cosmetics

MDPI

Review

Microbial Biosurfactants as Key Multifunctional Ingredients for Sustainable Cosmetics

Hamid-Reza Ahmadi-Ashtiani [1,2], Anna Baldisserotto [3], Elena Cesa [3], Stefano Manfredini [3,*], Hossein Sedghi Zadeh [3], Mostafa Ghafori Gorab [4], Maryam Khanahmadi [1,2], Samin Zakizadeh [1,2], Piergiacomo Buso [3] and Silvia Vertuani [3]

1 Department of Basic Sciences, Faculty of Pharmacy, Tehran Medical Sciences, Islamic Azad University, Tehran 194193311, Iran; ahmadi@iaups.ac.ir (H.-R.A.-A.); maryam.khanahmadi.1996@gmail.com (M.K.); samin.zac@gmail.com (S.Z.)

2 Cosmetic, Hygienic and Detergent Sciences and Technology Research Center, Tehran Medical Sciences, Islamic Azad University, Tehran 194193311, Iran

3 Department of Life Sciences and Biotechnology, Faculty of Medicine, Pharmacy and Prevention, Master Course in Cosmetic Sciences, University of Ferrara, Via Luigi Borsari 46, 44121 Ferrara, Italy; anna.baldisserotto@unife.it (A.B.); elena.cesa@unife.it (E.C.); sedghi@virgilio.it (H.S.Z.); bsupgc@unife.it (P.B.); vrs@unife.it (S.V.)

4 Catalysts and Organic Synthesis Research Laboratory, Department of Chemistry, Iran University of Science and Technology, Tehran 16846-13114, Iran; mostafaghafori@yahoo.com

* Correspondence: smanfred@unife.it

Received: 20 May 2020; Accepted: 9 June 2020; Published: 11 June 2020

Abstract: A polar head and an apolar tail chemically characterize surfactants, they show different properties and are categorized by different factors such as head charge and molecular weight. They work by reducing the surface tension between oil and water phases to facilitate the formation of one homogeneous mixture. In this respect, they represent unavoidable ingredients, their main application is in the production of detergents, one of if not the most important categories of cosmetics. Their role is very important, it should be remembered that it was precisely soaps and hygiene that defeated the main infectious diseases at the beginning of the last century. Due to their positive environmental impact, the potential uses of microbial sourced surfactants are actively investigated. These compounds are produced with different mechanisms by microorganisms in the aims to defend themselves from external threats, to improve the mobility in the environment, etc. In the cosmetic field, biosurfactants, restricted in the present work to those described above, can carry high advantages, in comparison to traditional surfactants, especially in the field of sustainable and safer approaches. Besiede this, costs still remain an obsatcle to their diffusion; in this regard, exploration of possible multifunctional actions could help to contain application costs. To highlight their features and possible multifunctional role, on the light of specific biological profiles yet underestimated, we have approached the present review work.

Keywords: surfactant; microbial biosurfactants; sustainable; multifunctional; cosmetic; hygenizing agents

1. Introduction

Surface-active compounds stand among the most commonly used chemicals in daily life. Production of a broad range of synthetic surfactants from petroleum resources increased considerably since the beginning of 20th century. With the increasing concerns toward sustainabile processes for both human and planet health, "biobased surfactants" have been actratting considerable interest. However, although natural surfactants derived from plant or animal sources by separation procedure, such as

extraction or precipitation, like soap (fatty acid salts), lecithin (phospholipids) or saponins (glycosides), are already used in households and industry [1], they are largely surpassed by the synthetic traditional ones. Thus, "biosurfactants", intended in the present work surface-active compounds with microbial origin, have been studied and considered as possible alternatives to traditional surfactants. In our opinion, there is poor clarity between the "commonly" termed biosurfactant, which would be more correct to define "botanical surfactants", and the "microbial" biosurfactants. The latter is natural too, but with the peculiarity of being obtained by microbial source. For example, saponin, which is commonly defined as a biosurfactant, is not obtained through microorganisms but by extraction from plants, so we believe confusing to name it as biosurfactant. For example, "Saponins" is the registered International Nomenclature of Cosmetic Ingredients (INCI0) name for commercially available cosmetic ingredients that comprise a class of water soluble high molecular weight glycosidal substances naturally occurring in a wide variety of plants and in some animals, obtained by extraction.

Surfactants are amphipathic molecules that can be divided into six categories: cleaning agents, emulsifying agents, foam boosters, solubilizing, wetting agents, and suspending agents, that make surfactants essential to many food, agricultural, and industrial processes [2]. These compounds are composed of a hydrophilic and a hydrophobic part that partition preferentially at the interface between fluid phases of different polarity and hydrogen bonding capacity, such as air/water or oil/water interfaces. As a result, surfactants reduce the surface tension as well as interfacial tension between distinct phases at surfaces or interfaces.

Adverse effects like skin irritation, interference with skin microbioma and enzyme activity alterations by chemical surfactants, prompted the research for effective but lower risk and environmental friendly alternatives. Biosurfactants have been classified in two general categories according to their molecular mass: low molecular weight surface active agents and high molecular weight surface active agents.

Glycolipids, fatty acids, phospholipids, neutral lipids, lipopeptides, and lipoproteins are the most important low molecular weight biosurfactants. Polymeric biosurfactants and particulate biosurfactants are considered high molecular weight biosurfactants [3].

Microorganisms produce biosurfactants to improve cell mobility, provide access to nutrients, or facilitate growth in the environment. They can be anionic or neutral according to their polar group [4]. The production of surfactants by some strains of bacteria and yeasts is of fundamental importance for the microorganism to have access to otherwise unusable nutrients. For example, if the nutrients are organic compounds in insoluble form, like hydrocarbons, the production of a surfactant allows the perfusion of the nutrient inside the cell otherwise not possible [5]. Rhamnolipids are examples of this type of biosurfactant that are produced by various *Pseudomonas* spp. [6,7]. Some other microorganisms like *Arthrobacter* spp., *Mycobacterium* spp., and *Rhodococcus erythropolis* through producing lipopolysaccharides surfactants or nonionic trehalose corynomycolates in their cell wall reorganize their cell wall structure. [8–10].

Some studies have highlighted the importance of several parameters concerning the use of biosurfactants in the cosmetic field, such as the hydrophilic–lipophilic balance (HLB), critical micelle concentration (CMC), and the ionic performance, showing that they are essential for proper use [11,12]. The CMC provides a measurement of biosurfactant efficiency [13]. Generally, biosurfactants have lower CMC compared with chemical surfactants, i.e., less surfactant is used for the maximal decrease on surface tension, so they are more effective and efficient [14].

HLB value is another crucial parameter for the correct use of biosurfactants in cosmetic products, as it provides a prediction of the emulsifying ability [15]. Depending on the HLB values, a biosurfactant can act as an emulsifier, wetting agent, or antifoaming agent, representing the most important functions [13]. Hydrophilic biosurfactants possess high HLB values unlike lipophilic biosurfactants that have low values. An emulsion is a heterogeneous system consisting in one immiscible liquid dispersed in another in form of droplets, which diameter normally exceeds 0.1 mm. Emulsions are typically water-in-oil (W/O) or oil-in-water (O/W) emulsions [5]. Biosurfactants with great solubility in

oil would be better stabilizers of W/O emulsions while biosurfactants with higher solubility in water will be better stabilizers of O/W emulsions. For dermatological applications, W/O emulsions need surfactants with HLB values between 1 and 4, as the lipid film on the skin favors oil-soluble active compounds [14,15]. These cosmetic formulations have a protective action and an occlusive property. However, O/W emulsions, including surfactants with HLB values between 8 and 16, cause a less greasy feeling, so they are more appreciated by the consumer [13].

Surfactants and biosurfactants are chemically categorized into anionic, cationic, nonionic, or amphoteric, according to their ability to dissociate in water and the resulting polar head charge in aqueous solution. The ionic behavior is also a crucial factor if an application in cosmetic formulations is considered [16,17].

The anionic surfactants have the greatest foaming, emulsifying, wetting properties if compared with the other types of surfactants or biosurfactants. However, studies indicated that anionic surfactants are more irritating to both eyes and skin than nonionic surfactants and the latter are more irritating than amphoteric surfactants. On the othen hand, cationic surfactants have proved notable anti-bacterial properties, as well as good emulsifier capacities [13]. As, in many cases, industrial processes involve the exposure to contaminants, pH, and temperature variations, it is necessary to focus on novel microbial products/biosurfactants effective under these conditions [18]. Degradation of microbial derived surfactants are always easier in comparison to synthetic surfactants [19]. Almost in all cases biosurfactants are considered low or nontoxic products and result appropriate for food, pharmaceutical and cosmetic uses despite the existence of a small number of studies attesting to the toxicity of some of these products [5].

