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Bioequivalence & Bioavailability International Journal
ISSN: 2578-4803

The Potential of Biosurfactants in the Pharmaceutical Industry: A Review

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Review Article
Volume 6 Issue 2
Received Date: October 10, 2022
Published Date: November 11, 2022
DOI: 10.23880/beba-16000176

Abstract

Surface-active substances known as "bio-based surfactants" come from a variety of sources, including plants, animals, microorganisms, marine life, synthetics, and semi-synthetics. Bio-based surfactants have a variety of uses, including in food, personal care, pharmaceutical, and industrial formulations as well as in agricultural and oil field chemicals and institutional and industrial cleaning. Nowadays, there is a significant demand for bio-based surfactants on the market as a result of the strict environmental rules that governments across the globe have placed on the use of toxins in detergents and growing environmental concerns among consumers. Due to their low toxicity and biodegradability, bio-based surfactants are acknowledged as a more environmentally friendly alternative to traditional petrochemical-based surfactants. Additional research going on for the creation of innovative biodegradable surfactants as a result, either by biological processes or from renewable resources (bio-catalysis or fermentation are included). Many such varieties, their properties, clinical assessment of surfactant formulations, use of bio-based surfactants, industrial state-of-the-art, and prospective markets for bio-based surfactants manufacturing are discussed in this paper.

Keywords: Synthetic; Semi-Synthetic Surfactants; Animal Surfactants; Microbial Surfactants; Marine surfactants; Plant-Based Surfactants

Introduction

The struggle against climate change, environmental degradation, ecological collapse, and in conjunction with all of these, the deterioration of human health, epidemics, and pandemics like the most recent COVID-19, pose the greatest risks to modern science [1]. Scientists from all across the world are tasked with the master goal of developing treatments for the long-term enhancement of both human and environmental health [2]. To prevent further environmental degradation, scientists are working to develop sustainable green methodologies [3]. However, when it comes to pharmaceutical sciences, the challenge goes beyond simply identifying diseases and formulating medications to characterizing the drug's bio-activity, delivery, and potential long-term effects on human health [4]. Therefore, inclusive methods are needed that could be crucial for the environment's sustainable development, eliminate externalities, and reduce associated climatic hazards to prevent the spread of diseases and pandemics [5]. All life on Earth requires a pure, unpolluted, and peaceful environment to be healthy. In this review, we discuss how a top class of environmentally friendly chemicals known as a "surfactant" is used in biochemical and medical research [6]. Surfactants may have a favorable effect on the environment and promote environmental sustainability. With examples like medication transport, vaccine development, cancer treatment, therapeutic and pharmaceutical sciences, and the prevention of pulmonary failure owing to COVID-19, we have specifically examined the role of this super-chemical in numerous fields [7]. Materials both organic and inorganic are solubilized by surfactants because they are amphoteric. Surfactants form micelles and reverse micelles once they reach their CMC (Critical Micellar Concentration), which function as nano-sized supramolecules in the solubilization and emulsification of medicines [8]. Surfactants' amazing property makes them especially helpful in the biomedical and biochemical industries for enhancing drug synthesis, purification, and delivery [9]. The use of various surfactant types to boost the solubility of the medicine is one of the tactics employed in recent years to address low solubility issue. Surfactants can act as wetting agents, which lower surface tension and make it easier for liquids to spread. Surfactants can additionally be utilized as emulsifiers and solubilizers. Surfactants are organic substances with hydrophobic tails and hydrophilic heads that are generated from petroleum, sugars, natural fats, and other sources (amphipathic) [10]. As a result, the polar (often water) and non-polar (typically oil) solvent affinities of these two components of a surfactant molecule differ. Synthetic surfactants fall into one of four kinds based on the charge of the head groups. Synthetic surfactants include cationic, anionic, zwitterionic, and neutral surfactants [11].

