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Review Article

Biosurfactants in Biomedical Fields

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Introduction

Biosurfactants are a group of surface-active molecules produced by microorganisms. The use of biosurfactants in the medicinal field has increased during the past decade. The antibacterial, antifungal antiviral and antitumoral activities make them relevant molecules for applications in combating many diseases and as therapeutic agents [1]. In fact, numerous investigations in the field of bio surfactants are leading to the discovery and description of many interesting chemical and biological properties and potential biomedical therapeutic and prophylactic applications. In this review, the application of bio surfactants in the medicinal field is discussed.

Therapeutical and Biomedical Applications

Antimicrobial activity

Research for new antimicrobial drugs remains a major concern nowadays because of the newly emerged pathogenic microorganisms and traditional ones, which have become virtually unresponsive to existing antibiotics. In addition, there are no novel or effective chemical antibiotics that have been discovered during the last few decades [2]. Metabolites from microorganisms have been recognized as a major source of compounds endowed with ingenious structures and potent biological activities [3]. Several bio surfactants have shown antimicrobial action against bacteria, fungi, algae and viruses. The lipopeptide iturin from *B. subtilis* showed potent antifungal activity. The inactivation of enveloped viruses such as herpes and retrovirus was observed with 80 mM of surfactin. Rhamnolipids inhibited the growth of harmful bloom algae species, *Heterosigma akashivo* and *Protocentrum dentatum* at concentrations ranging from 0.4 to10.0 µg/l. A rhamnolipid mixture obtained from *P. aeruginosa* AT10 showed inhibitory activity against the bacteria *Escherichia coli, Micrococcus luteus, Alcaligenes faecalis* (32µg/ml), *Serratia arcescens, Mycobacterium phlei* (16µg/ml) and *Staphylococcus epidermidis* (8µg/ml) and excellent antifungal properties against *Aspergillus niger* (16µg/ml), *Chaetonium globosum, Enicillium crysogenum, Aureobasidium pullulans* (32µg/ml) and the *phytopathogenic Botrytis cinerea* and *Rhizoctonia solani* (18µg/ml) [4]. Sophorolipids and rhamnolipids were found to be effective antifungal agents against plant and seed pathogenic fungi. The Manno-Sylerythritol Lipid (MEL), a glycolipid surfactant from *Candida antartica*, has demonstrated antimicrobial activity, particularly against Gram-positive bacteria. Recently, a *Staphylococcus* sp. strain 1E produced a lipopeptide biosurfactant with interesting antimicrobial activities against pathogenic bacteria such as *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and *Bacillus subtilis* [5]. In the same context, Huang et al., [6] evaluated the antimicrobial activity of surfactin and polylysine against *Salmonella enteritidis* in milk using a response surface methodology and showed *S. enteridis* to be very sensitive to both molecules with minimum concentrations of 6.25 and 31.25 µg/ml, respectively. The optimization of antimicrobial activity indicated that *S. enteridis* could be reduced by 6 orders of magnitude at a temperature of 4.45°C, action time of 6.9 h, and a concentration of 10.03 µg/ml (surfactin/polylysine weight ratio, 1:1).

Anticancer activity

The biological activities of seven microbial extracellular glycolipids, including mannosylerythritol lipids-A, mannosylerythritol lipids-B, polyol lipid, rhamnolipid, sophorose lipid, Succinoyl Trehalose Lipid (STL)-1 and succinoyl trehalose lipid-3 have been investigated [7]. All these glycolipids, except rhamnolipid, were found to induce cell differentiation instead of cell proliferation in the human promyelocytic leukaemia cell line HL60. STL and MEL markedly increased common differentiation characteristics in monocytes and granulocytes respectively. Exposure of B16 cells to MEL resulted in the chromatin condensation, DNA fragmentation and sub-G1 arrest (the apoptosis events sequence). It is evident that growth arrest, apoptosis and differentiation of mouse malignant melanoma cells can be induced by glycolipids[115]. In addition, exposure of PC12 cells to MEL enhanced the activity of acetylcholine esterase and interrupted the cell cycle at the G1 phase, with a resulting outgrowth of neurites and partial cellular differentiation [8]. This suggests that MEL induces neuronal differentiation in PC12 cells and provides groundwork for the use of microbial extracellular glycolipids as novel reagents for the treatment of cancer cells. Another report suggested that the cytotoxic effects of sophorolipid on cancer cells of H7402, A549, HL60 and K562 were investigated by MTT assay. The results showed a dose-dependent inhibition ratio on cell viability according to the drug concentration <62.5 g/ml. These findings suggested that the sophorolipid produced by *W. domercqiae* had anticancer activity [9]. Recently, the production and the anticancer activity of biosurfactant produced by the dematiaccous fungus *Exophiala dermatidis* were evaluated. The produced monolein demonstrated antiproliferative activity against cervical cancer (HeLa) and leukemia (U937) cell lines in a dose dependent manner. Interestingly, no cytotoxicity was observed with normal cells even when high concentrations were used. Cell and DNA morphological changes, in both cancer cell lines, were observed to be cell shrinkage, membrane bleeding and DNA fragmentation [10].