Chemically synthesized surfactants are, in most of the cases, non-biodegradable and able to remain in the natural environment for long periods resulting toxic in the long term. Thus, bioaccumulation and byproducts of these compounds can be dangerous to the environment. This class of compounds results not sustainable considering also manufacturing processes involving petroleum raw materiels. Lytic activity on human erythrocyte, heart toxicity, kidney toxicity, lung toxicity and also, blood coagulation disorders of chemically synthesized surfactants have been reported in scientific studies [20]. As concerns the cosmetic field, several studies indicate that synthetic surfactants are more aggressive towards the skin than biosurfactants and are capable of causing irritation and allergic reactions [13,20]. The reduction of the skin barrier function attributed to synthetic surfactants occurs after penetration or permeation of these compounds into the skin. In fact, they can compromise intercellular lipid structures in the epidermal surface, facilitating the penetration of various substances into the intercellular structures and increasing transepidermal water loss (TEWL) [13]. This activity is attributed to sodium lauryl sulphate and sodium laurate, both widely used anionic synthetic surfactants [21].

Compared to their chemically synthesized counterparts, microbial surfactants can overcome these issues, with low skin toxicity; excellent surface properties; and wide range adaptability of pH, temperature, and salinity. Biosurfactants have unique properties such as mild production conditions, multi-functionality, versatile interfacial properties and self-assembly into a variety of structures, high environmental compatibility, and biodegradablility. In other words, biosurfactants are sustainable and eco-friendly, while petroleum-derived surfactants are not, but both belong to the same regulation (Regulation No 1223/2009) in order to be used as cosmetic ingredients [13].

These are some of the reasons why scientists, both from environmental and health fields, call for regulations concerning the increased need of using microbially sourced surfactants as possible replacement to chemically synthesized ones [22]. The major limit to the expansion of the use of biosurfactants is still the paucity of production methods from inexpensive renewable resources. Various examples, in comparison with synthetic traditional surfactants, in terms of safety, efficacy and sustainability, will be discussed in the present work.

2. Materials and Methods

We collected and anaylzed data obtained from scientific and patent literature described in the present work. The present review was performed adopting the following databases; Pubmed, SciFinder, and Google Scholar. An extensive bibliographic research has been conducted using, in the first part of the research, the following key words, "biosurfactant", "surfactant", "cosmetics", and "microorganism". One-hundred-and-seventy-five articles were found, and 144 of them were approved for the writing phase; 31 articles were rejected because they are not relevant. The selected material focuses on the evaluation of structures, properties and effects of biosurfactants useful in the cosmetic and medicinal fields. Articles and patents in the English language have been selected. Particular attention has been paid to works that may open new research paths on innovative compounds. After the identification of works related to biosurfactants, a second phase of bibliographic research was carried out focusing on the individual classes of compounds in order to increase the amount of available material. The following keywords were selected, "Rhamnolipids", "Trehalose lipids", "Sophorlipids", "Mannosylerythritol lipids", "Cellobiolipids", "Surfactin", "Iturin", "Fengycin", "Lichenysin", "Gramicidin", "Polymyxins", "Megovalicin", "Corynomycolic acids", "Spiculisporic acid", "Phosphatidylethanolamines", "Emulsan", "Liposan", "Alasan", "Biodispersan", "Polysaccharide protein complex", and "Mannoproteins". One-hundred-and-three not previously cited works have been found in the second part of the bibliographic research. The process of bibliographic research has been conducted between June 2019 and March 2020 comprehending works from 1947 to 2020.

3. Results

3.1. Biosurfactants with Low Molecular Weight

3.1.1. Glycolipids

Glycolipids are composed of a hydrophobic lipid tail in combination with a carbohydrate moiety covalently linked or linked by a glycosidic bond [22,23]. Depending on the type of carbohydrate moiety, glycolipids can be subdivided into rhamnose lipids, trehalose lipids, sophorose lipids, cellobiose lipids, mannosylerythritol lipids, lipomannosyl-mannitols, lipomannans and lipoarabinomannanes, diglycosyl diglycerides, monoacylglycerol, and galactosyl-diglyceride [1].

Generally, glycolipid biosurfactants are recognized for their stability under harsh conditions of pH, salinity, and temperature [23]. Glycolipids derived from *Oleomonas sagaranensis* and *Candida sphaerica* demonstrated stability during temperature and pH variation with respect to surface tension reduction and emulsification activity, with acceptable activity in the case of excessive salt concentrations [24,25]. The activity and stability of a glycolipid bioemulsifier produced by *Streptomyces* spp. SS 20 was effective over a broad range of conditions: pH range 3 to 7, temperature range of 30 to 100 °C, and NaCl concentration up to 3% *w/v* [26].

Kim et al. (2002) showed that a glycolipid biosurfactant produced by *Candida antarctica* SY16 was able to emulsify vegetable oil at low concentrations, and its HLB value is ~8.8 [27]. Among all biosurfactants, glycolipids are the most studied in the cosmetic and personal care field [28]. Microbial glycolipids showed some significant properties depending on the specific case, such as the ability to diminish the surface and interfacial tension, emulsification and de-emulsification capacities, foaming potency, solubilization abilities, and pore-forming capacity [28]. Moreover, these compounds are recognized for their significant physicochemical properties, including stability upon severe conditions of pH, salinity, and temperature [23,26]. Thus, they are useful in the environmental field to enhance hydrocarbon solubility, mobility and biodegradation [21]. They are equally possible candidates for medicinal use because of antimicrobial, hemolytic, antiviral, anticarcinogenic, and immune-modulating activities of some compounds belonging to this class [20]. Moreover, because of the emulsification capacity and antiadhesive activity, they are potential additives in the food

industry [5]. In the field of agriculture, compounds belonging to the glycolipid class evidenced inhibition activity against specific phytopathogenic fungi, insect larvae and algal bloom [1].

Glycolipids are used also in polymer mixtures as functional additives for surface modification. Sophorolipids are able to increase the surface roughness, affect the thermomechanical properties of solvent-cast films of polyhydroxyalkanoate (PHA), reduce the degree of polymer crystallization with a potential use as plasticizer, and provide antimicrobial properties with controlled release from biopolimer films. Moreover, of note is the application of Mannosylerythritol lipids (MELs) in a biobased plastic film from an environmental compatibility viewpoint: the pretreatments with these glycolipids allow to control degradability and surface hydrophilicity of poly(lactic acid) (PLA) films, improving wettability.

In particular by adding directly glycolipid biosurfactants in a PLA plastic matrix, Fukuoka et al. (2018) observed the formation of a localized thin layer of glycolipids at the PLA–substrate interface, due to the self-assembling properties of microbial surfactants and their inclination to bring on a micro-phase separation in a polymer matrix. As a result, it has been noticed an increasing surface wettability located only at the surface of the plastic film [29].

Glycolipid biosurfactants can be produced from inexpensive raw materials that are available in large quantities, such as industrial wastes and oily byproducts including olive oil waste frying oil waste and hydrocarbons. In addition, the production efficiency of glycolipids using microorganisms has been improved, alongside progress in biotechnology as a result of the amelioration of fermentation conditions [30], the application of the solid-state fermentation process [31,32], and the optimization of production by means of response surface methodology [33–35].

Many studies have evaluated the toxicity of biosurfactants belonging to the class of glycolipids. As suggested by Kuyukina et al. (2007) [36], the biosurfactant glycolipid complex synthesized by *Rhodococcus ruber actinobacteria* is nontoxic, and the results of in vivo tests showed that it does not cause stimulation or inhibition of the experimental animal behavioral, it shows no deaths or loss of body weight over a 14-day observation period, and exhibits no significant effect on the proliferative activity of peripheral blood leukocytes [36]. Additionally, according to Gein et al. (2011) study, no cytotoxicity against human lymphocytes has been reported after an exposition to glycolipid biosurfactant from *Rhodococcus ruber* [37]. In another study, acute toxicity tests involving two species of marine larvae, namely, *Mysidopsis bahia* (shrimp) and *Menidia beryllina* (fish), demonstrated the low toxicity and safety of the glycolipidic biosurfactant JE1058BS produced by *Gordonia* spp. [38]. Unlike synthetic surfactants, microbial-derived surface-active compounds are easily degradable compounds in most of the cases due to their natural origin and chemical structure [23].

Munstermann et al. (1992) [39] evidenced the low toxicity of microbial-derived surface-active compounds like Trehalose dicorynomycolate and Trehalose tetraester from *Rhodococcus erythropolis* and Rhamnolipids from *Pseudomonas aeruginosa*, after a comparison with different synthetic surfactants. Additionally, a glycolipidic biosurfactant from *Pseudomonas aeruginosa* was considered non-mutagenic and nontoxic in comparison to the synthetic 'Marlon A-350' widely used in industry [40]. As reported by Das and Mukherjee (2005) [41], *P. aeruginosa* derived biosurfactants do not pose detrimental effect to the heart, lung, liver, and kidney but they can interfere with blood coagulation in the normal clotting time.

Morita et al. (2013) [42] demonstrated that Mannosylerythritol lipids—glycolipid biosurfactants produced by basidiomycetous yeasts such as Pseudozyma—show good properties compatible with the cosmetic use, and they can activate the fibroblast and papilla cells indicating a protective effect on skin cells.

