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Review Paper

Biosurfactants- A boon for therapeutics

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Abstract

Since the last decade, research has been underway to discover natural substances with therapeutic properties that can be exploited to treat a variety of ailments and enhance human health. One class of amphiphilic compounds of microbial origin that can interact with lipid membranes and other components of microorganisms and alter their physicochemical properties are biosurfactants. Due to this feature, biosurfactants are being studied more closely as prospective novel medications with potential uses in the clinical and therapeutic domains. The current review addresses biosurfactants' antimicrobial, antiviral, antibiofilm, and anticancer characteristics as well as their potential use in drug delivery systems.

Keywords: Therapeutic, Amphiphilic, Anti-microbial, Anti-viral, Anti-biofilm, Anti-cancer, Drug delivery systems.

Introduction

A structurally heterogeneous class of biomolecules known as biosurfactants are distinguished by their strong surface and emulsifying capabilities[1,2]. It has both hydrophilic and hydrophobic regions which are showed in Figure-1. It has amphipathic nature which is responsible for reduction in surface tension[3,4].

Biosurfactants are preferred for use in various formulation innovations and aggregation investigations due to their distinctive features that set them apart from chemical surfactants[5]. In terms of their performance on surfaces and at interfaces, biosurfactants have been demonstrated to be more potent and effective than chemical surfactants. Moreover, they are having ability of self-aggregating structures which are known as micelles (Figure-1). Biosurfactants' critical micelle concentration values have been shown to be much lesser compared to those of synthetic surfactants[6]. These characteristics allow for a reduction in the tension of a liquid surface while consuming significantly less biosurfactants[5]. When compared to chemical surfactants, these substances are environmentally safe and easily decompose into simpler metabolites.

Based on the molecular weight of the substance, biosurfactants are categorised: Low molecular weight and High molecular weight. Further they are classified according to their chemical structure in five groups named lipopeptides, glycolipids, fatty acids, particulate and polymeric biosurfactants (Figure-2).

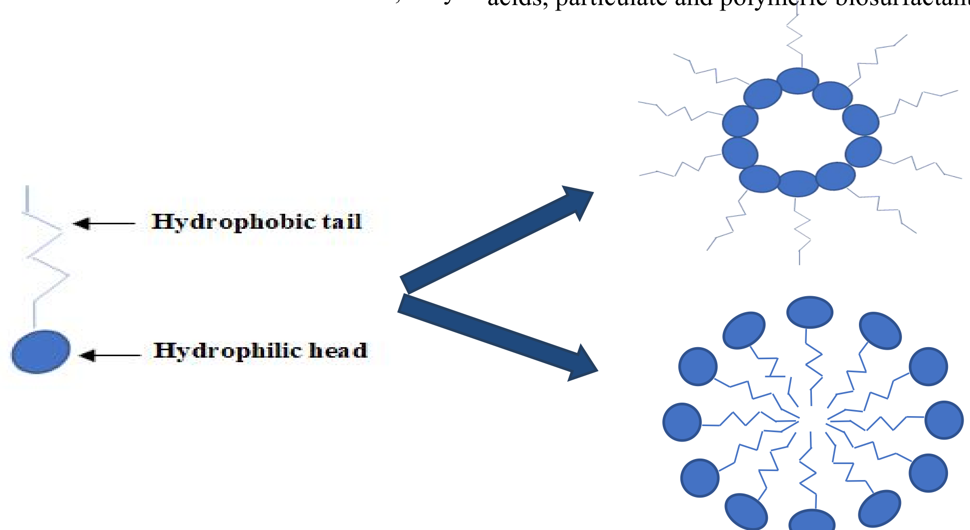

Figure-1: Biosurfactant molecule structure with reverse micelle structure and micelle structure.

