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BIOSURFACTANT THERAPEUTIC POTENTIALS: A REVIEW

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ABSTRACT

Natural products have proved to be an important source of novel antimicrobial agents and their uses in traditional medicine have brought about the discovery of several bioactive compounds. Biosurfactants are derived from many microorganisms and are classified as secondary metabolites. Some bacteria are capable of synthesizing chemical products that are essential in areas such as pharmaceuticals, biomedicine, and biotechnology. The study therefore reviews production of biosurfactants, their applications and unique physicochemical characteristics that make them suitable for commercial production of therapeutics. Biosurfactants different areas of exploit as antimicrobial agents and in drug delivery systems, are also reviewed. If well exploited, biosurfactants could be a potential candidate in the production of many therapeutics as well as biochemicals.

Keywords: Biosurfactants, Therapeutic agents, Biochemicals, Secondary metabolites, Drug delivery system

INTRODUCTION

Research into the production of bioactive compounds for manufacturing of drugs is a continuous process necessary to combat numerous illnesses and imagine and re-imagine infections especially those that have developed resistance to multiple drugs (Vieira *et al.*, 2021).

"Surfactant" is derived from the expression "surface active agent". They are organic compounds that possess molecules containing two different polar segments: the hydrophilic head (polar segment) and the hydrophobic tail (non-polar segment) (Vieira *et al.*, 2021). Being amphipathic, they possess both hydrophilic and hydrophobic properties. They are also capable of reducing the surface tension occurring between phases like liquid/gas, liquid/liquid, and solid/liquid of a system (Mohana *et al*., 2020). Biosurfactants refer to surfactants that are derived from microbial sources (Bjerk *et al*., 2021). Biosurfactants are a class of chemicals that exhibit amphiphilic properties, possessing hydrophilic (polar) and hydrophobic (non-polar) characteristics (Ghasemi *et al*., 2019).

Biosurfactants are also known as tension-active biomolecules synthesized by microorganisms such as bacteria, fungi, as well as certain plants and animals (Sena *et al*., 2018; Fenibo *et al*., 2019; Ceresa *et al*., 2023). They can be produced through bacterial fermentation of organic waste materials to facilitate the development of cost-effective bioprocesses (Ghasemi *et al*., 2019). The presence of a hydrophilic segment enables surfactant to exhibit solubility in polar medium while the hydrophobic segment facilitates solubility in non-polar medium, and these are distributed either through extracellular release or cellular surface localization (Vieira *et al*., 2021).

The production of biosurfactants in humans is observed in several areas of the body especially in the intestine due to its colonization by numerous bacteria including lactic acid bacteria (LAB). LAB are widely known in enhancing human health, mostly attributed to its capacity to synthesize many beneficial compounds including hydrogen peroxide, bacteriocin and fatty acids (short-chain) (Satpute *et al*., 2016). Surface-active chemicals that are useful in areas such as pharmaceuticals, biomedicine, and biotechnology can be synthesized by human-associated bacteria. And they play a significant role in regulating microbial equilibrium in the oral cavity and the vaginal (Reid *et al*., 2011).

Surfactants have been classified into chemical surfactants and biosurfactants on the basis of their origin (Santos *et al*., 2018). The class biosurfactants are derived from microorganisms capable of producing secondary metabolites that attach intracellularly or extracellularly throughout the process of growth (Santos *et al*., 2016; Mohana *et al*., 2020). Their categorization mostly revolves around their structural characteristics, the microorganisms responsible for their production and their molecular weight (Ceresa *et al*., 2021).

Furthermore, biosurfactants can be classified based on their molecular weight with smaller molecular weight molecules having a reduced surface tensions while greater molecular weight molecules effectively work as emulsion stabilizers. According to Mohana *et al.* (2020), these compounds can be categorized into phospholipids, glycolipids, lipoproteins, lipopeptides, etc. according to their molecular weight. There are two categories of biosurfactants namely the low molecular weight compounds capable of reducing surface tensions and this is being referred to as "biosurfactants" and the high molecular weight compounds capable of forming emulsion-stabilizing compounds being referred to as "bioemulsifiers," and this can be categorized into five groups namely lipopeptides, glycolipids, phospholipids, polymers and neutral lipids (Banat *et al*., 2010; Ceresa *et al*., 2021). Lipopeptides, including surfactin, fengycin, and iturin, as well as the glycolipids namely rhamnolipids, trehalose lipids, sophorolipids, etc. have been extensively researched (Mandal *et al*., 2013).

Chemically manufactured surfactants, including Tween 20/80, Brij35 and Triton X-100 have emerged as the prevailing contenders in the present market landscape (Lamichhane *et al.*, 2017). Nevertheless, chemically produced surfactants often raise concerns regarding their toxicity and limited biodegradability (Santos *et al*., 2016). Also important is the fact that the production of these energy sources is not sustainable in the long term, since they are generated from finite fossil fuel reserves. Additionally, the production costs of these energy sources are susceptible to fluctuations in the price of fossil fuels (Otzen, 2017). According to Vijayakumar & Saravanan (2015), significant research endeavors have been dedicated to the advancement of sustainable, renewable, and less hazardous environmental source of energy, such as biosurfactants in the last decades. The implementation of these developmental initiatives has led to the establishment of a

prosperous biosurfactant industry on a global scale. According to the findings of Vieira *et al*. (2021), this business valued at US 4.2 billion dollars in 2017 rose to US 5.52 billion dollars in 2022, exhibiting a cumulative annual growth rate of 5.6%. This growth is primarily attributed to increase in demand for environmentally friendly products, specifically biologically derived surfactants. These surfactants offer improved functionality in comparison to chemically synthesized alternatives, while also possessing the advantages of renewability and biodegradability. The global market for biosurfactants achieved a value of USD 1.2 billion in the year 2022. According to Ceresa *et al*. (2021), it is projected that the biosurfactant market would see a cumulative annual growth rate of 11.2%. This growth by the year 2027 is anticipated to yield a market value of USD 1.9 billion.