Rhamnolipids

Pseudomonas aeruginosa, among other organisms frequently cited as producers of bacterial surfactants, produce a class of glycolipids named rhamnolipids [14,43,44]. The rhamnolipid production by *P. aeruginosa*, was described for the first time in 1949 by Jarvis and Johnson [45]. These compounds

present a Rhamnose moiety as glycosyl head and a 3-(hydroxyalkanoyloxy) alkanoic acid (HAA) fatty acid tail, such as 3-hydroxydecanoic acid [46,47]. Mono-rhamnolipids and di-rhamnolipids are the two main classes of rhamnolipids, which consist of one or two rhamnose groups, respectively [48].

Rhamnolipids have anionic characteristics, and they are hydrophilic surfactants [49,50]. Reported CMC values show that glycolipids (e.g., rhamnolipid) together with lipopeptides (e.g., surfactin) exhibit the lowest values [13]. The rhamnolipids produced by *Pseudomonas aeruginosa* decreased surface tension of water to 26 mN m^{-1} and interfacial tension of water/hexadecane to value less than 1 mN m^{-1} [51]. The purified rhamnolipid lowered the interfacial tension against n-hexadecane to ~1 mN/m and had a CMC of 10 ± 30 mg/L, depending on the pH and salt conditions [52,53], whereas Xie et al. (2005) reported an hydrophilicity–hydrophobicity balance (HLB) of about 22–24 [54]. It was demonstrated that rhamnolipid surface activity remains unaltered over pH conditions ranging from 5 to 10 [55,56]. The efficiency of glycolipid biosurfactants towards synthetic emulsifiers has been described in numerous studies. In some works, *Pseudomonas aeruginosa*-derived rhamnolipid biosurfactants were found to be more efficient than the traditional synthetic surfactants: Tween 60 [57], SDS and polyoxyethylene [58], sorbitan monooleate [59], and SDS and Pluronic F-68 [60]. Cosmetics containing rhamnolipids have been patented and used as anti-wrinkle and anti-aging products. Piljac and Piljac (1999) patented cosmetic formulations containing one or more rhamnolipid biosurfactants (concentrations ranging from 0.001% up to 5%) to treat signs of aging, claiming also promising wound healing activities of these compounds [56]. Desanto (2008) also proposed the use of a rhamnolipid produced by *P. aeruginosa* in a shampoo formulation comprising 2% w/w of a rhamnolipid dissolved in an aqueous phase. The authors evidenced the antimicrobial effect and the consequent anti-odor activity of the formulation [61]. Rhamnolipids and sophorolipids were used in combination with other actives, in different cosmetic formulations like anti-dandruff, moisturizing agent, shampoo, body cleansers, and shower gels [13]. Moreover, an emulsion containing 1% of rhamnolipid compounds was successfully used for the treatment of *Nicotiana glutinosa* infected with tobacco mosaic virus and for the control of Potato virus X disease [62]. Oil-containing agricultural by-products and wastes can be used as feedstocks for rhamnolipid production [63,64]. Mohan et al. (2006) indicated that rhamnolipids are biodegraded under anaerobic and aerobic conditions, whereas Triton X-100 (2-[4-(2, 4, 4-trimethylpentan-2-yl)phenoxy]ethanol) is partially biodegradable under aerobic conditions and nonbiodegradable under anaerobic conditions [19]. Chrzanowski et al. (2012) discussed the efficient and good biodegradability of the rhamnolipid biosurfactants [64].

In another work a biodegradation test has been performed considering rhamnolipids in different types of soils. In the first two days of incubation of rhamnolipids in two types of soil (loamy and sandy soil), the biodegradation was below the expectations of the authors but the quantity of biodegraded rhamnolipids on the third day of incubation successfully increased. Ninety-two percent of the total amount of rhamnolipids considered in the test resulted degraded in both kinds of soils after seven days of incubation [65]. However, in another research on the biodegradation of these compounds in different types of soils the process of degradation completely occurred after 4 days [66].

Poremba et al. (1991) compared the toxicity of the chemical-derived surfactant (Corexit) with that of rhamnolipids and demonstrated that Corexit has greater toxicity against *Photobacterium phosphoreum*, with LC50 values ten times lower than those of rhamnolipids [67].

Rhamnolipids mixtures have been recently used in cosmetic formulations and skin care products, some of these applications can be found in patent literature: Schilling et al. (2019), for example, have developed a mixture of rhamnolipids with interesting foaming properties (stability and volume) and good physiological compatibility that can be used precisely for the above applications [68]. Rhamnolipids is a INCI registred name for Glycolipids produced by *Pseudomonas aeruginosa* and consist of Rhamnose linked to a β-hydroxyalkanoic acid grouping.

Trehalose Lipids

Trehalose lipids represent a wide group of glycolipids consisting in a disaccharide trehalose linked to mycolic acids, which are long-chain α-branched β-hydroxy fatty acids [34]. Trehalose is a non-reducing disaccharide in which the two glucose units are linked in an α, α-1,1-glycosidic linkage [69]. They are mainly produced by Gram-positive, high Guanine-Cytosine-containing bacteria, belonging to Actinomycetales, such as Mycobacterium, Nocardia, and Corynebacterium differing in their molecular size, structure, and degree of saturation [70].

A trehalolipid produced by *Rhodococcus* spp. [23] is able to produce stable emulsions to a broad range of conditions: pH 2–10, temperatures 20–100 °C, and NaCl concentrations 5–25% *w/v* [71]. Trehalose lipids from *Rhodococcus erythropolis* and *Arthrobacter* spp. lowered the interfacial and surface tension in culture broth from 1–5 and 25–40 mN m^{-1}, respectively [72]. The minimal interfacial tensions (between aqueous salt solutions and n-hexadecane) achieved with corynomycolic acids, trehalose monocorynomycolates, and trehalose dicorynomycolates were 6, 16, and 17 mN m^{-1} respectively. However, CMC for the trehalose lipids (approx. 2 mg/L) was more than 100 times lower than for the free corynomycolic acids [73].

Trehalose lipids showed good results in solubilization and biodegradation tests on numerous hydrophobic organic compounds. Moreover, trehalose presented antibacterial and antiviral properties [74]. Trehalose dimycolate (TDM) in an in vivo study conferred higher resistance to intranasal infection by influenza virus to mice [75].

Furthermore, the trehalose lipids produced by *Tsukamurella* spp. displayed inhibitory activity against Gram-positive bacteria, although the pathogenic strain *Staphylococcus aureus* was unaffected [74]. Gram-negative bacteria were either slightly or not inhibited at all [76].

In a study conducted on keratinocytes and fibroblasts, a *Rhodococcus* spp. 51 T7 derived trehalose tetraester demonstrated to be less irritating to skin than the commercial surfactant sodium dodecyl sulfate (SDS) [77].

In a recent study, two α,α-trehalose tetraesters with molecular weights of 876 and 848 were produced by *Nocardia farcinica* strain BN26. The experimental data disclosed in the study presented an interesting cytotoxic activity of the studied trealose tetraesters against malignant cells [78].

These biosurfactants were extracted, purified and characterized by spectroscopy and mass spectrometry. The cytotoxic activity was tested with the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) reduction test against malignant cell lines obtained from leukemia and solid tumors. More in particular the tested compounds evidenced interesting cytotoxic activity against BV-173 cells, SKW-3 cells and, on a smaller scale, on HL-60 cells [78].

Sophorolipids

Sophorolipids are amphiphilic molecules composed of a hydrophilic moiety, a sophorose disaccharide (2′-*O*-β-D-glucopyranosyl-β-D-glycopyranose) linked to the hydrophobic moiety, and a fatty acid long chain. Sophorolipids are mainly produced by yeast strains such as *Candida bombicola*, *Candida magnoliae*, *Candida apicola*, and *Candida bogoriensis* when grown on carbohydrates and lipophilic substrates. They are generally present in the form of disaccharide sophoroses (2-*O*-β-D-glucopyranosyl-D-glucopyranose) β-glycosidically linked to the hydroxyl group at the penultimate carbon of fatty acids [79].

A monoacylglycerol glycolipid produced by *Candida ishiwadae* [80], a mannosylerythritol lipid derived from *Candida antarctica* [81], and a sophorolipid derived from *Trichosporon asahii* [82] exhibited higher surfactant activities than several chemical surfactants. A *Bacillus methylotrophicus* USTBa produces a glycolipid resulted more effective than the surfactant SDS in hydrocarbon emulsion preparation [83]. The HLB values of these sophorolipids lie between 13 and 15, representing proper values in personal care and cosmetic formulations [84]. The sophorose lipids are not effective emulsifying agents but present surface activity and are able to lower interfacial tensions [85]. It was

not possible to generalize the use sophorolipids due to their poor solubility in acidic pH conditions characteristic of most cosmetic formulations [86].