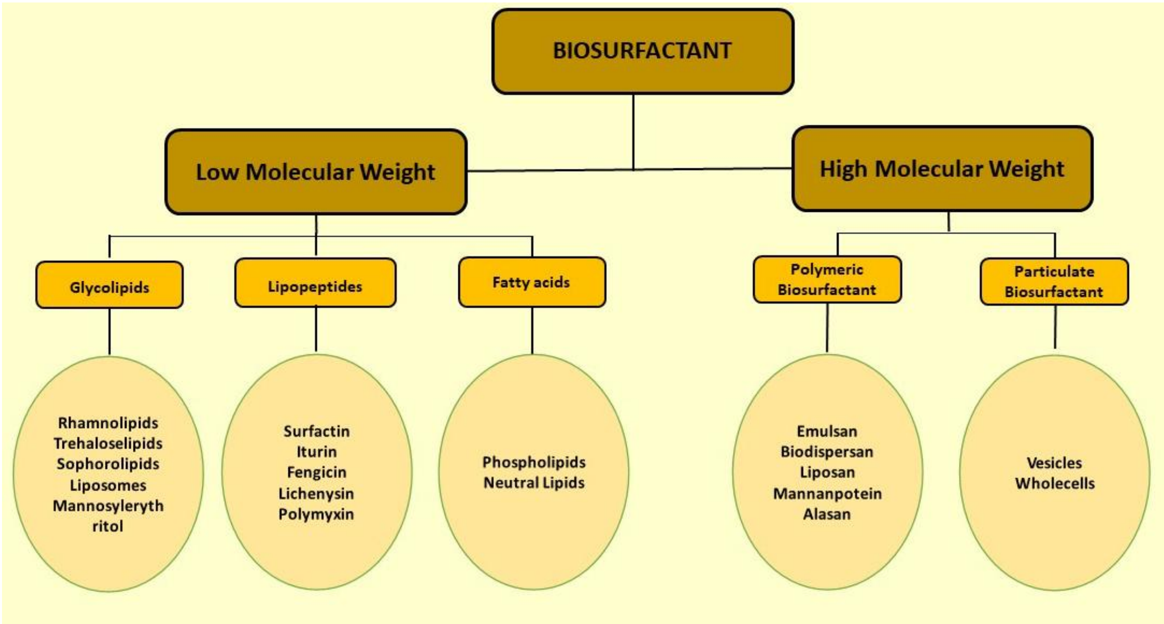

Figure-2: Classification of biosurfactant.

Since biosurfactants have distinctive chemical structures, it is essential to understand their functional modes of action along with their toxicity to humans if they are to be used in the health industry. Biosurfactants are being utilized in antibacterial, anti-adhesive, immunomodulation, and anticancer applications (Figure-2). The most potent antimicrobial substances are lipopeptides and glycolipids, which also serve as a valuable starting point for the development of novel antibiotics. It has been demonstrated that biosurfactants are involved in signal transmission, cell differentiation, and cell immune response, among other intercellular molecular recognition processes in mammalian cells. These molecules also act as antitumor agents by obstructing the development of cancer[7-9]. Additionally, several biosurfactants have demonstrated immunomodulatory properties[9].

Application of biosurfactant in various therapeutic fields

Antimicrobial activity of biosurfactants: Due to widespread overuse of antibiotics, many bacteria responsible for infections have acquired resistance to them, prompting the need for new and more potent antimicrobial drugs[10,11]. Numerous researches have clearly shown that biosurfactants have antimicrobial capabilities.

Researchers are looking for alternative antibacterial substances for medicinal and therapeutic applications as a result of multidrug resistance in microbes[12]. In a study by Gudina et al., the antimicrobial activity of a biosurfactant derived from *L. paracasei* sp. was evaluated using the microdilution method against *Streptococcus agalactiae*, pathogenic *C. albicans*, *Staphylococcus aureus, Staphylococcus epidermidis,* and *E. coli*, indicating the possibility of using it as a substitute for antibiotics against clinical pathogens[13]. Fengycins, surfactins, kurstakins, and iturins are antimicrobial lipopeptides from the *Citrobacter* and *Enterobacter* genera that have possibilities for use in medicine, cosmetics, and biocontrol, according to Mandal et al[14]. Glycolipids from *L. lactis* have been identified by Saravanakumari and Mani which have diverse antibacterial activities[15]. These biosurfactants may be safely used as medicinal agents and were safe to administer orally or topically.