There are numerous additional sources of surfactants, including animals, plants, bacteria, and the marine. Beractant, calfactant, poractant alfa, and Bovactant are a few examples of animal surfactants; derived from the lungs of various animal larvae [12]. Different kinds of proteins, polysaccharides, gums, and saponins are examples of plant surfactants. Lipopeptide, glycolipid, and polymeric biosurfactants are marine surfactants. Arthrofactin, bamylomycin, emulsan, flavolipid, iturin, rhamnolipid, surfactin, sophorolipids, and viscosin are examples of microbial surfactants [13]. A presentation of several surfactant types is shown in Figure 1. A lack or malfunction of pulmonary surfactant, which makes up the lung's lining components, causes respiratory distress syndrome (RDS). Animal-derived surfactant extracts can be obtained from either animal or human sources. Receiving treatment with animal-derived surfactant extract reduces the risk of lung injury (pulmonary interstitial emphysema) [14], lung rupture (pneumothorax), death, and chronic lung injury (bronchopulmonary dysplasia) or death in infants with established respiratory distress syndrome. From a variety of herbal resources, including leaves, stems, rhizomes, corms, roots, pods, flowers, fruits, seeds, exudates, etc., herbal bio-polysaccharides (also known as plant surfactants) are extracted. Herbal bio-polysaccharides have undergone extensive research over the recent decades and have been utilized as emulsifiers, gel formers, binders, stabilizers, thickeners [15], suspending agents, disintegrants, matrix formers, release retardants, mucoadhesive agents, film formers, coating materials, etc. in several drug delivery dosage forms, including suspensions, emulsions, tablets, capsules, gels, hydrogels. Bio-surfactants with marine origins provide several benefits, including high biodegradability, higher temperature and pH tolerance, low toxicity, high biocompatibility, strong foaming capacity, and improved emulsifying capabilities [16]. They can interact both specifically and non-specifically with biological molecules like proteins and lipid membranes, which enable them to be used for a variety of pharmacological activities such as antioxidant, anti-microbial, anti-cancer, anti-aging, and anti-inflammatory ones in addition to reducing interfacial tension. They can be used as multi-functional components in cosmetic and pharmaceutical formulations because of their numerous activities, which will lower the cost of the finished product [17]. These substances are well known for their variety of uses in the home, on one's person, in food, in medicine, and even at the industrial level. They can emulsify oily substances, making them both competent for oil exploration through the microbial enhanced oil recovery (MEOR) technique and particularly helpful as a cleaning agent for residential or industrial purposes [18]. Additionally, they have significant applicability as a potential weapon to combat petroleum-based contamination of oil and water. They can also be employed as a medicine delivery mechanism, an emulsifier in the baking industry, and an anti-adhesive agent. They are produced by a variety of microbes, including *Pseudomonas spp., Bacillus spp., Acinetobacter spp., Candida spp., Sphingomonas spp., Cryptococcus spp., Pseudozyma spp., Kurtzmanomyces spp., Rhodococcus spp.,* and *Arthrobacter spp* [19]. These surfactants' exceptional distinguishing qualities and applications might be beneficial for a wide range of bio-medical fields, such as dermatology, drug delivery, anticancer treatment, surfactant therapy, vaccine formulation, personal hygiene care goods, and many others [20]. They serve as stabilizers and are mostly utilized as an active ingredient in emulsions. Surfactants' ability to self-assemble is a very effective feature for medication delivery systems. Surfactants are inescapably going to have an impact on the solubility of the products in this regard as the majority of pharmaceutical medicines exhibit poor water solubility [21]. Surfactants are employed in medicinal beverages to solubilize vitamin E, vitamin D, other medicinal substances, and other essential oil components [22]. Surfactants are helpful in the formulation of creams, lubricants, gels, and ointments [23]. They also help drugs penetrate the body more deeply. Surfactants are additionally utilized to stabilize semisolid compositions. Many researchers have documented the antibacterial, anti-adhesive, antibiofilm, anti-inflammatory, and antioxidant properties of surfactants about their potential use in medicine over the years [24]. The source of surfactants and how they are used in the formulation are outlined in this work.

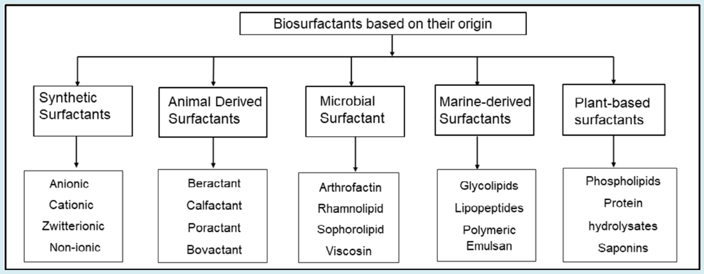

Figure 1: Schematic representation of the classification of Bio-surfactants.

Synthetic and Semi-Synthetic Surfactants

Anionic Surfactants

Negatively charged anionic surfactants include R-COO, RSO_4, and RSO_3. Due to their high hydrophilicity, anionic surfactants are employed as detergents and foaming agents in products like shampoos. Sodium dodecyl sulfate ($C_{12}H_{25}SO_4Na^+$), alkyl poly oxyethylene sulfate (R-$[CH_2CH_2O]$ nSO_4), and alkylbenzene sulfonate (R-C_6H_5-SO_3) are a few examples of anionic surfactants. SLS is used in medicated shampoos and as a preoperative skin cleanser [25]. Docusate sodium (dioctyl sodium sulfosuccinate) and docusate calcium (dioctyl calcium sulfosuccinate) act like detergents with HLB-10 and are used to soften the stool when it is desirable to lessen the discomfort or the strain of defecation [26]. On increasing concentration adverse effects like diarrhea and mild abdominal cramps.