Biosurfactants (BS) are metabolically produced from microorganisms involving enzyme-substrate reaction and fermentation process. They can otherwise be generated extracellularly through biocatalytic enzymes. The hydrophobic and hydrophilic portions of biosurfactants can be synthesized through two distinct ways: substrate-dependent synthesis for both portions or de novo synthesis for one portion while the other is induced by the substrate (Bjerk *et al*., 2021; Faisal *et al*., 2023).

Biosurfactant production method comprises four essential components, namely feedstock, inoculum, fermentation conditions, and downstream processing. The primary focus of research endeavors and technological advancements has been directed towards reduction of production costs together with improvement in yields while inoculum/microorganism component is considered the primary driving force behind the process. According to Geys *et al.* (2014), the determination of the maximal production potential and functioning of a biosurfactant product is crucial. The utilization of resilient new microorganisms and their hyper-production mutants/hybrids plays a pivotal role in advancing the biosurfactant industry Geys *et al*., 2014).

The biosurfactant's kind and output are typically particular to the species and are contingent upon the substrate employed for microbial growth and the environmental circumstances under which they are produced (Santos *et al.*, 2016). According to Banat *et al*. (2014), biosurfactants are primarily synthesized as secondary metabolites. The production of these compounds is primarily attributed to bacteria/yeast or filamentous fungi (Adu *et al*., 2020). Microbial producers encompass a diverse range of organisms, including bacteria such as *Acinetobacter, Lactobacillus, Bacillus, Burkholderia, Rhodococcus, Mycobacterium, Arthrobacter, Pseudomonas, Gordonia*, and *Nocardia*. Filamentous fungi such as *Aspergillus, Penicillium, Fusarium* and *Trichoderma* and *Ustilago*, as well as yeast species including *Kluyveromyces, Candida, Pseudozyma, Rhodotorula, Torulopsis* and *Saccharomyces* are also microbial producers (Santos *et al*., 2018; Fenibo *et al*., 2019; Ceresa *et al*., 2023).

Biosurfactants are acquired from microorganisms by separation techniques including extraction, precipitation and distillation not involving incorporation of organic synthesis before or during manufacture. Consequently, biosurfactants are sometimes referred to as naturally derived surfactants (Vijayakumar and Saravanan, 2015). The varied composition of biosurfactants arises from multiple microbial sources, specific substrate on which they are cultivated and specific circumstances employed during their development (Santos *et al*., 2016). Production of biosurfactants commercially involves identification and utilization of novel microbial producers derived from sustainable sources, including waste materials from agricultural/food processing and dairy industries, as well as vegetable oils and animals' fat. Additionally, advancements in fermentation, extraction, and purification methods have enhanced this process (Banat *et al*., 2014; Najmi *et al*., 2018).

Biosurfactants possess numerous benefits including human skin compatibility, low toxicity, biodegradability, stability and ability to perform well under extreme conditions of salinity, pH and temperature. Additionally, biosurfactants can be produced from cost-effective and renewable resources (Vijayakumar & Saravanan, 2015; Naughton *et al*., 2019; Adu *et al*., 2020). Furthermore, they exhibit a notable level of efficacy and demonstrate a commendable commitment to environmental sustainability (Banat *et al*., 2014; Vijayakumar & Saravanan, 2015; Ceresa *et al*., 2023).

Other advantages of these materials include their ability to possess specific actions or activities, their wide applicability, and their distinctive structures that have the potential to exhibit novel properties and find future uses (Diaz *et al*., 2016). The utilization of biosurfactant-derived products has demonstrated efficacy even when employed in limited quantities (Saimmai *et al*., 2019). Additionally, it is important to consider the potential for modifying the chemical composition of these substances via genetic engineering or employing biological and biochemical approaches in manipulating the metabolic end products. This approach allows for the customization of the substances to fulfill specific functional needs, as discussed by Swarnalatha and Rani (2019) and Ceresa *et al*. (2021). Moreover, it has been asserted that natural surfactants exhibit superior biodegradability and environmental friendliness compared to synthetic surfactants (Ceresa *et al*., 2021; Banat *et al*., 2021) and are more compatible with human skin (Adu *et al*., 2020), less toxic, and demonstrate efficacy even under extreme temperature, pH, and salinity conditions (Klosowska-Chomiczewska *et al*., 2011; Banat *et al*., 2014; Naughton *et al*., 2019).

The development of biosurfactants potentials has been affected by many challenges in areas such as the approaches taken in the investigations, source of microorganisms' species and costs in large-scale production (Naughton *et al*., 2019). Among problems being faced in biosurfactant production is high cost of production which hinders a large scale production (Saimmai *et al*., 2019). The entire production network from fermentation to recovery stage should be sustainable. The procedures used in biosurfactant synthesis are costly and the purification of the surfactants comes with some set back especially in pharmaceutical industries (Ceresa *et al*., 2021). Constrains are witnessed in separation and purification steps involved in some specific applications especially in pharmaceutical industries (Najmi *et al*., 2018; Ceresa *et al*., 2023). There is also a limitation in the use of biosurfactants obtained from pathogenic organisms because of the harm they may cause to human (Ceresa *et al.*, 2023).

Biosurfactants are being produced extracellularly by microbes that are of immense benefits in food, medicine, pharmaceutics and bioremediation (Karlapudi *et al*., 2020). Many researches are abound on the potential of biosurfactants as a drug candidate in many fields including anticancer drugs in anti-proliferative activity against cancer cells (Karlapudi *et al*., 2018), antimicrobial activity, oral cavity care and drug delivery (Naughton *et al*., 2019). Biosurfactants producing surface-active compounds also exhibit activities such as antiadhesive and anti-inflammatory activities (Jahan *et al*., 2020).

