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Review Article

RECENT POTENTIAL USAGE OF SURFACTANT FROM MICROBIAL ORIGIN IN PHARMACEUTICAL AND BIOMEDICAL ARENA: A PERSPECTIVE

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ABSTRACT
The use and potential commercial application of biosurfactant has increased during the past decade which can be used as emulsifiers, de-emulsifiers, wetting and foaming agents, functional food ingredients and as detergents in petroleum, petrochemicals, environmental management, agrochemicals, foods and beverages, cosmetics and pharmaceuticals and in the mining and metallurgical industries. Their antibacterial, antifungal and antiviral activities make them relevant molecules for applications in combating many diseases and as therapeutic agents. In addition to this their role as antiadhesive agents against several disease causing pathogens makes their utility as suitable antiadhesive coating agents for medical insertional materials which helps in the reduction in a large number of hospital infections without the use of synthetic drugs and chemicals. This review looks at the various pharmaceutical, biomedical and therapeutic perspectives on biosurfactant applications.
Key words: Biosurfactant, Antiadhesive agent, Antimicrobial activities, Antiviral activities,

INTRODUCTION

Biosurfactants (Microbial Surface Active Agents) have become recently an important product of biotechnology for industrial, pharmaceutical and biomedical applications. These are the amphiphilic compounds produced mostly on microbial cell surfaces or may be excreted extracellularly. This contains both hydrophobic and hydrophilic groups that confer the ability to accumulate between fluid phases and thus it is used in reduction of interfacial tension[1]. Unlike chemical surfactants, which are mostly derived from petroleum feedstock, these molecules can be produced by microbial fermentation processes using cheaper agro-based substrates and waste materials. During the past few years, biosurfactant production by various microorganisms has been studied extensively[2]. They are biodegradable and less toxic and are effective at extreme temperatures and pH values[3].

Most of the work on biosurfactant applications has been focusing on bioremediation of pollutants as it enhances the solubility and availability of hydrophobic pollutants, thus increasing their potential for biodegradation and also applied in the process of microbial enhanced oil recovery [4,5].Although the production of biosurfactants has steadily increased during the past decade the large scale production of these molecules has not been realized satisfactorily because of its high recovery and purification costs[6]. Their antibacterial, antifungal and antiviral activities make them as a relevant molecules for applications in combating many diseases and as a good therapeutic agent in recent days, so its draws the attention in the pharmaceutical and biomedical field[7]. Moreover they can be used as anti adhesive agents to the diseasing causing pathogens[8].

Here, we discuss some of the new and exciting applications and related developments of various microbial surfactants in the field of pharmaceutical and biomedical sciences and also to provide an overview of biosurfactant activities that could be exploited further in developing alternative drugs in the coming future.

Biosurfactant Classification

Biosurfactants are generally classified mainly by their chemical composition and microbial origin. It can be divided into low molecular mass molecules (providing lower surface and interfacial tension) and high molecular mass polymers (can be used as emulsion stabilizing agents)[9]. The brief classification of biosurfactant with their microbial sources has been summarized in the table-1.

Various Biological Activity of Biosurfactant

Biosurfactant have so many potential biological activities like anti cancer activity, anti microbial activity, anti adhesiveness, micro bubbles stabilization activity, anti-HIV and sperm immobilizing activity, immunomodulatory and various therapeutic activities which has been listed in the table-2.

Anti-cancer activity

The biological activity of several groups of biosurfactants like glycolipids, including mannosylerythritol lipids-A, mannosylerythritol lipids-B, polyol lipid, rhamnolipid, sophorose lipid, succinoyl trehalose lipid-1 and succinoyl trehalose lipid-3 have been investigated[19] .Except rhamnolipid, all these groups of biosurfactants were found to induce cell differentiation instead of cell proliferation in the human pro-myelocytic leukaemia cell line[20]. Mannosyl erythritol lipid is a group of surfactant glycolipid derived from *Candida antartica* enhances the differentiation of granulocytes. This glycolipid also induces the stage of apoptosis and differentiation of mouse malignant melanoma cells. The cytotoxic effects of sophorolipids on cancer cells of H7402, A549, HL60 and K562 were investigated by MTT assay in which a dose dependent inhibition ratio was noticed on cell viability [21, 22].