Cationic Surfactants

Cationic surfactants have positively charged functional groups such as primary (RNH_2), secondary (R_2NH), or tertiary. Alkylamine quaternary derivatives, such as alkyl trimethyl ammonium salts, dialkyl dimethyl ammonium salts, and alkyl benzyl dimethyl ammonium salts, make up the majority of cationic surfactants [27]. Fabric softeners and hair conditioners both use cationic surfactants. A diluted solution of benzalkonium chloride can be applied to burns and wounds, cleaned polyethylene tubing and catheters, and used to disinfect skin and mucous membranes before surgery. Albuterol nebulizers and eye drops also contain benzalkonium chloride as a preservative [28]. A compound made of cetylpyridinium that whitens teeth also reduces plaque and gingivitis.

Non-Ionic Surfactants

Non-ionic surfactants contain ether $[-(CH_2CH_2O)_nOH]$ / hydroxyl [–OH] hydrophilic groups. Thus, these surfactants are nonelectrolytes; their hydrophilic groups do not ionize. In order to stabilize water-in-oil (w/o) and oil-in-water (o/w) emulsions, non-ionic surfactants are frequently utilized. They are used for oral and parenteral formulations because of their low tissue irritation and toxicity [29]. The most commonly used non-ionic surfactants include Spans and Tweens [30]. A solubilizing ingredient widely used in dietary supplements, creams, ointments, lotions, and a variety of medical preparations (such as vitamin oils, vaccinations, and anticancer treatments), as well as an additive in tablets, is sorbitan fatty acid ester, a nonionic surfactant Table 1.

Type of Surfactant	Functional Group	Examples	References
Anionic Surfactants	Carboxylic Acids	Sodium stearate; Sodium lauryl sarcosinate; Cholic acid; Deoxycholic acid	[31]
	Sulfonic Acids	Sodium dodecyl sulphate, Ammonium dodecyl sulphate, Sodium lauryl ether sulphate	
Cationic-Surfactants	Amine-Based	Octenidine dihydrochloride, Triethylamine hydrochloride	[32]
	Quaternary Ammonium	Cetrimonium bromide, Cetylpyridinium chloride, Dimethyldioctadecylammonium chloride, Adogen Benzethonium chloride	

Zwitterionic surfactants	Carboxylic Acid /Quaternary Ammonium	Cocamidopropyl betaine, Amidosulfobetaine-16, C80 detergent	[33]
	Sulfuric Acid /Quaternary Ammonium	3-[(3-cholamidopropyl) dimethylammonio]-1-propanesulfonate, 3-([3-cholamidopropyl] dimethylammonio)-2-hydroxy-1 propanesulfonate, Lauryl-N	
	Phosphoric Acid	Hexadecyl phosphocholine (miltefosine)	
	Miscellaneous	Lauryl dimethylamine N-oxide	
Non-ionic Surfactants	Alkyl phenyl ethers	Triton, Nonoxynol-9	[34]
	Alkyl ethers of polyethylene glycol	Octaethylene glycol monododecyl ether,	
		Pentaethylene glycol monododecyl ether	
	Alkyl ethers of polypropylene glycol	Polypropylene glycol	
	Alkyl ethers of glycerol	Lauric acid, resulting in glycerol monolaurate	
	Derivatives of ethanolamine	Lauramide monoethylamine,	
		2-dimethylaminoethanol, Polyethoxylated tallow amine	
	Sugar-Based Surfactants	Octyl glucoside, decyl glucoside, lauryl glucoside (glycoside surfactant), Digitonin (polysugar surfactant), Tween 20/ Tween 80	
Semi- synthetic surfactant	Anionic	Methyl Ester Sulfonates (MES), Alcohol Sulphates (AS) and Alcohol Ether Sulphates (AES), Glycinate Amino Acid-Based Surfactants	[35]
	Cationic	Glycine Betaine Esters and Amides	
	Non-Ionic	Sugar Bio-Based Surfactants, Polysorbate 20, Polysorbate 80	
	Amphoteric	Cocoamidopropyl Betaine	

Table 1: Various types of surfactants with their example and functional group.

Amphoteric Surfactants

Anionic and cationic groups can both be seen in the same molecule of amorphous surfactants. The pH of the medium and the pKa of the ionizable groups affect their ionization state in the solution. For instance, the negatively charged (ionized) acidic functional groups, such as carboxylate, sulfate, and sulfonate, with pH > pKa [36], while at pH < pK_a basic functional groups, like amines, become positively charged (ionized). The extent of ionization of functional groups, that is, the proportion of molecules in solution that bears the positive or the negative charge, at a given pH is governed by the Henderson–Hasselbalch equation [37]. Lecithin is an ampholytic surfactant and is used for parenteral emulsions. Dimethylaminopropylamine reacts with fatty acids (lauric acid or its methyl ester) from various sources, such as coconut oil, to generate cocoamidopropyl betaine (CAPB) (semisynthetic surfactant) [38]. CAPB is utilized as a cosurfactant in cosmetics, pharmaceuticals, and detergents. CAPB does not irritate the skin or the mucous membrane of the eye, and when combined with anionic surfactants, it significantly lowers the latter's irritant effect [20].