Therapeutic properties of biosurfactant as an ideal candidate for drug production

Biosurfactants are amphiphilic compounds that consist of two distinct regions: a hydrophilic region, which can be composed of various compounds such as carbohydrates, amino acids, alcohols, peptides, phosphates or carboxylic acids; and a hydrophobic region with saturated or unsaturated fatty acids or hydrocarbon acids with linear or branched structures. These biosurfactants are capable of forming micelles according to Ceresa *et al*. (2023). The presence of an amphipathic structure facilitates decrease in surface tension

between phases that possess contrasting polarities, such as liquid-air, liquid-liquid, or liquid-solid interfaces (Chen *et al*., 2010[a]; Chen *et al*., 2010[b]; Ceresa *et al*., 2021). These entities possess capacity to assemble into molecular aggregates, such as micelles. The phenomenon of micellar aggregation in biosurfactants occurs when the concentration reaches critical micelle concentration (CMC) between 1 and 200 mg/L. It is noteworthy that the CMC of biosurfactants is around 10- to 40-fold lower than that of chemical surfactants (Martinotti *et al*., 2013; Ceresa *et al*., 2021). And this put biosurfactants at advantage over chemical surfactant if well exploited.

Due to their distinct structural arrangement and amphipathic nature, biosurfactants exhibit varying physicochemical properties such as improved surface activity, capacity to form micro- emulsion, efficient critical micelle concentration, cleaning and foaming (Banat *et al*., 2010; Ceresa *et al*., 2023). Surface and interfacial tension are fundamental properties. It is a phenomenon arising due to cohesive interactions between molecules at the surface of a liquid. Concentration of a surface- active chemical which is known as the critical micelle concentration (CMC), plays a crucial role in reducing surface tension. CMC refers to the lowest concentration at which surface tension is reduced and micelle production is induced. The composition of BS is contingent on the existence of hydrophobic and hydrophilic constituents, and while hydrophilic moiety is comprised of amino acids, peptides, mono-, di-, and polysaccharides, the hydrophobic moiety is composed of both saturated and unsaturated fatty acids (Vijayakumar & Saravanan, 2015; Mohana *et al*., 2020).

BS typically have a neutral or anionic charge and compounds that possess amine groups exhibit a cationic character (Santos *et al*., 2016; Adu *et al*., 2020). Varied composition of biosurfactants arises from distinct microbial sources, specific substrate on which they are cultivated and conditions under which they are grown (Santos *et al*., 2016).

Biosurfactants also exhibit additional noteworthy biological characteristics including potent antifungal, antibacterial and antiviral effects as well as anticancer, antioxidant and immunomodulatory properties (Naughton *et al*., 2019; Kamalakannan *et al*., 2020; Ceresa *et al*., 2021). Additional biological features include the capacity to modulate cell membrane permeability, facilitate emulsification processes and exhibit adhesion to biotic and abiotic bodies (Ceresa *et al*., 2021).

Various types of biosurfactants have distinct characteristics and demonstrate a diverse array of physiological functions, contingent upon the specific microorganisms responsible for their production. One of the notable characteristics of these traits is the ability to solubilize hydrophobic substances, bind heavy metals, exhibit virulence factors, engage in cell signaling through quorum sensing and build biofilms (Franzetti *et al*., 2011; Diaz *et al*., 2015). Sophorolipids are biosurfactants that are exhibiting antimicrobial properties against Gram-positive bacteria (Banat *et al*., 2014; Diaz *et al*., 2015), surfactin in Gram-negative bacteria and rhamnolipids are capable of disrupting biofilms (Diaz *et al*., 2016).

Production of Biosurfactants

Biosurfactants can be produced from microorganisms through enzyme-substrate reactions and various processes of fermentation. Also, it can be produced through enzyme extracellular activity as a biocatalyst (Arima *et al*., 1968). The following are types of biosurfactants according to their ways of production.

Glycolipids Group of Biosurfactants

Glycolipids are the most common among biosurfactants, followed by rhamnolipids, trehalolipids, sophorolipids, and mannosylerythritol lipids (MELs) having monosaccharide and disaccharide with long-chain aliphatic acids or hydroxy-aliphatic acids (Drakontis & Amin, 2020). The most important among the glycolipids are rhamnolipids mainly produced by *Pseudomonas* and *Burkholderia* species. To produce rhamnolipids, the sugar part and the hydrophobic acid part are first produced using specific enzymes (Abdel-Mawgoud *et al*., 2014; Drakontis & Amin, 2020) such as RhlA, RhlB, RhlC, RhlG, and RhlI as reported in the production of rhamnolipids from *P. aeruginosa* (Kiss *et al*., 2017). Through microbial fermentation different form of rhamnolipids can be obtained such as mono-rhamnolipids and di-rhamnolipids which differ according to number of rhamnose groups present in the molecular structure which is determined based on environmental and growth factors (Lawniczak *et al*., 2013).

Lipopeptides Group of Biosurfactants

The most common lipopeptide biosurfactant is surfactin synthesized using a non-ribosomal reaction with surfactin synthetase as a catalyst. A subunit in the catalyst called SrfD initiates the synthesis (Ndlovu *et al*., 2017)., iturin, lichenysin and arthrofactin are other lipopeptide biosurfactants produced using the same method (Das *et al*., 2008). *Bacillus subtilis* is commonly used in producing surfactin through the method of normal fermentation. Solid state fermentation (SSF) method can also be used. SSF is an act of growing microorganisms on or inside solid substrates without free water. Lubricating oil and peanut oil which are renewable resources are also being employed in the production of lipopeptide biosurfactants using *Pseudomonas aeruginosa* (Thavasi *et al*., 2011).

High-Molecular-Weight Biosurfactants

High-molecular-weight biosurfactants otherwise called bio-emulsifiers (BE) are produced by bacteria, yeast, and fungi. They are produced as complex mixtures of heteropolysaccharides, lipopolysaccharides, lipoproteins, and proteins which either attached to the cell surface or released and with varying physicochemical properties depending on the variety of microorganisms used in the production (Uzoigwe *et al*., 2015). The commonest bacteria species in the production of bio- emulsifiers are Acinetobacter and two examples of BEs produced commercially are Emulsan and Alasan (Mujumdar *et al*., 2019). Emulsan is produced through different fermentation methods such as batch, chemo-stat, immobilized cell system, and self-cycling fermentation. Mannoprotein, another type of BEs can be produced within the cellular wall of *Saccharomyces* spp. and *Kluyveromyces marxianus* and later released from the cell wall using heat treatments with pressure (Alizadeh-Sani *et al*., 2018). Various places of biosurfactant application are shown in Table 1.