In a study by De Rienzo et al. (2015) [87], sophorolipids exhibited bactericidal effects at concentrations of 5% (*v*/*v*) against *Bacillus subtilis* BBK 006 and *Cupriavidus necator* ATCC 17699. Moreover, at the same concentration the biosurfactant acted as an anti-biofilm agent disrupting biofilms formed by single and mixed cultures of *Staphylococcus aureus* ATCC 9144.

Studies by Kim et al. (2002) [88,89] investigated the comparison between sophorolipids produced by *Candida bombicola* ATCC 22214 with those produced by *Staphylococcus xylosus*, *Bacillus subtilis*, *Streptococcus mutans*, and *Propionibacterium acnes* at concentrations of 1, 4, 1, and 0.5 mg/L, respectively, showing significant antimicrobial effect in those produced by *C. bombicola* ATCC 22214.

Cox et al. (2013) [90] used a sophorolipid biosurfactant in combination with an anionic surfactant to develop cleansing formulations suitable for cosmetic use, like shampoo formulations and shower gels. The patented formulations included concentrations ranging from 1 to 20% (w/w) of sophorolipid together with 1–20% of a chemical anionic surfactant and 0–10% of a foam boosting surfactant. Kulkarni and Choudhary (2011) found that a sophorolipid produced by *Starmerella bombicola* in combination with cocoamidopropyl betaine (ratio 2:3) made a good body wash formulation [91]. The sophorolipids produced by *Torulopsis bombicolu* were reacted with alkylene oxides to produce a family of long-chain alkyl-sophorolipids [92]. These chemically modified compounds were found to improve the natural moisturizing factor. The oleylsophorolipid had an HLB value of 7–8 and showed compatibility to the skin [93].

The use of well-aerated bioreactors leads to the production of larger quantities of particularly active lactonic forms of sophorolipids: this aspect and the low price encourage their use in commercial formulations [94–96].

Krishnaswamy et al. (2008) reported potential uses of sophorolipids as topical microbiocides. Moreover, in particular, the authors hypothesize the use of these substances as topical antibacterial or antiviral agents. Because of the prevalence of HIV in women, there is a requirement and active research on efficacious and safe vaginal topical microbicide agents: among the potent spermicidal and virucidal agents, there are sophorolipid surfactants obtained from *Candida bombicola* and their structural analogs like the sophorolipid diacetate ethyl ester that may act similarly to nonoxynol – 9 as microbiocide [97]. These results are of particular interest on the light of the corona virus pandemia and the importance of prevention (i.e., personal hygiene) in less developed countrie.

Based on various studies, sophorolipids, nonionic surfactants, exhibit various functions and may serve as foaming, emulsifying and wetting agents, detergents, and solubilizers [98]. They may be used in cosmetic formulations against dandruff, acne and in body odors treatment, due to their bactericidal activity [99]. Sophorolipids have shown additional activities which make them interesting as possible active cosmetic ingredients usable as (1) desquamating and depigmenting agents, due to mild removal capacities of stratum corneum surface layers; (2) agents for cellulite treatment since they stimulate leptin synthesis in adipocytes; and (3) anti-age actives as both stimulators of collagen neosynthesis, fibroblast metabolism, and, in some cases, inhibitors of free radicals [28]. They are currently used in decorative cosmetics: eye shadow, lip cream, pencil-shaped lip rouge, and compressed powder [99].

Hirata et al. (2009) confirmed a low cytotoxicity of sophorolipids on human keratinocytes. The same study indicated that sophorolipids were easily biodegradable in comparison with synthetic surfactants that showed no biodegradability after 8 days of incubation [58]. Lee et al. (2008) investigated the blooms of marine algae, Cochlodinium, using the biodegradable biosurfactant sophorolipid with removal efficiency up to 90% after 30 min from treatment [100]. In a study by Klosowska-Chomiczewska et al. (2009), according to the OECD Guidelines for Testing of Chemicals (301C Modified MITI Test), the result of the biodegradability tests of sophorolipids produced by non-pathogenic yeast *Candida bombicola*, evidenced that biodegradation occurs almost instantly after the production of the compound by cultivation of the yeast [101]. Because of the low toxicity profile of sophorolipids obtained by *Candida bombicola,* they are currently widely used in food industries [102].

A recent study, concerning the drug delivery of the hydrophobic poorly bioavailable compound curcumin (Peng et al. 2018) [103], evidenced the interesting properties of sophorolipid compounds in their potential applications in drug delivery systems. These compounds have been used to produce sophorolipid-coated curcumin nanoparticles, which demonstrated to possess high loading capacity and encapsulation efficiency, enhancing the bioavailability of curcumin. These studies are particularly valuable and open new perspectives in the development of drug delivery systems including biosurfactants.

Mannosylerythritol Lipid

Mannosylerythritol lipids (MELs), which contain 4-*O*-β-D-mannopyranosyl-erythritol or 1-*O*-β-D-mannopyranosyl-erythritol as a hydrophilic head group and fatty acids as the hydrophobic chain, are the functional glycolipids abundantly produced by yeast strains of the genus Pseudozyma [1,104,105].

Mannosylerythritol lipids have variety of structures classified as follows.

- Number and position of the acetyl group on mannose or erythritol or both.
- Number of acylation in mannose.
- Fatty acid chain, length and their saturation [106].

Fukuoka et al. (2007) [107] determined the HLB of different MEL biosurfactants produced by *Pseudozyma antarctica*, applying two methods (Griffin's method and Kawakami's method). Mono-acylated MELs have higher HLB values (about 12), in comparison with di-acylated MELs that exhibited HLB value around 8, and with tri-acylated MELs with HLB values around 6. MEL-A and MEL-B are quite hydrophobic and demonstrate a superb surface activity with low CMC. They are naturally suited as emulsifiers, dispersants, and detergents. MELs showed remarkable properties compatible with cosmetic use, the most important are stimulation of fibroblast and papilla cells, repair of damaged hair, moisturization of dry skin, and antioxidant activity [42].

MELs also exhibited interesting antifungal activity that supported their suggested use in plant protection [108]. Takahashi et al. (2012) evaluated the antioxidant capacity of three MEL derivatives (named A, B and C) by using 1,1diphenyl-2-picryl hydrazine (DPPH) free radical method and superoxide anion scavenging assay with fibroblasts NB1RGB cells. MEL-C demonstrated the highest antioxidant activity and also presented significant protective effects in cells against oxidative stress. Based on this study and other works, MELs may be suggested as anti-aging and skin care ingredients. Furthermore, other studies proposed MEL as an active ingredient in skin care cosmetics to prevent skin roughness [109,110].

Kim et al. (2002) reported an efficient biodegradation of MEL produced by *Candida antarctica* compared to linear alkylbenzene sulfonate (LAS) and SDS. Other studies on the degradation of MELs evidenced that activated sludge microorganisms effectively biodegraded the MEL that is produced by *Candida Antarctica*. The degradation process duration of all the studied MEL biosurfactants is ~5 min. In the same condition, the synthetic LAS and SDS surfactants were poorly degraded after 7 days of incubation [88]. In a study conducted by Kim et al. (2002) regarding the toxicity of MELSY16 biosurfactant on mouse fibroblast L929 cells after 48 h of exposure, it emerged that MEL-SY16 is safe to human skin and eyes in comparison with synthetic surfactants [27]. Tomotake et al. (2009) evaluated the effect of MELs on SDS-damaged human skin cells, the results showed that MEL-A solutions (concentrations ranging from 5% to 10%) present potential moisturizing activity towards cultured human skin cells treated with SDS (1%) [111].

A suitable extraction, separation and purification of MELs is one of the main problems related to large-scale production of cosmetic or pharmaceutical products. In this regard, research on effective extraction methods are ongoing in our laboratories. Recently, Shen et al. (2019) developed a new extraction method for MELs using a combination of solvents methanol/water (pH 2)/n-hexane at a ratio of 2:1:1 (v/v) followed by 3:1:1, which can effectively remove oils and other impurities from the

fermentation broth. The addition of a last step of extraction with a mixture of methanol and n-hexane (1:1 v/v), able to remove traces of impurities results in an effectively purified product, with maintains surface activity and emulsification properties combined with high MEL recovery rate, claimed as potentially compatible with large scale production [112].

Cellobiolipids

Cellobiolipids are the group of glycolipids that include a cellobiose moiety as the hydrophilic part [113]. As described by Kulakovskaya et al. (2009), cellobiose lipids produced by *Pseudozyma fusiformata* and *Cryptococcus humicola* inhibit the growth of phytopathogenic fungi *Sclerotinia sclerotiorum* and *Phomopsis helianthi* [114]. An *Ustilago maydis*-derived cellobiose lipid showed in vivo phytopathogenic fungi inhibition [115]. Furthermore, the CL (Cellobiolipid) produced by *Cr. humicola* is very interesting, because it is an asymmetric bolaform surfactant, bolaamphiphilc [116], bearing the two different polar heads at opposing end of the hydrophobic core (Table 1).

