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Minireview

Glycolipid biosurfactants: Potential related biomedical and biotechnological applications

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ABSTRACT

Glycolipids, consisting of a carbohydrate moiety linked to fatty acids, are microbial surface active compounds produced by various microorganisms. They are characterized by highly structural diversity and have the ability to decrease the surface and interfacial tension at the surface and interface respectively. Rhamnolipids, trehalolipids, mannosylerythritol-lipids and cellobiose lipids are among the most popular glycolipids. Moreover, their ability to form pores and destabilize biological membrane permits their use in biomedicine as antibacterial, antifungal and hemolytic agents. Their antiviral and antitumor effects enable their use in pharmaceutic as therapeutic agents. Also, glycolipids can inhibit the bioadhesion of pathogenic bacteria enabling their use as anti-adhesive agents and for disruption of biofilm formation and can be used in cosmetic industry. Moreover, they have great potential application in industry as detergents, wetting agents and for flotation. Furthermore, glycolipids can act at the surface and can modulate enzyme activity permitting the enhancement or the inhibition of the activity of certain enzymes.

1. Introduction

Microbial derived surfactants or biosurfactants are firstly discovered as extracellular compounds in research into hydrocarbon fermentation, which started in the late 1960s.[1] They are produced by a wide variety of microorganisms. They decrease the surface and interfacial tension between individual molecules in the surface and interface respectively and they are endowed with diverse biological activities (such as antimicrobial, antiviral, hemolytic and insecticide activities).[2] They are amphiphilic compounds with a hydrophilic (amino-acid or peptides; di- or polysaccharides; anions or cations) and hydrophobic moieties (saturated or unsaturated fatty acid).

Biosurfactants can be classified according to different criteria. They can be classified owing to their molecular weight (high molecular and low molecular weight biosurfactants), ionic charges (anionic, cationic, non-ionic and neutral biosurfactants) and secretion type (intracellular, extracellular and adhered to microbial cells). However, the chemical structure presents the main criteria for the classification of microbial derived surface active compounds. In fact, we distinguish glycolipids, lipopeptides, particular surfactants, fatty acids, phospholipids, neutral lipids and polymeric surfactants.[2] In the present literature review, we will discuss the low molecular weight biosurfactant class: glycolipids.

Glycolipids are among the most popular biosurfactant. Structurally, they are constituted by a fatty acid in combination with a carbohydrate moiety and correspond to a group of compounds that differs by the nature of the lipid and carbohydrate moiety. Owing to the nature of carbohydrate moiety, glycolipids can be subdivided into rhamnose lipids, trehalose lipids, sophorose lipids, cellobiose lipids, mannosylerythritol lipids, lipomannosyl-mannitols, lipomannans and lipoarabinomannanes, diglycosyl diglycerides, monoacylglycerol and galactosyl-diglyceride.[1] Certain mannophosphoinositides, mannose lipid and mannose protein are also described. Rhamnolipids of *Pseudomonas* sp., trehalolipids of *Rhodococcus* and sophorolipids produced by yeast strain are the most known glycolipids.

The present review deals with the latest research and development in glycolipid type biosurfactants, including their main application in biomedicine and pharmaceutical industry. In fact, having the ability to induce pore and ion channels, they destabilize biological membranes disturbing their integrity and permeability permitting their use as antibacterial, antifungal, antiviral, antimycoplasma and hemolytic agents. Also, having the ability to alter the cell surface hydrophobicity, adsorption of biosurfactant on solid surfaces can inhibit the bioadhesion of pathogenic bacteria permitting their use as anti-adhesive agents and for disruption of biofilm formation. Also, glycolipids can act as moisturizers allowing their use in cosmetic. On the other hand, they have great interest for industrial applications for their foaming and wetting properties of

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glycolipids. Also, glycolipid biosurfactants can modulate enzyme activities for biotechnological applications: they can be recognized as activators and/or inhibitors of enzyme activities.

2. Structural diversity, main properties and production of glycolipids

As described in Section 1, glycolipids correspond to a fatty acid in combination with a carbohydrate moiety (Fig. 1). They consist to a group of compounds that differs by the nature of the lipid and carbohydrate moiety.

Rhamnolipids are the most studied biosurfactants. Their production by *P. aeruginosa* was described for the first time by Jarvis and Johnson (1949).[3] Since, several rhamnolipids producing bacterial strains were isolated. They correspond to one or two molecules of rhamnose bound to one or two molecules of β-hydroxydecanoic acid.[3]