Table 1: Various places of Biosurfactant application

Biosurfactant	Microorganism	Application	Reference
Rhamnolipid	*Pseudomonas putida, Pseudomonas aeruginosa*	Bioremediation	Jadhay *et al*., 2018
	Pseudomonas chlororaphis	Biocontrol agents	Jadhay *et al*., 2011
	Renibacterium salmoninarum	Bioremediation	Mahjoubi *et al*., 2018
Sophorolipid	*Candida apicola, Candida bombicola*	Emulsifying agents	Solaiman *et al.*, 2016
Glycolipid	*Rhodococcus spp.*	Bioremediation	Tripathi and Gang, 2014
	Tsukamurella spp., Arthrobacter spp.	Antimicrobial agent	Abdel-Mawgoud *et al.*, 2014; Mnif *et al*., 2018
Manosileritritol Lipid	*Candida antartica*	Anti-inflammatory agent	Silva *et al.*, 2018
Surfactin	*Kurtzmanomyces spp*	Biomedical applications	Patel and Desai, 1997; Chen *et al*., 2017
Lipopeptide	*Bacillus subtilis*	Bacterial growth inhibition, Biomedical applications	Do Valle Gomes and Nitschke, 2012
Lichenisina	*Bacillus licheniformis*	Antimicrobial agents	Gomaa, 2013
Glycolipoprotein	*Aspergillus niger*	Antimicrobial agents	Ansari *et al*., 2018

Physicochemical properties of Biosurfactants

Different microorganisms produce different types of biosurfactants with different bioactivity. Apart from their source, their physicochemical characteristics also influence their production and purification processes. There is therefore the need to understand and be able to manipulate these characteristics to achieve better yield of industrial standard (Drakontis & Amin, 2020). The following section discusses some important properties of biosurfactants that give them unique advantages in their industrial application.

Surface and Interfacial Tension

Amphiphilic compounds, such as bio-emulsifiers, have the capacity to lessen interfacial and surface tension. They can create kinetically stable emulsions thanks to this characteristic. In order to replace water or oil molecules, lower surface or interfacial tension, and lessen intermolecular forces between solvent molecules, the molecules are adsorbed on interfaces (air/liquid, liquid/liquid, and solid/liquid) (Drakontis & Amin, 2020). Compared to chemical surfactants, biosurfactants are more effective at reducing interfacial tension (Pereira *et al*., 2013). With surface activity ranging from 72 mN/m to 27 ± 2 mN/m (Alvarez *et al*., 2015) and interfacial tension of 3.79 ± 0.27 mN/m and 0.32 ± 0.02 mN/m in extreme physical and chemical circumstances (Al-Wahaibi *et al*., 2014), surfactin is a good example of an active surface biosurfactant. On the other hand, biosurfactant produced by *Candida lipolytica* UCP 0988 (Rufino *et al*., 2014) and arthrofactin produced by *Arthrobacter sp*. strain MIS38 (Morikawa *et al*., 1993) both exhibit poor surface activity. This is because, in contrast to synthetic surfactants, biosurfactants exhibit distinct features related to their chemical structure, such as branching or ring structures and an unclear polarity distribution (Kumar & Ngueagni, 2021). Surfactin assembles into spherical structures that enable low aggregation number structures to develop and close packing at surfaces (Shen *et al*., 2009). Due to their unique surface characteristics, saponins exhibit both a strong hydrogen connection between saccharide groups in the interfacial layer and a dense molecular packing at the phase interface (Penfold *et al.*, 2018). The resulting extremely compact surface layers are denser than those found in the majority of typical amphiphiles. The way biosurfactants bind to biomolecules is determined by these characteristics.

Self-Assembly, temperature, and pH

Balancing process called Micellization gives thermodynamically stable nanostructures. Micelles are formed by surfactants spontaneously in aqueous solvents at concentrations above the critical micellization concentration (CMC) (Lee & Woo, 1995). Because of their weak Van der Waals contacts and hydrophobic effect, biosurfactants can self-assemble. The efficiency of biosurfactants is based on surface tension; water has a surface tension of 72 mN/m, but some biosurfactants can lower this to 30 mN/m (Desai & Banat, 1997). A few variables that affect the micelle's size and form are the biosurfactant concentration, temperature, pH, pressure, salts, etc. Biosurfactants are more stable in extreme temperatures between 50 and 100 °C, a pH between 2 and 12, and a high concentration of salt are conditions (Al-Wahaibi *et al*., 2014; Dhundale *et al*., 2018). The creation of micelles in biosurfactants and rhamnolipids is determined by the repulsive forces of the head groups. Additionally, surfactin and rhamnolipids can reorganize their micelle production into bubble structures (Aveyard *et al*., 2003). As they change into vesicles at higher temperatures and lower pH levels, temperature is crucial for the synthesis of rhamnolipids (Wu *et al*., 2019). The structure of the hydrocarbon chain and the peptide sequence determine micelle formation in biosurfactants as the hydrogen bonds between the head groups of biosurfactants produce supramolecular structures with different morphologies (Liu *et al*., 2020) leading to different nanostructures being formed by biosurfactants (Cui *et al*., 2014).

Solubilization

According to Nagarajan and Ruckenstein (1991), the solubility of hydrophobic organic compounds in biosurfactant is contingent upon several factors, including the concentration of the surfactant, its pH, and any additions or salts that may alter the micelle size. By making amphiphilic molecules more hydrophobic, it is possible to boost the solubilization of hydrophobic substances such as rhamnolipids. The solubility of other molecules with substrate-specific biosurfactant properties is limited by the ability of biosurfactant molecules to form vesicles and micelles, which can emulsify or solubilize various hydrocarbons at varying rates (Shao *et al*., 2017). As demonstrated by rhamnolipids, which can solubilize n-alkanes at concentrations both above and below CMC (Satpute *et al*., 2019; Yang *et al*., 2020) with a solubilization efficiency of 3-5 higher order below CMC (Zhang and Miller, 1992), biosurfactants solubilize more readily than synthetic surfactants (Lopez-Prieto *et al*., 2020). An improvement in solubility is observed in the synergy formed between two biosurfactants namely rhamnolipid and

sophorolipid compared to glycolipid which is one biosurfactant (Percebom *et al*., 2018).