Table 1. Biosurfactants with glycolipid structure (low molecular weight).

Biosurfactant	Main Producing Strains	Properties/Activities	Structure	Toxicity
Rhamnolipids	*Pseudomonas aeroginosa*	Anionic Hydrophilic Surface active agents Surface activity unaltered over pH conditions ranging from 5 to 10 [55,56]	Glycosides composed of rhamnose moieties and 3-(hydroxyalkanoyloxy) alkanoic fatty acid tail attached via a glycosidic linkage [46,47].	Low toxicity profile (safe) [67]
Trehalose Lipids	*Rhodococcus erythropolis* *Actinomycetales*	Surface active agents Resistant to a broad range of conditions (pH and temperature) [71].	Trehalose disaccharide linked to mycolic acids [34]	Low toxicity profile Less irritating to skin than SDS (safe) [77]
Sophorlipids	*Candida* spp.	Surface active agents Amphiphilic surfactants [83].	Sophorose disaccharide linked to a fatty acid long chain [81].	Easy biodegradable Low toxicity profile (safe) [58]
Mannosylerythritol Lipids	*Pseudozyma antaractica*	Surface active agents with low CMC [107] Antifungal activity [108] Antioxidant activity [42]	Hydrophilic moiety 4-O-β-D mannopyranosyl-erythritol or 1-O-β-D-mannopyranosyl-erythritol linked to fatty acid chain [1,104]	Low toxicity profile Safe to human skin and eye [27]
Cellobiolipids	*Pseudozymafusiformata* *Cryptococcus humicola* *Sclerotinia sclerotiorum* *Phomopsis helianthi* *Ustilago maydis*	Surface active agents [116] Antifungal activity [114]	Group of Glycolipids that comprehend a cellobiose moiety as the hydrophilic moiety [113]	n. r.

n.r. = not reported

3.1.2. Lipopeptides and Lipoprotein

A lipopeptide is a molecule that includes a lipid-bound peptide [117]. Lipoproteins are surface-active biopolymers: soluble complexes of proteins and lipids that are able to transport lipids in the blood circulation of all vertebrates and even insects. Although the assembly, metabolism, structure, and receptor interactions of lipoproteins are characterized by their chemical composition, the most accepted classification of these structures is based on their hydrated density or mobility on agarose gel electrophoresis.

Furthermore, the classification into chylomicrons (CM), very low-density (VLDL), low-density (LDL), and high-density (HDL) lipoproteins is based on their comparative contents of protein and lipids that define the densities of this class of compounds. Only 1–2% of chylomicrons weight is composed of proteins, whereas HDL have about 50% protein content [118].

The biosurfactant cyclic lipopeptide (CLP) is stable over a wide range of pH (7.0–12.0) and heating even high temperatures does not lead to any loss of its interesting surface-active properties [21].

Lukic et al. (2016) evaluated the *Bacillus subtilis* SPB1 lipopeptide and found that isoelectric point is a significant parameter for its characterization [119]. Forester et al. (1999) considered a group of lipopeptides and found that their isoelectric point lies in the acidic pH range between 2.7 and 4.5. These molecules have a negative charge in aqueous dispersion at pH 6.5 that is the most likely reason for the stabilization of oil droplets against coalescence (emulsion stabilizing effect) [120]. Due to

these properties, lipopeptides are not considered as proper candidates for the stabilization of acidic formulations [119]. Lately, Rincon-Fontan et al. (2016) evaluated the adsorption of a lipopeptide biosurfactant obtained from a stream of the corn wet milling industry, showing that it was amphoteric and being trapped by both cationic and anionic resins [121]. Furthermore, Hajfarajollah et al. (2014) considered the antimicrobial and antiadhesive activity of a lipopeptide from a probiotic strain of *Propionibacterium freudenreichii* against bacteria and fungi. The results displayed that 40 g/L of biosurfactant inhibited 67% the adhesion of *Pseudomonas aeruginosa*, while a total growth inhibition of *Rhodococcus erythropolis* was obtained for a concentration of 25 g/L [122].

Cosmetic applications have been proposed for lipopeptides as emulsifiers [123] and anti-wrinkle agents [124,125]. However, beside this, lipopeptides are claimed to have activity towards T lymphocytes [126], for example they have been used to transfer an α-melanocyte stimulating hormone into target cells [126]. However, they find application in whitening cosmetics, such as a skin preparation containing tocopherol derivatives and ascorbic acid derivatives in association with lipopeptides [127] presenting antimicrobial activity, and are also suitable for the treatment and prevention of microbial infections [128–130].

In a study by Hwang et al., more than two-thousand compounds belonging to this class of biosurfactants have been tested in vivo, on male mice during 28 days, observing no considerable adverse effects on hematological parameters and serum biochemical data for a daily intake of doses lower than 47.5 mg/kg of body weight [131,132]. Moreover, Martinez et al. (2006) evaluated the skin irritation caused by arginine-derivative surfactants by using a keratinocyte cell line. Biosurfactants belonging to this class of compounds showed a lower eye and skin irritation potential if compared to synthetic surfactant SDS [133]. Sanchez et al. (2006) also proved that lysine-derivative surfactants show less cytotoxicity on HaCaT cells than SDS [85]. In general, cleansing cosmetics containing lipopeptides show excellent washability with extremely low skin irritation [134].

Surfactin

Surfactin is a lipopeptide-type biosurfactant that is produced by *Bacillus subtilis*. This is a Gram-positive, endospore-producing microorganism. Surfactin is composed of seven amino acids that are attached to the carboxyl and hydroxyl groups on long-chain fatty acids (C13 to C15) forming a close cyclic lactone ring structure [135]. The stability to temperature and broad pH conditions, allows the formulation of a large variety of cosmetic forms [136,137]. Surfactin is claimed to be one of the most useful biosurfactants identified to date [138].

Surfactin is an acidic substance, soluble in alkaline water, many organic solvents (ethanol, methanol, butanol, chloroform, and dichloromethane) [96], and also in a mixture of water and oil phase, according to surfactin's HLB of 10–12. The surface properties of surfactin have been compared with those of sodium lauryl sulphate (SLS). The surface tension of a 0.005% solution of surfactin was found 27.9 mN m^{-1}, while for SLS is notably higher (56.5 mN m^{-1}) at the same concentration [74]. CMC are much lower for biosurfactants than for many synthetic surfactants, in the case of surfactin values of 0.0025% (w/v) have been reported and of 0.001% for the *Pseudomonas aeruginosa* rhamnolipids [139]. Surfactin is composed of a mixture of isoforms, it has a molecular weight of 1007–1035 Da and is constituted by one heptapeptide presenting the amino acid sequence Glu-Leu-Leu-Val-Asp-Leu-Leu [140].

Regiospecificity of optically active amino acids, particularly leucine, in the structure of surfactin originates the amphiphilic nature and the surfactant properties [141,142].

The potential applications of surfactin are really wide range, going from medicinal, cosmetic to environmental [135]. One of its most important biological activities is the capacity of delaying the formation of fibrin clots by inhibiting the conversion of fibrin monomer to fibrin polymer [71]. However, the current therapeutic applications of surfactin are antimycoplasmal, antibacterial and antiviral, antiadhesive, anti-inflammatory, and recently anticancer. All these biological activities that will be discussed below are determined by the interaction of surfactin with target membrane.

1. Antimycoplasmal, antibacterial, and antiviral activity

Mycoplasmas are causative agents of respiratory inflammation and diseases of the urogenital tract. Antibiotics are mostly ineffective in treating these microorganisms because they cannot penetrate their cytoplasmic membrane [135]. Vollenbroich et al. (1997) discovered that surfactin can successfully treat mycoplasmas [143]. Moreover, Kracht et al. (1999) evidenced that the surfactin isoform presenting one negative charge exhibited a noticeable antiviral activity [144]. The activity displayed by surfactin is attributable to its ability in the formation of ion-conducting channels in bacterial lipid bilayer membranes by detergent-like action [145–147].

2. Anti-inflammatory applications

The amphiphilic structural features of surfactin enable it to interact with cell membranes and macromolecules, such as enzymes and lipopolysaccharides (LPSs) [148]. Many studies demonstrated that surfactin inhibits the inflammatory effect caused by the direct interaction of LPS with cells [149,150].

3. Anticancer activity

Recently, surfactin has presented a promising strategy for cancer treatments, due to its ability to induce cytotoxicity against different cancer types such as Ehrlich ascite carcinoma, breast and colon cancers, leukemia, hepatocellular carcinoma, and cervical cancer.

In Vitro, surfactin anticancer activity is associated with several mechanisms: apoptotis, growth inhibition, cell circle arrest, and metastasis reduction. The inhibition of cancer progression given by surfactin is involving mainly apoptosis, mediated by two different pathways: the increment of intracellular ROS formation and the change in phospholipids composition, decreasing in unsaturated fatty acids [151].

Concerning surfactin antiproliferative effect, a modulation in cell cycle regulatory proteins has been evidenced, such as tumor suppressor p53 and others, which are pivotal for cell cycle phase transition to block the proliferation of cancer cells.