Animal Derived Surfactants

Four proteins (two hydrophobic proteins and two hydrophilic proteins) have been identified in animal surfactants and labeled as surfactant proteins. Hydrophobic proteins (SP-B and SP-C) play critical roles in adsorption as well as in maintaining lung stability and SP-A and SP-D are extremely hydrophilic proteins or lectin proteins belonging to the collectin family [39]. Hydrophilic proteins are not found in any significant amounts in currently available animal-derived surfactants. The primary distinction between animal-derived and synthetic surfactants lacking surfactant proteins or surfactant protein analogs. SP-A, SP-B, and SP-C are apolipoproteins because they are phospholipid-associated [40]. Genetic disruption of SP-B expression results in a clear neonatal respiratory phenotype in both human infants and mice. Unlike SP-B gene mutations, which cause respiratory distress soon after birth, SP-C deficiency usually manifests as interstitial lung disease at a few months of age. SP-C metabolism disorders are typically inherited as autosomal-dominant genes with variable penetrance. SP-D functions include carbohydrate-domain recognition on pathogen surfaces to innate host defense of the lung. SP-C-deficient adult animals develop pneumonitis and emphysema, whereas SP-C knockout animals do not have any respiratory symptoms at birth, while deficiency of SP-B results in severe respiratory failure [41]. SP-D is required for the biogenesis of surfactant and its' packing into lamellar bodies by helping in the transfer of surface-active phospholipids from the membrane to the air-liquid surface.

There are two main categories of surfactants derived from natural sources: those obtained from saline extracts of minced lungs or alveolar lavages. After that, phospholipids, neutral lipids, and trace amounts of the hydrophobic surfactant-associated proteins SP-B and SP-C were obtained from saline extracts using organic solvents. Except for SP-A and SP-D, the lipid extracts contain the components of natural surfactants [42]. They also contain more neutral lipids and unsaturated phospholipids, which affect the surface characteristics. To enhance surface qualities, synthetic lipids can be introduced, or neutral lipids can be removed using liquid-gel chromatography. Making organic solvent extracts from alveolar lavages is another method for producing surfactants from animal sources. The technique of extracting with an organic solvent removes unnecessary proteins that could trigger immunological sensitization. In therapeutic settings, several commercial surfactants derived from bovine or porcine lungs are used [43]. These include calfactant, beractant, and poractant (Survanta, Curosurf, Infrasurf).

Currently Available Animal Surfactants

There are currently two families of exogenous surfactants, mammalian surfactants (extracted and purified from either lung lavages or lung minces) and synthetic surfactants. Natural Surfactants produced from bovine or porcine lungs or lung lavages are then purified and extracted with organic solvents. Their phospholipid concentrations are greater than 80%, and they all contain the low molecular hydrophobic proteins SP-B and SP-C, but not SP-A [40]. List of different types of formulations based on animal surfactants having antioxidants, anti-inflammatory, and antibacterial available in Table 2.

Animal Surfactants / Formulation	Source	Phospholipid + % Cholesterol	SP-B/ SP-C Composition (µg/µmol)	References
Beractant/ Suspension	Lipid extract of bovine lung and synthetic lipids	25 mg/ml (50% DPPC) +3	0–1.3/1-20	[44]
Calfactant/ Suspension	Lipid extract of bovine (calf) lung lavage	35 mg/ml (74% DPPC) + 5	5.4/8.1	[45]
Poractant alfa/ Suspension	An organic solvent of porcine lung purified by liquid gel chromatography	80 mg/ml (70% DPPC) + 1.6	2–3.7/5-11.6	[44]
Bovactant/ Powder	Bovine	50 mg/ml	2–5.6/1-12	[46]
BLES/ Suspension	Cow lung lavage	27 mg/ml + 4		[47]

Table 2: Differences in currently available animal-derived surfactants (SP-B and SP-C).

Poractant alfa- It is also known as Curosurf, and is made from a washed, centrifuged extract of minced porcine lungs, which is then purified further to remove neutral lipids [48]. When the high (initial) dose of phospholipids is utilized, it has the greatest phospholipid dose (200 mg/kg) and unit concentration (80 mg/mL) among the available animal-derived surfactant preparations. It reduces surface tension at the air-liquid interface of the alveoli in the lungs, thus stabilizing them against collapse under transpulmonary pressures [49]. Beractant - It is also known as Survanta, is a bovine minced lung extract beractant that also contains DPPC, palmitic acid, and tripalmitin to standardize its composition and make it similar to other natural lung surfactants [50]. Beractant has the lowest number of SP-B proteins among available animal-derived surfactants. By reducing surface tension on alveolar surfaces during respiration and stabilizing the alveoli against collapse at resting transpulmonary pressures, beractant replenishes lung surfactant and restores surface activity to the lungs [45]. Calfactant - Also known as Infasurf, is derived from calf broncho-alveolar lavage and reportedly contains more SP-B than either of the minced lung preparations. It decreases surface tension at the air-fluid interface on the alveolar surface [51]. Bovactant - It is made from lavaged bovine lungs and goes by the name Alveofact. It contains polar lipids and around 1% of the special low-molecular-weight hydrophobic proteins SP-B and SP-C [52]. BLES - It is also known as BLES, is derived from bovine lipid extract and contains hydrophobic proteins such as SP-B and SP-C [53]. Several methods for administering surfactants have been described and tested in clinical trials listed in Table 3.

