cellular membrane, inducing the outpouring of their cytoplasmic contents and the consequent death of the pathogen. This surfactant can be used as an alternative for the substitution of conventional drugs.

Introduction

The consumer concerns about the use of synthetic antimicrobials to improve the quality of life, led to a search for biodegradable compounds of natural origin [1]. The importance of biofilms control and the potential use of biosurfactants, as an antimicrobial agent, has enhanced the interest in these compounds, which are molecules with surfactant characteristics, produced by microorganisms and, although the similarity with petroleum based surfactants, they are considered superior and more advantageous, because of their ecological and sustainable nature [2]. Structurally, they are amphiphilic molecules, whereas the hydrophobic moiety is a long chain of fatty acid, hydroxy acid or α-alkyl β-hydroxy-acid and the hydrophilic moiety is generally a carbohydrate, amino acid, cyclic peptide, phosphate, carboxylic acid or alcohol [3].

Sophorolipids are secondary metabolites classified as extracellular glycolipids, primary produced by yeast *Candida bombicola*, from carbohydrates and lipids, being excreted as a mixture of related chemical structures [4]. They are composed of a disaccharide sophorose (O β-D-glucopyranosyl-2-1-β-D-glucopyranose) linked by a glycosidic bond between the carbon 1’ and the terminal (ω) or sub-terminal (ω-1) carbon of a fatty acid chain of 16 or 18 carbons [5]. They have no cytotoxicity and are accepted and approved by the FDA (Food and Drug Administration). Currently, they are the most applied biosurfactants in the industry and the products are available in commercial level.

These metabolites are produced in two principal structural forms, acidic and lactonic [6], which results in changes in the physical-chemical and biological properties, responsible for the different applicabilities of these compounds [7]. In relation to the producing microorganisms, there are several species of yeasts that synthesize different profiles of sophorolipids, highlighting *C. bombicola*, because of the high yields, which mainly produces sophorolipids in the lactonic di-acetylated form (6’,6”)- with monounsaturated fatty acids (C16 and C18) and in a minor extent, acidic non-acetylated or monoacetylated forms (6”) [8]. Therefore, because of these structural characteristics, sophorolipids have been reported with several applications, which are directly related to the composition of their acidic and lactonic forms. These applications are highlighted in agriculture, food, cosmetic, bioremediation and biomedicine with antimicrobial activity [9,10].

Antimicrobial activity of sophorolipids

The antimicrobial activity of sophorolipids is related to the synergistic effect of their sugar and lipid portions (surfactant
The interactions between carbohydrates and bacterial membranes have been studied for years [15], however, only recently, studies have attempted to show the impact of mono and disaccharides on the structure of membranes [16], such as the sophorose disaccharide present in the sophorolipid molecule, which is effective as a bactericidal agent, regardless if its lipid content is acidic or lactonic, being capable of inducing death of planktonic cells and biofilms of both Gram-positive and Gram-negative bacteria, although the negative group presents a more complex cellular envelope; both can be damaged by sophorose [17].

The peptidoglycan layer of Gram-positive bacteria is covered by polysaccharides, neutral acids and proteins. The surface of the Gram-negative bacteria is constituted by lipopolysaccharides with neutral pH, but when the carboxylic and phosphate groups are ionized, they confer anionic charges. These negative charges make the bacterial membrane more hydrophilic [18] compared to Gram-positive bacteria. The sophorolipids, due to their amphiphilic characteristics, decrease the hydrophobicity of both bacterial groups, but because of the majority composition in fatty acids, they exhibit a greater tendency to hydrophobicity, leading to a more significant performance in hydrophobic microorganisms (Gram-positive) [19,20].

The antimicrobial activity of sophorolipids depends on the concentration, treatment time, composition of fatty acids and the predominance of acid and lactonic forms [21,22], as well as the sugar group of the molecule [23]. Lactonic forms have better surface tension properties and antimicrobial activity [24]. Furthermore, it is known that the acetylated forms have better biological and physical-chemical properties [25].

Sophorolipids from C. bombicola produced in palmitic, stearic and oleic acids were applied to Gram-positive bacteria (Enterococcus faecium, Aerococcus viridans, Staphylococcus xylosus, S. cohnii and S. equorum) Gram-positive endospore-forming (B. licheniformis, B. pumilus and B. mycoides) and Gram-negative bacteria (Pseudomonas luteola, Enterobacter cloacae, E. sakazakii and Vibrio fluvialis), obtaining MIC from 4.88μg.mL⁻¹ to 19.5μg.mL⁻¹, demonstrating effect in all bacteria studied [26]. Similar studies by different authors have shown that sophorolipids (SL) from C. bombicola were also able to reduce Escherichia coli O157: H7 population. Applications with 0.5% and 1.0% of SL-oleic and SL-palmitic reduced planktonic cell cultures after 1 to 2 hours of incubation. Although, only 0.1% of SL-stearic was sufficient to reduce colonies of E. coli O157: H7 after 2h, or its eradication at concentrations of 0.5 to 1.0% [27].