Anti-microbial activity

The antimicrobial activity of two biosurfactants obtained from probiotic bacteria namely *Lactococcus lactis*-53 and *Streptococcus thermophilus*-A, against a variety of bacterial and yeast strains[23]. The lipopeptide iturin from *Bacillus subtilis* showed potent antifungal activity[24]. A rhamnolipid mixture obtained from *Pseudomonas aeruginosa*-AT10 showed inhibitory activity against so many microorganisms like *Escherichia coli*, *Micrococcus luteus*, *Alcaligenes faecalis, Mycobacterium phlei.* It also possesses the antifungal properties against *Aspergillus niger* , *Chaetonium globosum* and the strain of *Aureobasidium pullulans* [25.] The mannosyl erythritol lipid is a group of glycolipid obtained from *Candida antartica* has demonstrated antimicrobial activity particularly against Gram-positive bacteria[26].

Biosurfactant as Anti-adhesives

The probiotic strains like *Lactobacillus plantarum*-299v and *Lactobacillus rhamnosus*-GG inhibit the adhesion of *Escherichia coli* to the intestinal epithelial cells by stimulating epithelial expression of mucins as these are the key producer of biosurfactant [27]. A surfactant produced by *Streptococcus thermophilus* has been used for fouling control of heat-exchanger plates in pasteurizers, as it can be able to retard the colonization of other thermophilic strains of *Streptococcus* which are responsible for fouling. More over pretreatment of stainless steel surfaces with a biosurfactant obtained from *Pseudomonas fluorescens* inhibits the colonization and adhesion of *Lactobacillus monocytogene*- L028 strain[28]. It was observed that *Rothia dentocariosa*, which is one of the strains responsible for the failure of valve prosthesis but this can be avoided when this prosthesis is exposed to biosurfactant obtained from *Streptococcus thermophilus*-A . Recently it was also demonstrated that the rate of microbial adhesion with a rhamnolipid biosurfactant containing solution was significantly reduced for a variety of bacterial and yeast strains isolated from explanted voice prostheses to silicone rubber[29]. A biosurfactant of *Pseudomonas fluorescens* was found to inhibit the adhesion of *Listeria monocytogenes*-LO28 to the stainless steel surfaces.*Lactobacilli sps.* are important in the maintenance of the healthy urogenital flora. There are some reports of inhibition of biofilm formed by uropathogens and yeast on silicone rubber by biosurfactants produced by *Lactobacillus acidophilus* [33, 34].

Biosurfactant for the Stabilization of Micro bubbles

Currently, applications of biosurfactant-based micro bubbles are focused mainly on ultrasound diagnosis and therapy[30.] Extensive studies have been performed on the use of micro bubbles as ultrasound contrasting agents. These types of micro bubbles are usually encapsulated in a shell of surfactant, protein, lipid or polymer to increase stability with *in vivo* condition. Their advantages include fragility when exposed to moderate energy ultrasound and ease of preparation. A wide range of substances such as drugs, DNA and virus particles can be bound to the shells of the micro bubbles with biosurfactant making them potential delivery systems for drugs and genes[31,32].

Anti-HIV and Sperm Immobilizing activity of Biosurfactant

The increased occurrence of human immunodeficiency virus (HIV) in women aged groups of 15–49 years have been identified as the urgent demand for a female-controlled effective and safe vaginal topical microbicide.The sophorolipid produced by *Candida bombicola*[33] and its structural analogues have been studied and proved its 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[34]. Its virucidal activity against HIV and sperm-immobilizing activity against human semen are similar and equivalent to those of nonoxynol-9[35].

Sterilizing agents in surgical

The biosurfactant from *Lactobacillus fermentum* was reported to inhibit *Staphylococcus aureus* infection and its adherence to surgical implants . More over Surfactin which is obtained from *Streptococcus thermophilus* able to decrease the amount of biofilm formation by *Salmonella typhimurium* and *Proteus mirabilis* in PVC [36]. Pre-treatment of silicone rubber with *Streptococcus* *thermophilus* surfactant can able to inhibit the adhesion of *Candida albicans*-87 up to 85%, whereas surfactants from *Lactobacillus fermentum* and *Lactobacillus acidophilus* adsorbed on glass surface can inhibit the number of adhering uropathogenic cells of *Enterococcus faecalis* up to 77% [37].

Immuno modulatory action of Biosurfactant

Sophorolipids are the best modulators in the immune response. It has been demonstrated previously that sophorolipids decreased sepsis related mortality at the interval of 36 hours *in vivo* in a rat model of septic peritonitis by adhesion molecules and cytokine production and also decreasing the IgE production *in vitro* in U266 cells by affecting plasma cell activity. The results show that sophorolipids is down regulating important genes involved in IgE-pathobiology in order to decrease IgE production in U266 cells. Hence the sophorolipids can be used as an anti-inflammatory agent and can be a novel potential therapeutic in the process of altered IgE regulation[38].