Types	Methods	Device used	Instruments	References
MIST (Minimally invasive surfactant Treatment)	Quick SF	Soft catheter Device name: Neo fact	Laryngoscope & intra-pharyngeal guidance device	[54]
	Laryngeal Mask	A special device placed in the hypopharynx	No Laryngoscope No forceps	
	Hobart	Semi-rigid vascular catheter Device name: for example, Lisa Cath	Laryngoscope No forceps	
LISA (Less Invasive Surfactant Administration)	Sonsure	Flexible nasogastric tube	Laryngoscope& Magill forceps	[54]
	Take Care	Flexible nasogastric tube	Laryngoscope No forceps	
	Cologne	Flexible suction catheter	Laryngoscope & Magill forceps	
Intrapartum	Intra-amniotic Surfactant instillation	The vicinity of the fetus's mouth and nose via an ultrasound-guided needle	No Laryngoscope No forceps	[55]
	Pharyngeal Surfactant	Injection into the pharynx Flexible short tube and syringe	No Laryngoscope No forceps	
Non-invasive	Aerosol Nebulization	Nebuliser with mask/ prologues	No Laryngoscope No forceps	[56]
Invasive	INSURE	Endotracheal tube	Laryngoscope No forceps	[57]

Table 3: Methods for administering surfactants and tested in clinical trials.

Microbial Surfactant

Biosurfactants, also known as microbial surfactants, are structurally varied and heterogeneous groupings of surface-active amphipathic molecules produced by bacteria [58]. They can lower surface and interfacial tension and have a wide range of industrial and environmental uses. When compared to synthetic surfactants, biosurfactants are favored surface-active molecules because of their lower toxicity and safety. Using biosurfactants instead of surfactants in microemulsion formulations improves safety and reduces toxicity and gastrointestinal irritation that are commonly linked with or caused by surfactant use. Biosurfactants are a class of structurally diverse amphipathic compounds that have potential uses in a variety of biological domains, including gene transfer, antibacterial, anticancer, and wound healing [38]. Biosurfactant production is influenced by both the producer strain and the cultural conditions [59]. As a result, several factors like carbon and nitrogen source, environmental factors, pH aeration and agitation, metal ion concentration incubation time, and salt concentration influence, not just the amount of biosurfactant used, but also the type of product created.

Various Types of Microbial Surfactant

List of various types of microbial surfactants with their mechanism of action and uses listed in Table 4. Arthrofactin- It is a potent cyclic lipopeptide (composed of three non-ribosomal peptide synthetases) produced by bacteria *Pseudomonas sp*. MIS38 [60]. It's Nucleotide -binding domains (NBD) are the engines of ABC transporter that translocation by ATP hydrolysis and a set of ATP binding motifs, that multiple ATP-dependent active transporter systems are responsible for the production of arthrofactin [16]. Used as non-therapeutic cosmetic, use as a Moisturizer for skin, mucosa, and dry skin. Effect of arthrofactin in Mild toxicity at a lower concentration. It can act as a Moisturizing agent [38]. Bamylomycin- is a macrolide antibiotic drug that inhibits autophagy at the late stage. It inhibits vacuolar H (+)-ATPase (V-ATPase), which results in the inability of the lysosome to acidify. It has low toxicity, effectiveness at extreme temp., and high biodegradability. Used as Anticancer [61]. Emulsan- Typically, it is amphiphilic and tends to have more or less soluble either in water or in oil [62]. Its High molecular weight biosurfactants form a stable water-in-oil emulsion which aids oil mobility, and viscosity reduction and prevents drop coalescence. Used as Transport of crude by pipelines. It is a potent emulsifier. Flavolipid- It acts as an anionic surfactant. Inhibits metastatic cancer cell migration. Use in bioremediation. Flavolipid is Weakly cytotoxic and relatively biocompatible. Used in antimicrobial activity [63]. Iturin- Nonribosomal cyclic lipopeptide produced by *Bacillus subtilis.* Iturin inhibits β-amino fatty acid of C-14 to C-17 of homologous compounds and isomers for each lipopeptide**.** Used in Fermentation optimization**.** It has Lower toxicity. The advantage of iturin is as Antifungal agent [64]. Rhamnolipid- It is an Anionic surfactant. Act on the target cell by disrupting cell surface structures, thereby liberating the intracellular contents of the plant pathogen. Used as Plant pathogen eliminator. It has slightly toxic [65]. Surfactin**-** It is an anionic cyclic lipopeptide antibiotic produced by the bacteria Bacillus subtilis [66]. Immunomodulating biosurfactants stimulate the immune system by increasing the ratio of lymphocyte transformation and migration of polymorph nuclear cells. Used as Immunological adjuvants. No adverse effect level of 500 mg/kg surfactin. The advantage of surfactin is, it is an Anticancer agent [67]. Sophorolipids- It is a yeast glycolipid anionic biosurfactant used as a biodegradable low-foaming surfactant [68]. Its mechanism is to halt cell replication in favor of cell differentiation and adsorption to a substratum modifies the surface hydrophobicity thereby interfering with microbial adhesion and desorption process. Used as Anti-adhesive agents. Sophorolipids have Potential biosurfactants due to low eco-toxicity. The advantage of sophorolipid is its Anti-cancer activity [69]. Viscosin- It is an anionic microbial surfactant. The bacterium becomes able to adhere to the broccoli heads and cause decay of the wounded as well as unwounded florets of broccoli. Used as the wetting agent. Sophorolipids have some benefits like Anticancer activity, and Antiviral activity [70].