Antiviral activity of biosurfactants: Biosurfactants have been studied for their antiviral abilities against numerous enveloped viruses over the past thirty years. The inhibitory effects of biosurfactants were caused by the establishment of ion channels in viral capsids and lipid envelopes, the absence of viral adsorption/penetration-related proteins, and the suppression of viral membrane fusion[16-18]. Surfactin, which has the finest applicability in the medical field, has potent antiviral properties[19,20]. It was suggested that surfactin exhibits antiviral activity as a result of physicochemical interactions between the lipid membrane of the virus and the membrane-active surfactant. This alters permeability and at greater concentrations, ultimately leads to the micelle effect, which causes the membrane system to disintegrate[21]. Several viruses, including the Newcastle disease virus, the pseudorabies virus, the porcine parvovirus, and the bursal disease virus, were shown to have their activity greatly inhibited by the in vitro tests with surfactin and fengycin *from B. subtilis*. Secondly, they were able to prevent viral infections and viral replication[22].

The anti-inflammatory and antiviral effects of biosurfactants have been proven through cytokines (TNF-, IL-6, IL-8, IL-12, IL-18, and IL-1), and toll-like receptors-2 (TLR-2).

Following an inflammatory reaction, these elements can lead to the release of proteins with cationic charges and other reactive oxygen species, such as lysozyme, which has therapeutic uses. When administered as therapeutic agents against viral infections, the reactive oxygen species created have anti-inflammatory and antiviral effects. These can be used to treat the cytokine storm, which affects the lungs and is a common finding in COVID-19 patients. Though it hasn't been proven or validated, this theory has been presented as a potential mechanism that may be used to create treatments for viral infections like COVID-19[23].

Finally, biosurfactants can be used in formulations for handwashing and cleaning agents to stop the transmission of viruses because they are sustainable natural materials with low cytotoxicity[24]. Despite the fact that none of the antiviral BS uses have reached the clinical testing stage, it is crucial to note that interest in the field is still considerable, partly because pre-clinical research implies that they have the potential to be used in pharmaceutical products. But in order to provide innovative and successful solutions for preventing disease outbreaks, BSs must be produced using affordable and simple procedures, widely commercialised, and effectively integrated into industrial processes[25].

Anti-biofilm activity of biosurfactants: In their environment, microorganisms can be found as free-living cells or, more frequently, as immobilised sessile bio-film forms attached to different surfaces[26,27]. According to Lopez et al. biofilms are microbial complexes created by one or more bacteria on surfaces to help them survive, reproduce, and carry out other crucial tasks[28]. Due to their close ties to chronic health care-associated infections (HAI), antibiotic resistance, and other biological problems, biofilms are a major problem[29,30]. Infections caused by medical devices are challenging to treat and manage, necessitating rigorous multidrug treatments and, in the majority of instances, implant removal as a last resort[31,32]. The healthcare system is still facing a significant problem in the hunt for efficient methods to combat the development of biofilms and the emergence of resistant microbes[33,34]. Because of their intriguing antibacterial, anti-adhesive, and anti-biofilm capabilities biosurfactants have shown to be helpful in winning this war during the past 20 years[35,36]. By inhibiting microbial adherence as well as microbial cell viability, biosurfactants limit biofilm formation[36-41]. Biosurfactant change the chemical and physical characteristics of abiotic surfaces when used as coating agents to prevent microbial adhesion (e.g., by reducing roughness and hydrophobicity)[42,43].

Anti-cancer activity of biosurfactants: Millions of individuals globally are at extremely high risk for developing cancer[44], so any advancement that increases survival is a top priority internationally. Cancer is a serious threat to human health due its unpredictability. Various approaches have been used over the years, including looking for new medications, therapies, or biomarkers. Despite all these endeavors, a successful focused, selective, and non-toxic therapy is still lacking.