Therapeutic Applications of Biosurfactant

In order to generate monoclonal antibodies for the serological detection of drugs, antibodies and toxins a suitable and effective adjuvant is needed. It was proved that bacterial lipopeptides constitute potent nontoxic and nonpyrogenic immunological adjuvant when mixed with conventional antigens. A group of synthetic lipopeptide (N-palmitoyl-S-[2, 3-bis (palmitoyloxy)-(2R, S)-propyl-]-(R)-cysteinyl-serine) which is coupled to a T_h cell epitope efficiently enhanced the specific immune response against low molecular weight compounds in different species. A marked enhancement of the humoral immune response was obtained with the low molecular mass antigens with iturin, herbicolin and microcystin which are coupled to poly-L-lysine in rabbits and in chickens[39].One of the most important groups of organisms being studied for their use as an effective probiotic are members of the *Lactobacilli* group, which have the potential to prevent pathogen colonization and help to restore the normal microbial flora[40].

In spite of the immense potential of the biosurfactants in this field, their use still remains limited, possibly because of their comparatively high production cost, as well as their toxicity towards human systems. More research on human cells and human natural micro biota required to be performed in order to justify the potential need of biosurfactants in the biomedical area.

CONCLUSION

A host of interesting features of biosurfactants have led to a wide range of potential applications in the pharmaceutical and biomedical field. They are useful as antibacterial, antifungal and antiviral agents, and they also have the potential for use as major immunomodulatory molecules adhesive agents and in vaccines and gene therapy. Successful commercialization of every biotechnological product mainly depends largely upon its bioprocess economics. At present, the prices of microbial surfactants are not competitive with those of the chemical surfactants due to their high production costs and low yields. Hence, they have not been commercialized extensively. For the production of commercially viable biosurfactants, process optimization at the biological and engineering level needs to be improved. Improvement in the production technology of biosurfactants has already enabled a 10 to 20 fold increase in productivity, although further significant improvements are required.

However, the use of cheaper substrates for the production of biosurfactant with recombinant and mutant hyper producing microbial strains and optimal growth and production conditions having efficient multi-step downstream processing methods can make biosurfactant production economically feasible in the coming future.

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Table-1: Classification of different microbial surfactants.

Biosurfactant Classes	Sub Classes	Source	References
Glycolipids	Rhamnolipids	*Pseudomonas aeruginosa*	10
	Trehalose lipids	*Rhodococcus erithropolis*	
	Mannosylerythritol lipids	*Candida antartica*	10 12
Lipopeptides	Surfactin/iturin	*Bacillus subtilis*	13
	Lichenysin	*B. licheniformis*	
	Serrawettin	*Serratia marcescens*	14 15
Phospholipids	*Corynebacterium lepus*		16
Surface-active antibiotics	Gramicidin	*Brevibacterium brevis*	11
	Antibiotic TA	*Myxococcus xanthus*	
	Polymixin	*Brevibacterium polymyxa*	12
Polymeric surfactants	Alasan	*Acineto bacter radioresistens*	17
	Liposan	*Candida lipolytica*	18
	Lipomanan	*Candida tropicalis*	

Table-2: Examples of biological activity of biosurfactant.

Biosurfactant Type	Biological Activity	References
Surfactin	Antimicrobial and antifungal activities. Inhibition of clot formation. Haemolysis and formation of ion channels in lipid membranes. Antitumor activity against carcinoma cells.	42,43,44,45
Rhamnolipid	Anti-adhesive activity against several bacteria and yeast strains. Antimicrobial activity against *Mycobacterium tuberculosis*.	40,41
Iturin	Antimicrobial activity and antifungal activity against mycosis. Enhance the electrical conductance of biomolecular lipid membranes. Destroy the membrane structure of yeast cells.	46
Pumilacidin	Antiviral activity against herpes simplex virus 1 (HSV-1).	47
Mannosylerythritol lipids	Antimicrobial, immunological and neurological properties.	48,49,50
Glycolipid	Anti-adhesive activity against several bacterial and yeast strains.	51,52
Lichenysin	Chelating properties that might explain the membrane-disrupting effect of lipopeptides.	53,54