Surfactants	Mechanism	Used as	Toxicity effect	Benefit	References
Arthrofactin (potent cyclic lipopeptide)	Nucleotide-binding domains (NBD) are ABC transporter that translocation by ATP hydrolysis and a set of ATP binding motifs	Moisturizer for skin, mucosa, and dry skin.	Mild toxicity at lower concentration	Moisturizing agent	[71]
Emulsan (amphiphilic)	It form a stable water-in-oil emulsion that aids oil mobility, viscosity,reduction and prevents drop coalescence	Transport of crude by pipelines	Mild toxicity	potent emulsifier	[72]
Flavolipid (anionic)	Inhibit metastatic cancer cell migration	bioremediation	Weakly cytotoxic and biocompatible	Antimicrobial activity	[16]
Halobacillin (Nonionic)		Moistening, dispersing, emulsifiers, and foaming agents	Low toxicity, biodegradability	Anticancer activity	[73]
Iturin (Nonribosomal cyclic lipopeptide)	Inhibit β-amino fatty acid of C-14 to C-17 of homologous compounds	Fermentation optimization	Lower toxicity	Antifungal agent	[74]
Rhamnolipid (Anionic)	act on the target cell by disrupting the cell surface structures	Plant pathogen elimination	Slightly toxic	Antimicrobial activity	[75]
Surfactin (Anionic cyclic lipopeptide)	inhibits fibrin clot formation, cAMP, platelet, and spleen cytosolic phospholipase A2 (PLA2)	Immunological adjuvants	No adverse effect level of 500 mg/kg surfactin.	Anticancer agent	[76]

Sophorolipids *(Anionic*)	1. halt cell replication in favor of cell differentiation. 2. adsorption to a substratum modifies the surface hydrophobicity thereby interfering with microbial adhesion and desorption process	Anti-adhesive agents	low eco-toxicity	Anticancer activity	[77]
Viscosin (Anionic)	bacterium becomes able to adhere to the broccoli heads and cause decay of the wounded as well as unwounded florets of broccoli.	wetting agent	Lower toxicity	Anticancer activity, Anti-viral activity	[78]

Table 4: Various types of microbial surfactants with their mechanism of action and uses.

Marine-Derived Surfactants

Low- and high-molecular-weight biosurfactants are marine surfactants. Glycolipids and lipopeptides are included under low molecular weight whereas polysaccharides and lipoproteins are included under high molecular weight biosurfactants [79]. Low molecular weight biosurfactants are used more frequently than high molecular weight biosurfactants because of their strong surface tension reduction potential.