Sophorolipids produced by C. bombicola on coconut and corn oils were tested against S. aureus and E. coli. The synthesized from corn oil was more efficient for E. coli, and coconut oil for S. aureus [21]; this demonstrates the varied action mechanism of different sophorolipids as an antimicrobial agent in the various pathogenic strains. It was also tested by other authors in B. subtilis and Pseudomonas aeruginosa, obtaining a MIC of 5.0; 10.0μg.mL⁻¹, respectively [20].

Enterococcus faecalis and P. aeruginosa, bacteria responsible for nosocomial infections, were inhibited by purified acidic sophorolipids from C. bombicola, predominantly non-acetylated (C18), at 25 mg.mL⁻¹. At 20 mg.mL⁻¹, an inhibitory effect on the growth of E. faecalis was observed, with no formation of colonies [22]. On the other hand, the mixture of sophorolipids without purification, containing 75% of lactonic and 25% of acidic was effective against E. coli at 1 mg.mL⁻¹ and S. aureus at 15-150μg.mL⁻¹, [28]. Sophorolipids produced from glucose and lauryl alcohol were tested in Gram-negative bacteria (E. coli ATCC 8739 and P. aeruginosa ATCC 9027), Gram-positive (S. aureus ATCC 6358 and B. subtilis ATCC 6633) and yeast C. albicans ATCC 2901 [29]. The results showed complete inhibition when compared to SL-oleic and SL-linolenic. The inhibition was 30μg.mL⁻¹ for E. coli and 1μg.mL⁻¹ for P. aeruginosa at 2 and 4h, respectively; for S. aureus was 6μg.mL⁻¹; B. subtilis 1μg.mL⁻¹ and C. albicans 50μg.mL⁻¹, after 4h of treatment.

The acidic and lactonic forms of sophorolipids from Rhodotorula babevae YS3 presented antifungal action against Colletotrichum gloeosporioides, Fusarium verticillioides, Fusarium oxysporum, Corynespora cassicola and Trichophyton rubrum verified by MIC of 62 μg.mL⁻¹, 125 μg.mL⁻¹, 1,25 μg.mL⁻¹, ≥2,000μg.mL⁻¹ and ≥1,000μg.mL⁻¹, respectively [30]. Synergistic actions of diacetylated lactonic sophorolipids (SL-oleic) with cefalor and tetracycline have been described, demonstrating that the activity of conjugated antibiotics was enhanced for E. coli ATCC 8739 and S. aureus ATCC 29737 [31]. Sophorolipid conjugated with caprylic acid (0.8%) increased the inhibition of P. aeruginosa PA01, Bacillus subtilis NCTC 10400, S. aureus ATCC 9144 and E. coli NCTC 10418 [32]. In another study, the same authors verified the combination of sophorolipids and rhamnolipids (0.04% / 0.01%) against biofilms of P. aeruginosa ATCC 15442, S. aureus ATCC 9144 and a mixed culture of both, obtaining positive results about the synergism of this molecule with different compounds [33].

The activity of sophorolipids from C. bombicola was compared with thiamine dilauryl sulfate (TDS) in the presence of alcohol against Salmonella spp. and Listeria spp. The lactonic sophorolipids presented superior antimicrobial activity in Listeria spp. than in Salmonella spp. The populations of Listeria spp. were reduced from 7.2 log CFU.mL⁻¹ to an undetectable level after treatment of 1min with 0.1% (w/v) of SLP and TDS.
in the presence of ethanol (20%). TDS was more effective than sophorolipids against *Salmonella* spp. and *Listeria* spp., but both of them are capable of causing cell lysis; demonstrating that sophorolipids and TDS in the presence of ethanol can be used to inactivate pathogens, especially Gram-positive bacteria [34].

**Conclusion**

This review presented the potentials of this glycolipid and their applications as an antimicrobial and antifungals agent. Sophorolipids can be used to repair infectious diseases, as therapeutic agents, sanitizers and germicides in several sectors, highlighting the main bacteria of food borne illness and contamination, both Gram-positive and Gram-negative, can be inhibited by antimicrobial activity of sophorolipids produced by *Candida bombicola*. Considering the significance of the development of new sustainable strategies, combined with the importance of controlling the formation of biofilms and being a non-toxic product, sophorolipids present a promising perspective for an excellent antimicrobial agent.

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