Emulsifying Property

Emulsion is not balanced even if it is kinetically stabilized. The composition of the liquid phases, the chemical structure and physicochemical qualities, the temperature and pressure, and the process all affect its structure, stability, and appearance (Kaisu & Alexandridis, 2016). Processes of breaking down emulsion include skimming, flocculation coagulation, Ostwald maturation, and coalescence. Phase separation occurs due to difference in densities between oil and water phases leading to a phenomenon called creaming where the emulsion droplets migrate as a function of the gravitational field (Russel *et al*., 2021). Naturally, an emulsifier must be rapidly adsorbed on the surface of oil droplets and rapidly reduces the interfacial tension to facilitate droplet breakdown and formation of small droplets (McClements & Gumus, 2016). Biosurfactant derived from quillaja saponin extract is frequently utilized as an emulsifier in the food sector. Pseudocapitin II, which is generated by *P. fluorescens* BD5, has superior emulsifying activity to synthetic surfactants Tween 20 and Triton X-100, and it emulsifies the aromatic and aliphatic hydrocarbons more successfully (Janek *et al*., 2010). Greater effect on emulsion droplet size reduction is observed in rhamnolipids than in lecithin and monoglycerides ensuring thermal stability (Russel *et al*., 2021).

Biosurfactant areas of exploit as a Drug

Biosurfactants are characterized by antifungal, antibacterial, and antiviral activities, and they also possess immunological, neurological, and anticancer properties (Ceresa *et al*., 2021). They have the ability to inhibit the formation of fibrin clots and increase the electrical conductivity of bimolecular lipid membranes. Furthermore, they can act as agents that inhibit adhesion and the formation of biofilms on medical devices due to their ability to lower surface tensions between liquids that do not entirely mix, which inhibits hydrogen bonding and improves interactions between hydrophilic and hydrophobic substances.

Additionally, they have potential applications in transplantation (Sharma *et al*., 2021; Inamuddin *et al.*, 2022). Furthermore, biosurfactants are employed to enhance specific physical–chemical features of particular pharmaceutical formulations and also to increase the efficacy and performance of the pharmaceutical products. Biosurfactants are crucial to the development of self-emulsifying drug delivery systems (SEDDS), liquid, semi-solid, and solid drug stability, particle size control, and micro- and nano-based drug delivery systems (Ceresa *et al*., 2021; Ismail *et al*., 2021).

As an antiviral agent

Protein coatings known as capsids envelop the genetic material of viruses. On the other hand, virions' capsids are encased in lipid bilayers and include viral proteins that promote adhesion to host cells (Hegazy *et al*., 2022). According to Rodrigue *et al*. (2006), biosurfactants' amphiphilic characteristics enable them to facilitate interaction with the hydrophobic domain within the lipid membrane of encapsulated viruses, hence causing rupture.

Several studies have shown that some biosurfactants are capable of rendering viruses inactive through physiochemical processes (Vollenbroich *et al*., 1997; Mohana *et al*., 2020), perturbing viral membrane structures and destroying the outer covering (Shah *et al*., 2005). Biosurfactants' hydrophilic property is attributed to the presence of acetyl groups that facilitate their anti-viral characteristics (Borsanyiova *et al*., 2016). Moreover, the viricidal actions are rendered inactive by the hydrophobic properties associated with a certain number of carbon atoms (Kracht *et al*., 1999; Mohana *et al*., 2020). According to Kracht *et al*. (1999), monomethyl esters show viral inactivation against the Semliki forest virus, and biosurfactants with fatty acid chains containing fifteen carbon atoms and a single negative charge show high levels of inactivation. The efficacy of biosurfactants in inhibiting viral activity has been validated through official approval, as evidenced by the acquisition of patents for their application in the treatment of several viral strains (Gross & Shah, 2007; Bonvila *et al*., 2009).

Glycolipids groups of biosurfactants have been well-researched. Sophorolipids, which are produced by *Starmerella bombicola* and function as biofilm disruptors, antimicrobials, immunomodulators, and anti-inflammatory agents, are example of glycolipid. Previous research (Shah *et al*., 2005; Gross & Shah, 2007; Smith *et al*., 2020) has demonstrated that sophorolipids are active against HIV and the Herpes virus through acetylation of the sophorose head groups, hence boosting their antiviral activities.

The findings of these investigations can be utilized to understand the mechanism of action of the enveloped virus SARS-CoV-2 (Mohana *et al*., 2020). Biosurfactants (BSs) penetrate the bi-layered lipid membrane of host cells and interact with the viral cell membrane, altering its permeability and ultimately rupturing the membrane system. The viral envelope and capsid protein break down more readily at higher concentrations of BSs. There is a formation of micelles from the disrupted and encapsulated lipid envelope and spike protein resulting in viral inactivity. The so-formed micelle can function as liposomes capable of delivering drugs to the infection site and render protection when there is a hazard (Nakanishi *et al*., 2009). This property of BSs to form micelles would therefore be an effective drug delivery system in treating SARS-CoV-2 infection Mohana *et al*., 2020).

As an antibacterial agent

The escalating prevalence of multi-resistant bacteria has resulted in a diminishing efficacy of conventional antimicrobial agents, hence emphasizing the pressing necessity for alternate strategies (Marquez & Quave, 2020; van Duin & Paterson, 2020). Biosurfactants have been demonstrated to exert significant influence on the proliferation of several pathogenic microorganisms including Gram-positive and Gram-negative bacteria alongside fungal species.