Lipopeptides

The lipopeptide molecules mainly consist of an acyl tail (Hydrophobic part) and a short linear oligopeptide sequence (Hydrophilic part) connected with an amide bond. The hydrophilic peptide part consists of cationic and anionic residues and sometimes non-proteinaceous amino acids [79]. The most important groups of lipopeptides are surfactins, fengycins, iturins, aneurinifactin, and gramicidins [80]. Lipopeptide surfactant is divided into different groups based on their structure with isoforms containing different D and L amino acids. Surfactin is produced by *Bacillus sp*. Structurally it is a cyclic heptapeptide connected by β-hydroxyl fatty acid (13–15 C-atoms) and a loop of seven amino acids such as L-asparagine (Asn), L-leucine (Leu), glutamic acid (Glu), L-leucine (Leu), L-valine (Val) and two D-leucines connected via lactone linkage [81]. It shows low critical micelle concentration (CMC) and can reduce the surface tension from 72 to 27 mN/m with a concentration of less than 5% by volume. It shows anti-bacterial, anti-viral, anti-fungal, and anti-mycoplasma activities and is utilized as an emulsifier, stabilizer, and surface modifier. Iturin is a lipopeptide obtained from *B. velezensi*. This lipopeptide is made up of seven amino acids, including Tyrosine (Tyr), Asparagine, Serine (Ser), Glutamine (Gln), Proline (Pro), Glutamate (Glx), and Threonine (Thr), with a hydrophobic tail that is between C14 and C17 in length. Compared to surfactins, it has a lower tendency for hemolysis. It had six different types, including iturin A and C, bacillomycin D, F, and L, and mycosubtilin. It shows strong antifungal activity against *Penicillium expansum*, *Botrytis cinerea,* and *Alternaria alternate*. It has strong surface activity and destabilizing effect. Fengycin is obtained from *B. subtilis.* Fengycin is decapeptides joined with β-hydroxyl fatty acid chain (C14-C18) in linear form and cyclization occurs between the phenol side chain of an amino acid at position 3 and the C-terminal of an amino acid at position 10 [82]. Because of its direct interactions with lipid bilayers and sterol molecules, this lipopeptide can alter the structure and permeability of cell membranes. It shows strong antifungal activity against filamentous fungi. Kurstakin is obtained from *B. thuringiensis* [83]. Structurally they are partial heptapeptides with different fatty acids connected through the amino acid. The residues present in the Kurstakin are Thr, Gly (Glycine), Ala (Alanine), Ser, His (Histidine), and Gln. Locillomycin was obtained from *B. subtilis*. They are nonapeptides made up of amino acids such as Thr, Gln, Asp, Gly, Asn, Asp, Gly, Tyr (Tyrosine), and Val (Valine) [84]. Pseudofactin-II is a cyclic octapeptide having a molecular weight of 1038.69 g/mol, containing amino acids Gly Ser Thr Leu, arranged in the following order Gly-Ser-Thr-Leu-Leu-Ser-Leu-Leu in which palmitic acid is linked with the peptide moiety [85]. It promotes health and shows its biotechnological applications by inhibiting microbial growth and showing its anti-adhesive activity against pathogenic microbes. It also terminates the adhesion towards different bacteria like *Escherichia coli, Enterococcus faecalis, E. hirae, S. epidermidis, Proteus mirabilis,* and *Candida albicans*.

Glycolipids

Glycolipids are structurally composed of a fatty acid chain along with a carbohydrate moiety. They are divided into various types based on the nature of the lipid and carbohydrate moiety. Rhamnolipids are obtained from *Pseudomonas sp.* Some experiments showed that rhamnolipids are more efficient than synthetic surfactants like Tween 60, SDS and polyoxymethylene, sorbitan monooleate and SDS and Pluronic F-68 and they are easily biodegrading under aerobic and anaerobic conditions

[86]. Rhamnolipids obtained from *P. aeruginosa* have been shown to have more efficiency than various synthetic surfactants like Tween 60, SDS and polyoxymethylene, sorbitan monooleate and SDS and Pluronic F-68 [87]. They show anti-phytopathogenic activities including antifungal activities. They inhibit the growth of plant pathogens including *Oomycetes, Ascomycota*, and *Mucor spp*. of fungi and are thus utilized in agriculture for plant protection [88]. GRP3-derived rhamnolipids from *Pseudomonas sp.* were utilized as a biocontrol agent against damping-off disease in Chilli and tomato nurseries by the lysis of the plasma membrane of zoospores of *Pythium* and *Phytophthora* fungi. Sophorolipids are produced by yeast strains such as *Candida bombicola*, *Candida magnoliae*, *Candida apicola* and *Candida bogoriensis* when grown on carbohydrates and lipophilic substrates [89]. The minimum inhibitory concentrations were found to be in the range of 2.5 to 10 mg/ml for individual sophorolipid derivatives and 0.009 to 10 mg/ml for sophorolipid combinations [90]. Trehalose lipids are the glycolipids made up of mycolic acid [91] attached with trehalose disaccharide and are generally obtained by Gram-positive bacteria of *Actinomycetales* such as *Mycobacterium, Nocardia,* and *Corynebacterium*. Because it is insoluble at low pH levels therefore it is extracted using the acid precipitation technique [92].

Polymeric Biosurfactants

Emulsan is the extracellular emulsifying agent produced from *Acinetobacter calcoaceticus* RAG-1 and is responsible for the stabilization of the hydrocarbon-in-water emulsions. Some studies have been showing that emulsan can emulsify the hydrocarbons efficiently, even in very low concentrations (<0.001 to 0.01%), and therefore utilized as an emulsion stabilizer in various fields. Alasan polymeric biosurfactant is derived from *Acinetobacter radioresistens* KA-53 [93]. Structurally it is a polymer made up of a combination of high molecular weight polysaccharide and protein components, which on separation leads to loss of emulsifying activity. Pharmaceutically it has been utilized for the stabilization of hydrocarbon-in-water emulsions. Biodispersan is obtained from *Acinetobacter calcoaceticus A2* and utilized in dispersing limestone in water [94]. It consists of mainly four reducing sugars; glucosamine, 6-methylaminohexose, galactosamine uronic acid, and unidentified amino sugar (51.4 kDa). Liposan biosurfactant is derived from *Candida lipolytica*. Mannoprotein is obtained from *Saccharomyces cerevisiae.* Only water immiscible substrates can produce this emulsifying agent and it affects the metabolism of these substrates [95].