Surfactin treatments can also arrest metastasis in terms of invasion, migration, and colony formation of cancer cells, by downregulating the expression of matrix metalloprotenaise-9 (MMP-9) causing the inactivation of cell signaling pathways.

However, one of the major limits of surfactin application as anticancer agent is the hemolytic activity, above 0.05 g/L. In this way, nanoformulations for surfactin delivery may be a solution in order to reduce toxicity, thanks to to their ability to achieve the drug in cancer cells [151].

4. Antiadhesive applications

Biosurfactants in some cases have antiadhesive properties that inhibit the production of biofilm and the adhesion of bacteria in infected sites [150–154]. Seydlová (2008) have shown that surfactin inhibits the formation of biofilms by *Salmonella typhimurium*, *Salmonella enterica*, *Escherichia coli*, and *Proteus mirabilis* [149]. This activity may have potential biomedical applications, especially in surgical devices and implants [135].

5. Environmental applications

Surfactin is able to accelerate the biodegradation of hydrocarbons [155]. Lipopeptide biosurfactants such as surfactin and fengycin that are produced by *Bacillus* spp. are effective in transporting heavy oil [155,156]. Whang et al. (2008) examined the biodegradation of diesel and evaluated two biosurfactants: surfactin and a rhamnolipid have been reported to enhance the biodegradation of pollutants in diesel-contaminated soil and water [156].

6. Biocontrol applications

Debois et al. (2015) found that surfactin exposition-induced immunity prepares plants to better resist further pathogen infections and involves only restricted expression of defence-related molecular events and does not inhibit seedling growth [157].

7. Other application

Surfactin has excellent foaming properties if compared with sodium dodecyl sulphate and bovine serum albumin [158,159]. As previously mentioned, surfactin is also a good candidate as an active or as a component in the nanotechnology field. On one side, nanoformulation (such as polymeric nanoparticles and nanofibers, polymeric micelles, microemulsion, and liposomes), containing surfactin as an active, offers high drug loading capacity, enhanced bioavailability, prolonged circulation time and protection against degradation, specific targeting and ease of manipulating drug release.

On the other side, surfactin can act as a surface-active component, wetting and solubilizing agent, an emulsifier, or as building block of nano-carrier thanks to its self-assembly ability. This feature can be used not only pharmaceutical field but also for cosmetic, environmental and industrial uses [151]. Sodium Surfactin is a INCI registred name for a lipopeptide composed of amino acids and fatty acids and is produced by the fermentation of Bacillus subtilis.

Several articles describe applications of surfactin as stabilizing agent in developing metal nanoparticles (NPs), for example, Reddy et al. (2009a-b) reported 2-month stability of gold and silver NPs using this lipopeptide [160,161]; Singh et al. (2011) used a surfactin produced by *B. amyloliquifaciens* KSU-109 as stabilizer of cadmium sulfide nanoparticles for 4-months [162]; and, recently, Krishnan et al. (2017) have investigated the application of surfactin from *Brevibacillus brevis* KN8(2) in the nanocrystalline silver nanoparticles' synthesis, as active compound against *Pseudomonas aeruginosa* infections, with a minimum inhibitory concentration of 10 µg/mL [163].

A study by Hirata et al. (2009) shows that surfactin resulted a biodegradable biosurfactant as other sophorolipids. In the same study the biosurfactant has been compared to other synthetic surfactants that showed no biodegradability after 8 days [58].

Hwang et al. (2008) administered different concentrations of surfactin C from *Bacillus subtilis* (0, 125, 250, and 500 mg/kg of body weight/day) to pregnant mice during the period of main organogenesis [132].

The results displayed that the biosurfactant did not show maternal toxicity, fetotoxicity or teratogenicity, and thus it was concluded that the intake of 500 mg/kg per day in mice did not enforce any harmful effects [132,159]. A research made by Hwang et al. (2009) showed a necrosis of hepatocytes at high dose (1.000–2.000 mg/kg) of surfactin C by oral administration to rats while there was no toxic effects at lower dose of surfactin C, confirming its NOAEL (no observed adverse effect level) to be 500 mg/kg [164].

However, Duarte et al. (2014), using the same concentration and exposure time that inhibited the viability of human T47D and MDA-MB-231 breast cancer cells, described a cytotoxic action of purified surfactin from *B. subtillis* 573 against human normal MCT-3T3-E1 fibroblast cell line [165].

Despite the promising surfactin activities, there are remarkable issues that prevent large-scale use related to the poor performance of available production methods. Low production yield has been detected in already known producing bacterial strains. Research projects aimed at improving production yield are underway, a very recent study by Wu et al. (2019) developed a metabolic engineering method working on *Bacillus subtilis* 168, which is normally a nonproducer of Surfactin strain. The surfactin biosynthetic activity has been successfully restored in the nonproducing strain through a modulation of metabolic processes involved in the surfactin biosynthesis previously observed in the wild MT45 strain, known for high production capacities. This work provides new possibilities regarding the large-scale uses of surfactin as a biosurfactant in cosmetic and pharmaceutical products allowing acceptable production yields [166]. Such studies open new perspectives on large productions of this type of active compounds and are to be encouraged.

Iturin

Iturin is a lipopeptide containing seven α-amino acid residues closed through a lactam ring by a reaction between the amino group of the fatty acid moiety and the carboxyl group of the C-terminal amino acid [167]. The lipopeptides of the iturin group are defined by the presence of a β-amino fatty

acid (C_{14}-C_{17}), as the lipid moiety [168]. Iturin is a mixture of three compounds (A, B, and C) of comparable molecular weight (M = 1000), among which iturin A is the most active [167].

The CMC values (at 25 °C) of iturins, determined from surface tension data, are in the range 2 to 8 × 10^{-5} M. They are not very affected by the presence of 0.1 M electrolytes and temperature variations [116]. These data confirm the effectiveness of iturin if compared to the values of other surfactants as Triton X-100 (CMC = 2.5 × 10^{-4} M) [169]. Iturin from *Bacillus subtilis* was found to be active even after autoclaving in the pH range of 5 to 11. This compound presents a shelf life of 6 months at −18 °C [170].

Crude iturin A was submitted to clinical trials for the treatment of dermatomycoses and resulted active in a large antifungal spectrum. This compound was lately found to be very active against most phytopathogenic fungi and appeared as a good candidate as an alternative to common fungicide drugs. The fungicidal activity was observed both with resting and growing cells, the hypothesis of an inhibition of a metabolic process has been excluded. Iturins have a lytic activity on yeast spheroplasts and human erythrocytes but only have a limited antibacterial activity against some Micrococcus and Sarcina strains [167]. Besson et al. (1976) studied the antifungal properties [171] and Singh and Cameotra (2004) reported the antibacterial property of the iturin lipopeptide produced by *Bacillus subtilis* [172]. Iturin A presented low toxicity and low allergenic effects [167].

Even in the case of Iturin, the problems related to the poor production yield greatly limit the possible uses in large productions. Recent studies focus on strategies aimed at improving production processes. In a very recent work by Dang et al. (2019) the bacterial strain *B. amyloliquefaciens* LL3 was engineered in order to become an effective producer of a mixture of four Iturin A homologs, seen as effective antifungal agents, through promoter substitution. The authors developed a combined strategy involving pleiotropic regulators overexpression and optimized culture conditions. Further studies are needed to optimize these techniques and clarify in detail the mechanisms involved in the production of these compounds [173].

Fengycin

Fengycin is a cyclic lipodecapeptid containing β-hydroxy fatty acid with a side chain length of 16–19 carbon atoms. Like the other lipopeptides produced by *Bacillus subtilis*, fengycin appears as a mixture of various isoforms which show differences both in the length and branching of the β-hydroxy fatty acid moiety, as well as in the peptide ring of amino acid composition [174].

The term fengycin encompass two compounds, the difference is in the change of one amino acid [167]. Fengycin A is a combination of L-Ile, 1 L-Pro, 1 D-allo-Thr, 3 L-Glx, 1 D-Tyr, 1 L-Tyr, 1 D-On, and 1 D-Ala, whereas in fengycin B the D-Ala is replaced by D-Val [87]. Fengycin presents ten amino acids, whereas iturin and surfactin has seven amino acids respectively [175,176].

Fengycin, as well as Iturin, is a surface-active agent with both lipophilic and hydrophilic moieties that presents a wide anti-fungal activity [177]. The mechanism underlying this last activity is not clear but it is assumed that fengycin has the ability to disintegrate the cell membrane by pore formation or a change of the structure of the lipid membrane. Fengycin and surfactant type lipopeptide(s) are able to interact with the plant cells, where these lipopeptides interact with the bacteria and induce the immune response to detect bacterial species related to the plant [178]. Fengycins present low hemolytic activity and strong antifungal activity [179].