Furthermore, unlike manufactured medications, biosurfactant molecules have unique antibacterial modes of action. Reducing the hydrophobicity of cell surfaces, rupturing the integrity of cell membranes, raising membrane permeability, impeding membrane functions like transport and energy production, changing the conformation of proteins, inhibiting the quorum-sensing system, and suppressing gene expression are some of these mechanisms. Since microbes find it difficult to adapt to these defense mechanisms, biosurfactants are important in the creation of environmentally friendly, long-term strategies to fight microbial infections (Satpute *et al*., 2019; Ceresa *et al*., 2021). *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, Methicillin Resistant *Staphylococcus aureus*, *Escherichia coli*, *Acinetobacter baumannii*, and *Klebsiella pneumonia* were among the clinical pathogens against which the antimicrobial efficacy of the rhamnolipid mixture GBB12 derived from *Shewanella*

algae was observed (Amirinejad *et al*., 2022; Gharaei *et al.*, 2022).

The pharmaceutical and biomedical sectors are currently focused on investigating Lactic Acid Bacteria (LAB) capable of producing biosurfactants that are both cell-bound and excreted. This is mostly because these biosurfactants have shown to have inhibitory effects on the growth of several bacteria, fungi, and viruses that cause infections (Yang *et al*., 2021; Thakur *et al*., 2023). Cell-bound biosurfactant produced from Lactobacillus rhamnosus, which was isolated from human breast milk, shows inhibition on multiple bacterial pathogens, such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli*, according to a recent study conducted by Patel *et al*. (2021). Additionally, it was discovered that by altering the integrity and viability of bacterial cells, biosurfactant made it easier to remove pre-formed biofilms. Glycolipid synthesized by *Lactobacillus plantarum* was obtained from yoghurt sample and found capable of reducing the virulence of *Pseudomonas aeruginosa* and *Chromobacterium violaceum*. This effect was achieved by disrupting the quorum-sensing regulatory mechanism. According to Patel *et al*. (2022), the biosurfactant under investigation showed an inhibitory effect on the synthesis of certain enzymes, including LasB elastase and LasA protease, and the creation of biofilms.

As antifungal agent

In a separate investigation, it was observed that *Lactobacillus crispatus* BC1 generated non- homogeneous lipopeptide during co-incubation circumstances to exhibit a moderate level of antibiofilm activity and dislodging activity against *Candida albicans* isolates and other strains of *Candida*. The biological impact subsequently amplified by incorporating lipopeptides within conventional liposomes and further augmented by coating the nano-carriers with hyaluronic acid, resulting in reductions of biofilm formation and biofilm dispersal (Abruzzo *et al*., 2021). The antifungal and antibiofilm properties of glycolipid HRB1 against *Magnaporthe grisea* and *Alternaria* spp. as well as *Pseudomonas aeruginosa* were investigated by Manikkasundaram *et al*. (2022). The researchers concluded that glycolipid exhibited antifungal, antioxidant, anticancer, antibiofilm and anti-quorum-sensing properties.

As an immunomodulatory agent

Biosurfactants have exhibited immunomodulatory properties, rendering them significant entities within the realm of immunology. These naturally occurring chemicals possess the ability to operate as ligands, thereby attaching to immune cells and exerting an influence on their activation and functionality. The effects of these substances on B cells, T cells, neutrophils, macrophages, and other immune cell populations have been shown in earlier research. The production of cytokines and chemokines as a result of this stimulation is essential for producing an effective adaptive immune response (Sarangi *et al*., 2022). In a study by Thakur *et al*. (2021), it was shown that rhamnolipids could act as immunomodulators, controlling humoral and cellular immune responses to promote the release of pro-inflammatory cytokines. Moreover, biosurfactants have the ability to balance pro- and anti-inflammatory molecules and regulate immunological disorders at the regulatory level.

As antiadhesive/antibiofilm agent

Medical devices that are implanted within the body provide an advantageous surface for the attachment and proliferation of bacteria in the form of biofilms. These biofilms are recognized as a significant contributor to the occurrence of healthcare-associated illnesses (Caldara *et al*., 2022). Microbial cells then show surface adherence after a conditioning film composed of proteins, organic compounds, and ions is deposited. This adhesion leads to the formation of micro-colonies, which subsequently expand into intricate communities that are embedded inside an exopolysaccharide matrix. According to Singh *et al*. (2017), microbial cells in their sessile forms undergo physiological changes that render them resistant to host defense mechanisms and significantly less susceptible to a range of antimicrobial drugs, with a reduction in susceptibility of up to 1000-fold.

In order to reduce the formation of biofilm on medical equipment, biosurfactants may prove to be useful coating agents. Thin, uniform films can be generated using these substances on diverse surfaces, offering several advantages including improved wetting, decreased surface tension, and hindrance of microbial adhesion (Tambone *et al*., 2021; Ali *et al*., 2022), as well as a pronounced disruption of cellular organization and extensive damage to cell walls (Kannan *et al*., 2021). The utilization of several biosurfactants namely sophorolipids, rhamnolipids and lipopeptides, has been observed as a means to mitigate the adhesion of *Candida albicans* and Staphylococcus spp. culture on silicone surfaces. The research of Ceresa et al. (2021) provided an example of its application.

In wound healing

The term "wound healing" refers to a basic biological process that involves four separate phases that occur sequentially: hemostasis, inflammation, proliferation, and remodeling (Guo & Dipietro, 2010). Antimicrobial properties of sophorolipids have been widely discussed in literature (Diaz *et al*., 2016). These properties have been found to contribute to the notable wound healing activity of sophorolipids in comparison to commercially available creams (Hentati *et al*., 2021). This discovery aligns with the results of Afsharipour *et al*.'s (2021) investigation into the impact of lipopeptides (LPBs) on angiogenesis, wherein they observed that LPBs increase tube formation and facilitate endothelial cell migration, signifying a significant progression in the angiogenesis process.

As an anticancer agent

Even with significant progress made in the field of cancer treatment, cancer remains the second leading cause of death worldwide. In 2020, the World Health Organization (WHO) provided data indicating an expected 10 million fatalities, accompanied by a surge in new cases reaching 19.3 million (Sung *et al*., 2021). Because of their remarkable characteristics, including selectivity, biodegradability, and low toxicity, microorganisms - more especially, bacteria - have attracted a lot of attention as a potential source of novel anti-cancer medications (Dan *et al*., 2021). Furthermore, in recent times, biosurfactants have surfaced as a promising therapy option for a variety of cancer types, including liver, pancreatic, breast, oral, lung, and cervical cancers (Meena and Kanwar, 2015; Dan *et al*., 2021). The study conducted by Gudiña *et al*. (2013) has presented evidence indicating the potential therapeutic capacities of these substances in the treatment of cancer. In particular, they have demonstrated the capacity to regulate particular biological processes in mammalian cells, so preventing the abnormal progression of cancer.