Plant-Based Surfactants

Surfactants derived from plants can be found in several sections of the plant, including the roots, stems, seeds, fruit, and leaves. They are amphiphilic substances (hydrophobic and hydrophilic) that include phospholipids, proteins or protein hydrolysates, and saponins. Proteins [96] and polysaccharides are examples of natural emulsifiers/stabilizers that are being employed in the food sector and might be used to stabilize pharmaceutical emulsions. These natural polymers are already used in the pharmaceutical industry for things like capsule formation (gelatin), tablet binder (gum Arabic, chitosan, Hypromellose), suspending agent (gum Arabic, Hypromellose), mucoadhesive formulations (chitosan), extended-release tablet matrix (Hypromellose), and so on [97]. Because of their propensity to adsorb at the oil-water interface and promote emulsion stability, several proteins can operate as emulsifiers. Most polysaccharides act as emulsion stabilizers by producing an extensive network in the continuous phase, which becomes very viscous and can even form a gel. Only a few polysaccharide derivatives have surface characteristics that allow for oil-water interface adsorption. Combining the qualities of proteins and polysaccharides under the right conditions (concentration, protein-to-polysaccharide ratio, pH, ionic strength, and temperature) might be an effective way to promote emulsion stability. List of proteins formulations derived from Plant-based surfactant in Table 5.

Surfactant	Composition	Formulation	Reference
Whey proteins	α-lactalbumin, β-lactoglobulin, Lactoferrin, BSA	protein supplements, nutrition products, weight management products	[98]
Caseins	αs1, αs2, β, κ caseins	Nutritional supplementation, foods, cosmetics	[99]
Pea proteins	vicilin, legumin, albumins (21%, 4–53 kDa), globulins (66%, 150–400 kDa), glutelins (12%)	carriers for encapsulation, controlled release, targeted delivery, protection of essential oils, phenolic compounds, and vitamins	[100]

Xanthan gum	1,4-linked β-D-glucose residues, having a trisaccharide side chain attached to alternate D-glucosyl residues, side chains are β-D-mannose- 1,4 β-D-glucuronic acid1,2- α -D-mannose.	a suspending and stabilizing agent in oral and topical formulations, the production of sustained-release matrix tablets,	[101]
		Synthesis of environment-friendly Bio composite	
Alginates	α-(1-4)-l-guluronic acid, α-(1-4)-d-mannuronic acid	alginate emulsion-based edible films to protect microencapsulated aroma compounds	[102]
Carrageenans	α -d-galactose, β-d-galactose	Oral extended-release tablets, Microcapsules, Microspheres,	[103]
		As a stabilizer of micro/nanoparticles	
Hyaluronic acid	D-glucuronic acid, N-acetyl-D-glucosamine	cosmetic filler, facial contours, Ophthalmic lubricant treatment of pain in patients with osteoarthritis of the knee	[104]
Gum Arabic	Arabinogalactan, Glycoprotein, Arabinogalactan-Protein.	insulin-loaded nanoparticles based on ionic gelation, encapsulate and control the release of endoglucanase,	[105]
Galactomannans	β-(1-4)-d-mannose, α-(1-6)-D-galactose.	Tablet matrix, sustained-release formulations	[106]
HPMC	partly O-methylated and O-(2-hydroxypropylated) cellulose	Matrix tablets, controlled release formulations, Liquisolid tablets, HPMC capsules, Floating Drug delivery systems like micro balloons, floating tablets, and granules.	[107]
Lecithin	Phosphatidylcholine, Phosphatidylethanolamine,	Creams lotions, foundations and cleansing creams, sunscreens, soaps, bath oils, shampoos, and Hair conditioners	[108-109]
	Phosphatidylinositol,		
	Phosphatidic acid		

Table 5: Plant-based surfactant formulations.

Conclusion

Over the past few years, eco-friendly surfactant-based products have been widely distributed by surfactant producers. Several innovative surfactant types based on renewable building blocks have been developed as a result of increased consumer awareness and a commitment to sustainable development. These surfactants are a popular substitute for novel formulations in the industrial and consumer industries due to their enhanced biodegradation properties and low toxicity. However, since pricing must be as competitive as their fossil counterparts, these "drop-in" surfactant molecules, which seek to replace their petrochemical-based equivalents directly, confront a significant barrier. Additionally, only a small number of high-end green products have found success on the market, even though several consumer goods and personal care companies have expressed interest in 100% bio-based surfactants. To determine customer willingness to pay premium pricing for non-commodity items, further analyses and surveys must be conducted. The global demand for both petroleum- and bio-based surfactants will continue to grow, while manufacturers are challenged to strike a balance between cost-effective formulations and efficient performance. This is due to the rise in innovative formulations to satisfy consumer, governmental, and sustainability demands.

Acknowledgments

NA

Declaration of Interest Statement

The authors declare that they have no conflict of interest.

Statement of Human and Animal Rights

This article does not contain any studies with humans and animal subjects performed by any of the authors.

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