Immuno modulatory action

Sophorolipids are promising modulators of the immune response. It has been previously demonstrated that sophorolipids, decreased sepsis related mortality after 36 h *in vivo* in a rat model

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of septic peritonitis by nitric oxide modulation, adhesion molecules and cytokine production and decreased IgE production *in vitro* in U266 cells possibly by affecting plasma cell activity. The results show that sophorolipids decrease IgE production in U266 cells by down-regulating important genes involved in IgE pathobiology in a synergistic manner. These results continue to support the utility of sophorolipids as an anti-inflammatory agent and a novel potential therapy in diseases of altered IgE regulation [11].

Anti-human viral infection

The increased incidence of Human Immunodeficiency Virus (HIV)/AIDS in women aged 15–49 years has identified the urgent need for a female-controlled, efficacious and safe vaginal topical microbicide. To meet this challenge, sophorolipid produced by *C. bombicola* and its structural analogues have been studied for their spermicidal, anti-HIV and cytotoxic activities. The sophorolipid diacetate ethyl ester derivative is the most potent spermicidal and virucidal agent of the series of sophorolipids studied. Its virucidal activity against HIV and sperm-immobilizing activity against human semen are similar to those of nonoxynol-9. However, it also induces enough vaginal cell toxicity to raise concerns about its applicability for long-term microbicidal contraception. In addition, the succinyl-trehalose lipid of *Rhodococcus erythropolis* has been reported to inhibit herpes simplex virus and influenza virus [12].

Anti-adhesive agent

Dairy *S. thermophilus* strain produces a biosurfactant which causes its own desorption from glass, leaving a completely non-adhesive coating [13]. Busscher et al. also showed that biosurfactant released by *S. thermophilus* inhibited adhesion onto silicone rubber and the growth of several bacterial and yeast strains isolated from explanted voice prostheses. Rodriguez et al., [14] using an artificial throat model, showed that biosurfactants obtained from probiotic strains greatly reduced microbial numbers on voice prostheses and also induced a decrease in the airflow resistance of voice prostheses after biofilm formation, which may constitute a mechanism by which the lifetime of indwelling silicone rubber voice prostheses can be prolonged. Velraeds et al., also reported on the adhesion inhibition of pathogenic enteric bacteria by a biosurfactant produced by *Lactobacillus strain* [15].

Agents for stimulating skin fibroblast metabolism

The use of sophorolipids in lactone form comprises a major part of diacetyl lactones as agents for stimulating skin dermal fibroblast cell metabolism and more particularly, as agents for stimulating collagen neosynthesis, at a concentration of 0.01 ppm at 5% (p/p) of dry matter in formulation. This is applicable in cosmetology and dermatology. The purified lactone sophorolipid product is of importance in the formulation of dermis anti-ageing, repair and re-structuring products because of its effect on the stimulation of dermis cells. By encouraging the synthesis of new collagen fibres, purified lactone sophorolipids can be used both as a preventive measure against skin ageing and used in body creams, body milks, lotions and skin gels for the. Antiadhesive agents in surgicals: Pre-treatment of silicone rubber with *S. thermophilus* surfactant inhibited by 85% the adhesion of *C. albicans* [16], whereas surfactants from *L. fermentum* and *L. acidophilus* adsorbed on glass, reduced by 77% the number of adhering uropathogenic cells of *Enterococcus faecalis*. The biosurfactant from *L. fermentum* was reported to inhibit *S. aureus* infection and adherence to surgical implants [17]. Surfactin decreased the amount of biofilm formation by *Salmonella typhimurium*, *S. enterica, E. coli* and *Proteus mirabilis* in PVC plates and vinyl urethral catheters. The property of SLs to stimulate the metabolism of skin fibroblast cells is valuable for the formulation of skin care products [17].

Conclusion

Interesting biosurfactants features has led to a wide range of potential applications in the medical field. They are useful as antibacterial, antifungal and antiviral agents, and they have the potential use as major immunomodulatory molecules and adhesive agents and in vaccines and gene therapy. Biosurfactants have been used for gene transfection, as ligands for binding immunoglobulins, as adjuvants for antigens and also as inhibitors for fibrin clot formation and activators of fibrin clot lysis. Promising alternatives to produce potent biosurfactants with altered antimicrobial profiles and decreased toxicity against mammalian cells may be exploited by their genetic alteration. Furthermore, biosurfactants have the potential to be used as anti-adhesive biological coatings for medical insertional materials, thus reducing hospital infections and use of synthetic drugs and chemicals. They may also be incorporated into probiotic preparations to combat urogenital tract infections and pulmonary immunotherapy.

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