As a result, cell viability, proliferation, and migration are suppressed. Adu *et al.* (2020) discovered that some

biosurfactants, specifically glycolipids and lipopeptides, possess the ability to hinder the growth and survival of cancer cells. A recent study by Haque *et al*. (2021) looked at the fundamental mechanism by which glucolipids, bolalipids, acidic and lactonic sophorolipids, and glucolipids affect cancer cells. Glucolipids have the ability to prevent tumor cell migration by upsetting actin filaments, according to research done on three distinct cell lines: the mouse skin melanoma cell line (B16F10), the lung cancer cell line (A549), and the breast cancer cell line (MDA-MB 231). Furthermore, it has been shown that glucolipids and lactonic sophorolipids both promote the production of reactive oxygen species inside of cells. Additionally, it was discovered that the biosurfactants reported in a study by Haque *et al*. (2021) caused alterations in the potential of the mitochondrial membrane, which finally resulted in necrosis, the process that kills cells.

Anti-inflammatory potentials of biosurfactants

Involved in the secretion of arachidonic acid (AA) is phospholipase A2 (PLA2). The term "cytosolic phospholipase-A2 (cPLA2)" encompasses a range of different forms of PLA2. The inflammatory response is initiated as a result of the release of arachidonic acid (AA), which undergoes conversion into various inflammatory mediators. An essential function of arachidonic acid (AA), a precursor to eicosanoids, is to regulate and sustain the inflammatory process. The ability of biosurfactants (BSs) to detect their structural characteristics is attributed to toll-like receptors (TLR-2). These BSs establish communication with cell membranes and macromolecules, leading to the inhibition of cPLA2, which in turn triggers anti-inflammatory responses (Mohana *et al*., 2020).

The pro-inflammatory cytokines were seen to decrease while anti-inflammatory cytokines levels increased in fish and rat models following administration of surfactin (Giri *et al*., 2016). Zhang *et al.* (2015) reported that *Bacillus subtilis*-derived surfactin might block signaling pathways that are triggered by lipopolysaccharides. Furthermore, it was revealed that Surfactin inhibited macrophage function and reduced the expression of IL-12. Furthermore, a decrease in TLR-4 protein expression was seen in conjunction with an increase in the anti-inflammatory effect. Pro-inflammatory cytokines were significantly reduced when *Staphylococcus aureus*-derived surfactin was applied. It also inhibited the lipoteichoic acid-induced signaling pathway, which raised STAT-3 phosphorylation and decreased heme oxygenase-1 (HO-1) synthesis. Surfactin's effectiveness as an anti-inflammatory and neuroprotective medication has been shown in earlier research (Park *et al.*, 2013; Mohana *et al*., 2020).

Restricted number of other researches were undertaken, which yielded findings about the possible impact of beta-glucans derived from yeast species possessing anti-inflammatory properties. Vakil *et al*. (2010) report that the administration of Sophorolipids (SLs) derived from *Candida bombicola* led to a decrease in the level of immunoglobulin E (IgE) and a reduction in the mRNA expression of interleukin-6 (IL-6), TLR-2, and signal transducer and activator of transcription 3 (STAT3). It was also discovered that using SLs reduced pulmonary inflammation. As a result, the research results show that SLs can act as anti-inflammatory agents and a potentially useful therapeutic chemical by reducing the expression of IgE coding genes (Bluth *et al*., 2006a).

According to Hardin *et al*. (2007), the administration of SLs in a rat model experiment resulted in a decrease in mortality associated with sepsis. Additionally, it was observed that SLs exhibited anticipated anti-inflammatory properties. In a separate investigation utilizing a rat model, the administration of SLs was found to have a positive impact on the survival rate, as well as a reduction in the levels of nitric oxide and modulation of inflammatory responses (Bluth *et al*., 2006b). Mohana *et al*. (2020) found that both natural and synthetic SLs exhibit significant spermicidal, anti-inflammatory, and anti-HIV properties. Suppression of inflammatory cytokine expression by SLs suggests that SLs hold potential as a therapeutic approach for managing chronic inflammatory disorders through their anti-inflammatory and immunomodulatory effects.

Pseudomonas antarctica has been shown to release mannosyl erythritol lipids, which have demonstrated inhibitory effects on inflammatory mediators, thereby exhibiting anti-inflammatory properties (Mohana *et al*., 2020). Hence, it can be inferred that biosurfactants derived from bacterial and yeast species have anti-inflammatory properties making them qualified as alternative therapeutic interventions in the management of inflammatory disorders.

Biosurfactant uses in drug delivery systems

Drug delivery systems are particularly important in the pharmaceutical and medical sciences industries. They serve as tools that enable the precise delivery and release of active components via various pathways to various bodily parts in accordance with the disease's features and the required treatment impact. Drug distribution is more effective and safe when this capability is used (Mnif & Ghribi, 2015).

The ability to load medications optimally without any drug loss, improved water solubility and bioavailability, and regulated transport of the active ingredient across membranes to the appropriate area are only a few benefits of using biosurfactants in drug delivery systems. These advantages contribute to maximizing the efficacy of the system (Ceresa *et al*., 2023). Nanoparticles, microemulsions, nanoemulsions and liposomes are representatives of different categories of drug delivery systems. Nanoparticles are defined as particulates that exhibit dispersion with size range from 10 to 1000 nm. Nanospheres or nanocapsules might be utilized for their preparation. Nanoparticles have been employed in diverse therapeutic approaches, such as drug administration, owing to their distinctive physical characteristics. These particles possess the potential for controlled release and can safeguard drugs or other biologically active molecules from their surrounding environments. Consequently, this enhances the bioavailability and therapeutic effectiveness of these substances (Zieli'nska *et al*., 2020).