Biosurafactants have been suggested as potential anticancer agents in an enormous number of studies[7,45]. According to Gudiña et al., lipopeptides and glycolipids have the potential to be employed as anti-cancer drugs that block the progression of cancer[7]. These substances are thought to have a role in a number of intercellular molecular recognition processes like signal transduction, cell differentiation, and immunological response, amongst many others[46]. Additionally, they have important characteristics that any anti-cancer treatment should have, such as low toxicity, high efficacy, and easy biodegradability[11]. Biosurfactants have an impact on cancer and tumour cells by either suppressing proliferation or inducing apoptosis. For instance, the glycolipid mannosylerythritol lipid induced apoptosis and growth arrest in mouse melanoma cells[47,48]. Monoolein biosurfactant has been shown to have antiproliferative effect against leukaemia and cervical cancer by Chiewpattanakul et al.[49]. The anticancer efficacy of a glycoprotein produced from *L. paracasei* was also tested against two breast cancer cell lines. After 48 hours, a decline in cell viability was noticed. Also, both cell lines showed evidence of cell cycle arrest[50].

Biosurfactants as drug delivery systems: Biosurfactants are one of the most promising biomolecules in the pharmaceutical industry due to their structural variety, stability, micelle-forming ability, biological compatibility, and low toxicity, all of which are beneficial in the designing of treatments[62]. Micelles are self-aggregating biosurfactant structures that can act as powerful emulsifiers and have antibacterial properties crucial to the development of drug - delivery systems. The use of biosurfactant-based microemulsion drug delivery systems can enhance the loading capacity, bioavailability, or release control of current medicines.

Conclusion

There has been significant increase in therapeutic applications biosurfactant research in science community worldwide. A future strategy of reducing bacterial infections, biofilm development, and proliferation may be accomplished by the use of the biosurfactant either by itself or in combination with other antibiotic or chemotherapeutic medications. Its extraordinary surface and interface activity, biodegradability, emulsifying properties, thermal resistance, and low toxicity are only a few of their special qualities that make them extremely promising to address a wide range of healthcare problems. As well, they have attracted several researchers owing to their novel pharmaceutic potential, which includes anticancer medicines, agents that promote wound healing, agents that combat viruses, agents that regulate immune systems, and agents that deliver drugs. The benefits of utilizing biosurfactant over chemical surfactant in several therapeutic applications are emphasised in this review paper.

Table-1: Application of biosurfactants in different therapeutic fields.

Activity	Type of Biosurfactant	Action	References
Antibiofilm activity	Rhamnolipid	*Pseudomonas aeruginosa*	51
	Rhamnolipid	*Pseudomonas aeruginosa, Staphylococcus aureus*	52
	Surfactin	*Bacillus tequilensis*	53
Anti-cancer Activity	Surfactin or surfactin-like biosurfactants	Hepatocellular carcinoma (Growth inhibition, apoptosis induction)	54
	Sophorolipids	Liver cancer (Growth inhibition, cell cycle arrest, apoptosis induction)	55
	Mannosylerythritol lipids (MELs)	Myelogenous leukemia	56
Anti-microbial activity	Surfactin	*B. cereus, L. monoctogens, Staphylococcus aureus, Streptococcus pneuminiae, Salmonella typhimurium, Serratia marcescens, Klebsiella pneumoniae*	57
	Sophorolipid	*P. aeruginosa* (MTCC 424), *Escherichia coli* (MTCC 723), *B. subtilis* (MTCC(441), *S. aureus* (MTCC 9886)	58
Anti-viral activity	Rhmnolipid	HSV-1 and HSV-2	59
	Sophorolipid	HIV, Epstein Barr virus (EBV), Coxsackie viruses (CVB1-6, CVA7, and CVA9), Murine Herpes virus (MHV-68), Influenza Virus A (H3N2 subtype)	60 61

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