Trehalose lipids represent a wide group of glycolipids, constituted by a disaccharide trehalose linked to mycolic acids, which are long-chain α-branched-β-hydroxy fatty acids.[4] They are mainly produced by Gram-positive, high GC content bacteria of Actinomycetales such as *Mycobacterium*, *Nocardia* and *Corynebacterium* and they differ in their structure, size and degree of saturation.[5] Sophorolipids are mainly produced by yeast strains such as *Candida bombicola*, *C. magnoliae*, *C. apicola* and *C. bogoriensis* when grown on carbohydrates and lipophilic substrates.[6] They are generally present in the form of disaccharide sophoroses (2-*O*-β-D-glucopyranosyl-D-glucopyranose) linked β glycosidically to the hydroxyl group at the penultimate carbon of fatty acids.[6] In addition, we can enumerate the lipids of cellobiose or ustalagic acid that corresponds to a cellobiose with an *O*-glycosidic bond with the ω-hydroxyl group of the 15,16-dihydroxyhexadecanoic acid or 2,15,16-trihydroxyhexadecanoic acid.[7] They are mainly produced by *Ustilago maydis*, *Pseudozyma* sp., *Sympodiomycopsis paphiopedili* and *Cryptococcus humicola*.[7,8] Mannosylerythritol lipids or ustilipids is another interesting subclass of glycolipids. It consist of a mannose and erythriol, 4-*O*-β-D-mannopyranosyl-meso-erythriol as hydrophilic groups, as well as fatty acids of different hydrocarbon chains bound by acylation to the molecule of mannose, as the hydrophobic portion. Moreover, Joshi-Navare et al.[9] and Vollbrecht et al.[10,11] reported the production of certain xylolipids and lipids of oligosaccharide biosurfactants respectively. Xylolipids consisted of a molecule of xylose, methyl-2-*O*-methyl-β-D-xylopyranoside bound to hydrophobic fractions of the octadecanoic acid mainly produced by *Lactococcus lactis* and *Pichia caribbica*.[9] Lipids of oligosaccharides are a complex mixtures of different compounds which generally are di-, tri- and tetrasaccharides, such as trehalose bound to molecules of glucose and galactose, which are bound to acetyl groups and fatty acids with C_4 to C_{18} chain length that are mainly produced by *Tsukamurella* species.[10,11]

Microbial glycolipids showed many interesting functional properties such as the ability to reduce the surface and interfacial tension, the emulsification and de-emulsification capacities, the foaming potency, the solubilization and mobilization abilities and the pore-forming capacities.[1] Also, they are recognized by great interesting physic-chemical properties including stability to drastic conditions of pH, salinity and temperature.[12–14] Owing their natural origins, they are recognized as low or non-toxic.[15–20] Also, they well known by a good biodegradability[21–23] encouraging their use as alternatives to synthetic surfactants. So, they have the potential to be used in environmental field as enhancing of hydrocarbon solubility, mobility and biodegradation.[1] They are also potential candidates in biomedicine and therapeutics for their great antimicrobial, hemolytic, antiviral, anti-carcinogenic and immune-modulating activities.[1] Moreover, owing a broad spectrum of emulsification capacity and anti-adhesive activity, they have the potential to be used in food industry.[1] In agriculture field, they permitted the inhibition of certain phytopathogenic fungi, algal bloom and larvae of insects.[1] Table 1 enumerates the major glycolipids sub-classes, biological activities and microbial sources.

Glycolipid biosurfactants can be produced from inexpensive raw materials that are available in large quantities, such as industrial wastes and oily byproducts including hydrocarbons, frying oil waste and olive oil waste. In addition to these, the production efficiency of glycolipids using microorganisms has been improved along with the progress of biotechnology by the amelioration of fermentation conditions,[45] the application of solid state fermentation process[80–82] and the optimization of production by means of the response surface methodology.[83,84] Generally, the yields of bioconversion are always so high that they permitted the retention of huge quantity of glycolipid biosurfactants for diverse applications. Generally, they are released in the extracellular medium of the fermentation broth. However, they can be attached to the cell surface.[4] Different strategies are developed to extract, purify and identify glycolipids. They are designated in accordance to the physic-chemical properties and the potential use of the microbial derived surface active compounds and its wanted degree of purity. Among the most used techniques of extraction of glycolipids, we can present the acid precipitation, the solvent extraction and foam fractionation.[85–87] For purification, various strategies were developed such as membrane ultrafiltration techniques,[88] ionic exchange chromatography[89] and adsorption–desorption on resins[90] and adsorption–desorption on wood activated carbon like charcoal.[91] Also, developed techniques like high performance liquid chromatography, hydrophobic interaction chromatography[48] and gel filtration[92] are well used to fractionate and purify glycolipid compounds. Generally, a multi-step recovery strategy, using a sequence of concentration and purification steps, is more effective.[2] In such a multi-step recovery for biosurfactants, it will be possible to obtain the product at any required degree of purity.[2]

3. Glycolipids in biomedicine and pharmaceutical industry

3.1. Membrane permeabilizing activity and related application

Biosurfactants are well known by their membrane permeabilization properties as they can induce pore and ion channel formation in lipid bilayer membrane. So, they are able to destabilize membranes disturbing their integrity and permeability. Also, pore formation in membranes may cause trans-membrane ion influxes, including Na^+ and K^+, which result in membrane disruption and cell death. These structural fluctuations acting therefore on biological membrane integrity can explain the primary mode of the antibiotic action resulting in the important biological activities of biosurfactants including antibacterial, antifungal, antiviral, anti-mycoplasma and hemolytic activities.[93] In this aim, glycolipid biosurfactants are well known by their antibacterial, hemolytic, antiviral and anti-tumor activities. In fact, *Pseudomonas* derived rhamnolipids,[94,95] *Rhodococcus* derived trehalose lipids,[96] yeast derived sophorolipids[97] and mannosylerythritol lipids[98] are well recognized by their pore forming abilities and membrane permeabilizing properties. These activities enable the application of biosurfactants in diverse fields' especially in agriculture as biocontrol agent, in food industry as preservative agent to control microbial invasion and especially in medicine and pharmaceutics as anti-pathogenic bacteria; antiviral and as inhibitors of fibrin clot formation, etc.

As the interaction with the membrane could be the ultimate responsible for these actions, it is of great interest to get insight into the molecular mechanism of the interaction of purified glycolipid biosurfactants with the various phospholipid components of biological membranes. Ortiz et al.[99] studied the interaction of dirhamnolipid biosurfactants with phospholipid membranes by means of calorimetry, FTIR and X-ray diffraction. The partition