Microemulsions and nanoemulsions are colloidal systems consisting of combination of water, oil, and surfactants. According to McClements (2012), these particles exhibit diminutive droplet sizes, hence facilitating the improvement of medication solubility and stability. Liposomes are bi-layered vesicles that are created through the hydration process of a combination of cholesterol and phospholipids. According to Sriwidodo *et al.* (2022), one way in which drugs can enhance their effectiveness is by impeding their clearance from the circulatory system and shielding them from the potentially adverse effects of their biological surroundings. The utilization of biosurfactants in medication delivery is facilitated by their distinctive surface-active characteristics and associated advantages. According to Ma *et al*. (2022), sophorolipids have been employed as ecologically sustainable delivery agents with scalable and cost-effective nanopesticide systems useful in agronomic applications.

Nanoparticles

In recent times, biosurfactants have garnered considerable

interest as feasible alternatives for the synthesis and manufacturing of eco-friendly bioactive nanoparticles that could potentially supplant synthetic surfactants. Several recent studies have documented biosurfactants as a useful alternative to traditional surfactants in nanoparticle synthesis. According to these research (Hazra *et al*., 2013; Sarma & Prasad, 2021; Sharma *et al*., 2023), biosurfactants have a great deal of potential in a variety of biomedical applications, including drug delivery systems, antibacterial capabilities, controlled release mechanisms, and anticancer effects.

i. Nanoparticles with Antibacterial Activity

In the domains of biomedical research and nanotechnology, the use of biosurfactants in the production of antimicrobial nanoparticles is a promising project. Nanoparticles from biosurfactants have exhibited significant promise in addressing bacterial infection due to their ability to effectively eliminate bacterial organisms through various pathways (Ceresa *et al*., 2023). Biosurfactants possess the ability to function as reducing agents, stabilizers and templates throughout the process of nanoparticle synthesis. Consequently, they facilitate the attainment of meticulous regulation over the surface characteristics, size and shape of the nanoparticles. In contrast, the incorporation of metal nanoparticles into biosurfactants leads to an additional augmentation of their antibacterial efficacy, hence promoting their diffusion across biological systems and mitigating undesirable interactions with non-specific entities (Ceresa *et al*., 2023).

ii. Nanoparticles for Drug Delivery

With a focus on transdermal administration and cancer therapy, numerous researches have been done on the use of lipopeptides or rhamnolipids in stabilizing nanoparticles in drug delivery systems (Ceresa *et al*., 2023).

Microemulsions and Nanoemulsions

Micro- and nanoemulsions are widely used dispersion systems that are essential to enabling accurate and effective medicine delivery via a variety of administration routes. It is noteworthy that the distinctions between micro- and nano-emulsions are not only dictated by their size despite many implications of their respective names, as both types of systems can encompass droplets in diameters less than 100 nm. Major differentiation among them is found in the approach employed to attain the size of droplets: nano-emulsions need a mechanical reduction procedure, while micro-emulsions manifest spontaneously (Ascenso *et al*., 2021).

Liposomes

There has been an increasing trend in the use of biosurfactants in the production of liposomes used for medication delivery. This is done as a substitute for PEG-lipids, which have the potential to induce hypersensitive reactions (Chen & Zhang, 2022). Glycolipids such as rhamnolipids have been utilized to construct liposomes, as evidenced by the utilization of rhamnolipid-modified curcumin-loaded liposomes (Cheng *et al*. 2019). Biosurfactants inclusion in liposome compositions has various benefits. To begin with, it has been observed that the utilization of biosurfactants can effectively augment the stability and integrity of liposomes. Additionally, these compounds have the potential to optimize the effectiveness of drug delivery, prolong the shelf life of liposomes, and prevent undesirable aggregation (Cheng *et al*., 2019; Chen & Zhang, 2022). Furthermore, it has been demonstrated that the inclusion of biosurfactants increases the biocompatibility and biodegradability of liposomes, potentially reducing any negative toxicological effects (Cheng *et al*., 2019; Ceresa *et al*., 2021).

Biosurfactant as an antioxidant

Many biosurfactants demonstrate biological properties such as antioxidant, immunomodulatory, and anticancer properties (Kamalakannan *et al*., 2020; Ceresa *et al*., 2021). It has been established that a number of biosurfactants have antioxidant qualities, and these properties have been used in the pharmaceutical formulation process. *Pseudozyma antarctica* and *Ustilago maydis* produce a class of glycolipids known as mannosyl erythritol lipids (MELs), which have biochemical and interfacial characteristics (Bakur *et al*., 2019; Giri *et al*., 2019; Ceresa *et al*., 2020). The best antioxidant activity and capacity to scavenge free radical ions is exhibited by MEL-C (Coelho *et al.*, 2020). It is used in the skincare and cosmetics industry. RW1 is another biosurfactant that *Bacillus subtilis* produces and with a strong antioxidative activities (Yalcin & Cavusoglu, 2010; Abbot *et al*., 2022). *Micromonosproa* sp. produced diazepinomicin (ECO-4601) and NP7, a biosurfactant of marine origin made by *Streptomyces* sp. exhibit anti-oxidant properties (Koppula *et al*., 2012; Karthikeyan *et al*., 2022).

CONCLUSION

In conclusion, this review outlines the synthesis of biosurfactants, their uses, and the special physicochemical characteristics that render them appropriate for use in the commercial manufacture of therapeutic agents. The many therapeutic applications of biosurfactants were covered. Biosurfactants wide range of potential applications such as being used as drug candidates in anticancer, antiproliferative, antimicrobial in wound healing, dermatological, oral cavity care, and in drug delivery systems, were discussed.

The development and commercial application of biosurfactants face several challenges, such as high production costs linked to costly raw materials, optimization challenges, low yields, and inefficient purification processes stemming from lengthy and complex separation and purification steps. This challenge can be overcome by making some advancements in yield and purification techniques of biosurfactants production. Subsequent researches will focus on replacing chemical and synthetic surfactants with microbial surfactants.

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