Recent studies, as well as the present study, focus on production problems. A study by Qing-gang et al. (2018) deals with the role of the two-component system consisting in the regulator PhoP and its sensor kinase PhoR in *Bacillus subtilis* strain NCD-2 in the production of fengycin. Fengycin is synthesized in *Bacillus subtilis* nonribosomally by a complex composed of five fengycin synthetases organized in the order FenC-FenD-FenE-FenA-FenB [180].

Inactivation of phoR or phoP genes has been shown to cause a significant reduction in fengycin production.

The production of the active compound takes place preferentially under low phosphate conditions by a positive regulation of the fengycin synthetase gene FenC. Thus, the PhoR/PhoP two-component system positively regulates fengycin production in Bacillus subtilis NCD-2 under low-phosphate conditions. Further studies are needed to fully understand the mechanisms involved in *Bacillus subtilis* production of fengycin and the strategies to further enhance the production yield [181].

Viscosin

Viscosin is a surface active cyclic lipopeptide which is composed of a hydroxydecanoic acid attached to a peptide of nine amino acids, seven of which form a lactone ring. At the critical micelle concentration of 4 mg/L, viscosin is able to reduce the surface tension of water to 27 mM m^{-1} [177,182]. Viscosin was first described in 1951 and was isolated as an antimycobacterial substance from *Pseudomonas viscosa* [183].

At the same time, Groupe et al. (1951) demonstrated promising antiviral activity of viscosin against bronchitis virus and influenza A virus [184].

In a more recent study, the production of viscosin by the bacterial strain *Pseudomonas libanensis* M9-3 has been reported. The minimum surface tension measured between air and water, at the detected a CMC of 54 mg/L, in this case is 28 mM m^{-1}. Viscosin has proven to be able to form stable emulsions even at very low concentrations in the finished product (7.5 mg/L). It has to be noted that values of CMC reported by the different studies do not match, which may be due to different methods adopted for the measurement and by different purification procedures. Further studies are needed to understand the mechanisms that regulate the production of viscosin by *Pseudomonas* strains and develop strategies to increase the production yield [185].

Lichenysin

Lichenysin contains a peptide moiety with seven amino acids and a β-hydroxy fatty acid of 12–17 carbon atoms. Six varieties are reported and named lichenysin A, B, C, D, G, and surfactant BL86: lichenysin A is the most aboundant isoform. Lichenysins, due to the presence of Glu and/or Asp residues, are anionic surfactants [140]. Lichenysin, which acts as a potent surfactant, can reduce surface tension to 28.5 mM m^{-1} and presents a CMC of 15 mg L^{-1}. Lichenysin A is very similar to surfactin, differing only by 1 Da in molecular mass, attributable to the substitution of glutamic acid for glutamine in the first amino acid position. This small difference remarkably affects the physicochemical properties of lichenysin, in particular regarding the surface tension reduction [140].

Lichenysin B and BL86 have a very low CMC (10 mg L^{-1}) if compared to other synthetic surfactants under optimal conditions [47]. These two lichenysins have the capacity to reduce the surface tension of water from 72 to 27 mM m^{-1} [186]. McInerney et al. (1990) stated that lichenysin produced by *Bacillus licheniformis* resists to temperatures up to 50 °C, pH between 4.5 and 9.0 and NaCl and $CaCl_2$ concentrations up to 50 and 25 g L^{-1}, respectively [187].

Lichenysins are most powerfull anionic cyclic lipoheptapeptide biosurfactants produced by *Bacillus licheniformis* [140] in hydrocarbonless medium with glucose as main carbon source [188]. Lichenysins specifically inhibit the formation of biofilm of pathogenic strains, has an emulsifying capacity and permeabilizes membranes by a colloid-osmotic process.

Lichenysin A produced by *Bacillus licheniformis* BAS50 has interesting antimicrobial properties slightly lower than those of surfactin [140]. A native form of lichenysin A showed relevant antimicrobial activity against *Acinetobacter calcoaceticus*, *Alcaligenes eutrophus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas fluorescens* cells [189]. Additionally, some studies evidenced lichenysins anti-inflammatory and antitumor activities [190].

In order to allow large-scale use, it is necessary to increase the production yield of this biosurfactant. Zhu et al. (2017) attempted to add lichenysin precursor amino acids in the growth medium of the producing strain *Bacillus subtilis* observing that this procedure does not increase the production yield that, surprisingly, decreases. The production of a *codY* knockout strain (CodY is a transcriptional

regulator in many Gram-positive bacteria that controls the expression of many genes involved also in the lichenysin production) improved the production by 31% to 2356 mg/L with a production efficiency improved by 42.8% to 98.2 mg/L-h after addition of precursor amino acids [191].

Gramicidin

Gramicidin is a surface-active agent belonging to the lipopeptide biosurfactants class presenting interesting antibiotic activity. Gramicidin is a mixture of three compounds: gramicidin A, B, and C, making up 80%, 6%, and 14%, respectively [192], which derive from the soil bacterial species *Bacillus brevis* [192].

Bacillus brevis produces the cyclo-symmetric decapeptide antibiotic called Gramicidin S. In solution, the molecule Gramicidin S exists in the form of a rigid ring with the two positively charged ornithine side chains constrained to one side of the ring, and the side chains of the remaining hydrophobic residues oriented toward the opposite side of the ring [193].

Gramicidin S binds strongly to negative surfaces and polyanions, turning them into lipophilic structures. Two molecules of Gramicidin S are able to form a stable coordination complex with one molecule of ATP that is able to partitions into organic solvents [73].

Polymyxins

Polymyxins are fermentation products of the bacteria *Bacillus polymyxa* discovered for the first time in the 1940s; these compounds have been demonstrated to have antimicrobial activity [194]. They are large, cyclic polypeptides and are positively charged [195]. Among the five polymyxins that were initially discovered (polymyxins A–E), only polymyxin B and polymyxin E (colistin) entered into clinical use, because they were less nephrotoxic [196]. Polymyxin B differs from polymyxin E (colistin) by a single amino acid [197]. A branched-chain fatty acid is connected to the terminal 2,4-diaminobutyric acid. The structures of polymyxins differ in substituents at residues 3 (Dab or D-Ser), 6 (D-Leu or L-Ile), or 7 (D-or L-Dab) [198]. Dab residues, together with the hydrophobic side-chain of the fatty acid, give to these antibiotics the surface-active properties of a cationic surfactant [73].

The polymyxins, as other lipopeptides, are surface active biosurfactants presenting antimicrobial activity against a broad range of Gram-negative aerobic bacilli. These compounds are able to effectively disperse microbial biofilms. However, mechanisms of acquired resistance to these antimicrobial agents have been reported that are still being elucidated [195]. The most common mechanism is LPS (lipopolysaccharide) modification, which interferes with the initial interaction between the negatively charged LPS and the positively charged peptides of the polymyxins [199,200].

Antibiotic TA (Megovalcin)

Antibiotic TA (producer strain isolated from Tel Aviv), is also known as megovalicin, myxovirescin, or M-230B [201–204]. Antibiotic TA is a macrocyclic secondary metabolite produced by myxobacteria. TA has a novel structure that consists of 28-membered macrolactam-lactone [205].

TA is a rapid bactericidal agent and has activity against many Gram-negative and some Gram-positive bacteria [190]. Antibacterial activity of TA is interesting, as it exhibits no toxicity toward protozoa, eukaryotic cells, fungi, rodents, and humans [206].

This compound shows antiadhesive properties against many bacterial strains, it can be defined an antiadhesive antibiotic, and, at the same time, it strongly adheres to a variety of surfaces. For these reasons, Antibiotic TA has been suggested for the treatment or prevention of biofilm infections, such as periodontal diseases or infections correlated to the use of medical devices [207–211] (Table 2).

Table 2. Biosurfactants with lipopeptidic and lipoproteic structure (n.r.= not reported).

Biosurfactant	Producing Strain	Properties/Activities	Structure	Toxicity
Surfactin	*Bacillus subtilis*	Surface-active agent with low CMC. [74] Stability to temperature and broad pH condictions [136,137] Antiadhesive properties [148] Anti-inflammatory activity [149,150] Antiviral activity [144] Antibacterial activity [149] Anticancer activity [151] Good candidates of nanoformulation as an active or as stabilizing agent. [151]	Lipopeptide composed of a seven amino acid moiety attached to the carboxyl and hydroxy groups on long-chain fatty acids (C13 to C15) [135]	NOAEL is 500 mg/kg. At high dose (1000–2000 mg/kg) it causes necrosis of hepatocytes [164]
Iturin	*Bacillus subtilis*	Surface-active agent Stability to temperature and broad pH conditions [120,170] Antifungal activity [171] Antibacterial activity [172]	Lipopeptide containing seven α amino acid residues closed through a lactam ring attached to a fatty acid moiety [167]	Low toxicity and low allergenic effects (lytic activity on human erythrocyte is reported) [179]
Fengycin	*Bacillus subtilis*	Surface-active agent [177] Antifungal activity [81]	Cyclic lipodecapeptide containing ß hydroxy fatty acid with a chain length of 16–19 carbon atoms [174]	Modest Hemolytic activity is reported [179]
Viscosin	*Pseudomonas viscosa*	Surface-active agent [182] Antimycobacterial [183]. Antiviral activity [184]	Hydroxydecanoic acid attached to a peptide of nine amino acids, seven of which form a lactone ring [177]	n. r.
Lichenysin	*Bacillus licheniformis*	Anionic surfactant [140]. Stability to temperature and broad pH conditions [187] Antimicrobial activity [140] Anti-inflammatory activity [190] Antitumor activity [190]	Peptide moiety composed of seven amino acids attached to a β-hydroxy fatty acid of 12–17 carbon atoms [140].	n. r.
Gramicidin	*Bacillus brevis*	Surface-active agent [197] Antimicrobial activity [192]	Mixture of three compounds named gramicidin A, B and C, making up 80%, 6%, and 14%, respectively [192]	n. r.
Polymyxins	*Bacillus polymyxa*	Surface-active agent [195] Antimicrobial activity [195]	Cationic polypeptide structure consisting of five different compounds (polymyxin A–E) [195,196]	n. r.
Antibiotic TA (Megovalicin)	*Myxobacteria*	Antiadhesive/antibiotic activity [205] Rapid bactericidal [205] High adhesive properties toward abiotic material [207–211]	Macrocyclic structure consisting of a 28-membered lactone ring [206]	No toxicity toward protozoa, eukaryotic cells, fungi, rodents and humans [207]

3.1.3. Fatty Acids, Phospholipids, and Neutral Lipids

Some bacteria and yeast strains are able to produce a large amount of phospholipid and fatty acid biosurfactants during growth in a culture medium containing n-alkanes [212].

Phospholipids are found in any microorganism, but there are few examples of notable extracellular production. All phospholipids contain a glycerol unit esterified to two fatty acids and one phosphate group that may be involved in additional substitution. Interestingly, *Thiobaciflus thiooxidans* produces different phospholipids that have been isolated from the cell-free culture broth [213].

Fatty acids and lipids are found in all microbial cells and are often observed as extracellular products [214–216]. Most of these lipids, including alcohols, carboxylic acids, esters, and mono-, di-, and triglycerides, have been shown to have some degree of surface activity. Most of the examples of neutral lipids or fatty acids extracellular production by bacterial strains involve organisms growing on hydrocarbons. This fact suggests that they may be important for hydrocarbon emulsification [213]. Corynomycolic acids and other hydroxy fatty acids have been shown to be much more effective surfactants in comparison with simple fatty acids [217].

The hydrophilic/lipophilic balance of fatty acids is clearly associated with the length of the hydrocarbon chain. For lowering the surface and interfacial tensions, the most active saturated fatty acids are in the range C12 ± C14 [73].

Corynomycolic Acids

Some bacterial strains, like *Nocardia erythropolis* (ATCC 4277) and *Corynebacterium lepus*, are able to produce a complex of fatty acids containing hydroxyl groups and alkyl branches [73]. One of these complexes of fatty acids, named corynomycolic acid, is a highly effective biosurfactant [218].

Corynomycolic acids (R^1-CH(OH)-CH(R^2)-COOH) obtained from *Corynebacterium lepus* present interesting surfactant activity, they can efficiently lower the surface tension of an aqueous solution. Similarly, to 2-hydroxy fatty acids, the surface properties of corynomycolic acids are relatively insensitive to pH and ionic strength; they result active in pH conditions ranging from 2 to 10 [73].

Spiculisporic Acid

Spiculisporic acid is a γ-butenolide derivative isolated for the first time from cultures of a marine derived fungus named Aspergillus spp. HDf2. Tabuchi et al. (1977) developed an efficient production method for 4,5-dicarboxy-4-pentadecanolide (spiculisporic acid) from glucose by means of a bioindustrial process using *Penicillium spiculisporum*. This compound presents one n-decyl group as a hydrophobic group and two carboxyl groups and one lactone group as hydrophilic moieties. Its needle-like crystals are insoluble in water at room temperature [219–222]. Ishigami et al., in 1983, studied the surface activity of various spiculisporic acid salts evidencing interesting results, CMC values range from 3.9×10^{-3} to 1.7×10^{-1} mole/liter [223].

Phosphatidylethanolamines

Phosphatidylethanolamines belong to the class of phospholipids and are present in biological membranes [224]. It has been observed that some species of microorganisms are able to enhance the solubility and to metabolize long-chain n-alkanes, in many cases this activity has been attributed to the production of extracellular components by hydrocarbon-grown bacteria. Käppeli and Finnerty (1979) reported the production by hexadecane-grown *Acinetobacter* spp. HO1-N, of extracellular membrane vesicles with a phospholipid composition mainly consisting in phosphatidylethanolamine. The vesicles production resulted in an enhanced solubility of hexadecane in the aqueous growth medium. Hexadecane resulted bind to the extracellular phospholipid vesicular component in the form of microemulsion [225] (Table 3).

Table 3. Fatty acid, phospholipid, and neutral lipids biosurfactants. N.r. = not reported.

Biosurfactant	Producing Strain	Properties/Activities	Structure	Toxicity
Corynomycolic Acids	*Nocardia erythropolis* and *Corynebacterium lepus*	Surfactant activity, emulsifying agents [73,218] Stability to broad pH conditions [73]	Fatty acids containing hydroxyl groups and alkyl branches [73]	n.r.
Spiculisporic Acid	*Aspergillus* spp HDf2 and *Penicillium spiculisporum*	Surfactant activity, good CMC values [223]	4,5-dicarboxy-4-pentadecanolide [219]	n.r.
Phosphatidylethanolamines	*Acinetobacter* spp HO1-N	Vesicles-forming emulsifying agents [224,225]	1,2-diacyl-*sn*-glycero-3-phosphoethanolamine [224,225]	n.r.

3.2. Biosurfactants with High Molecular Weight

3.2.1. Particulate Biosurfactant

Particulate biosurfactants are produced by some bacterial strains in the extracellular space. They are organized in vesicles capable of forming microemulsions that influence both mobility in the hydrocarbon medium and the eventual alkane uptake of the cell [226].

Vesicles

Vesicles are membrane-bound organelles. Their function is to transport material throughout the cell. A typical vesicle consists of a phospholipid bilayer surrounding a lumen or interior space [227].

An example of this type of biosurfactant presenting emulsifying activity is the vesicles produced by *Acinetobacter* spp. strain HO1-N previously described. With a diameter of 20 to 50 nm and a density of 1.158 g/cm^3 are composed of proteins, phospholipids, and lipopolysaccharides [228].

Whole Microbial Cells

The research has identified so far chemical products excreted during microbial growth active as biosurfactant agents. Additionally, the cell itself can be considered a biosurfactant. In some cases, cell suspensions of bacteria demonstrated to generate surface and interfacial tension reductions, together with significant emulsification or demulsification activity. The cell surface is composed of a miscellany of hydrophobic and hydrophilic moieties. Microbial cells due to their hydrophobic nature display surface activity, thus they can be classified as biosurfactants [213]. Different species display a variety of hydrophobicities measured by a saline contact angle on a cell lawn [228]. Other factors such as culture age and broth composition also affect cell hydrophobicity [229]. Neufeld and Zajic (1984) proved that entire cells of *Acinetobacter calcoaceticus* 2CA2 are capable to act as emulsifiers, in addition to the production of an extracellular emulsifier [230].

3.2.2. Polymeric Biosurfactant

A large number of bacterial species from various genera produce exocellular polymeric surfactants composed of protein, polysaccharides, lipoproteins, lipopolysaccharides, or complex mixtures of these biopolymers.

Emulsan

Emulsan is an anionic polymeric emulsifying agent presenting a very asymmetric structure with a molecular weight average of 9.9×10^5 [231]. It consists of an anionic D-galactosamine-containing polysaccharide backbone with fatty acid side chains attached by amide and ester linkages and a non-covalently bound protein [231,232]. Emulsan is a complex produced by *Acinetobacter* RAG-1, its surface activity is attributable to the presence of fatty acids constituting 15% of the emulsan dry weight, which are bonded to the polysaccharide backbone via O-ester and *N*-acyl linkages [233,234].

Emulsan results usable in a wide variety of hydrocarbon-in-water emulsions, it forms a consistent film at the interface between the two phases [235]. Furthermore, Pines and Gutnick (1981) evidenced the role of emulsan as a bacteriophage receptor on the cell surface of *Acinetobacter calcoaceticus* RAG-1 [236,237]. Emulsan is a very effective emulsifying agent for hydrocarbons in water even at concentrations in the range 0.001 to 0.01%. It is one of the strongest known emulsion stabilizers able to resist inversions even at a water-to-oil ratio of 1:4 despite these emulsions divided into two layers over the long term [238].

Recent studies disclosed new potential pharmaceutical uses of emulsan. A study by Yi et al. (2019) describes the potential use of emulsan obtained from *Acinetobacter calcoaceticus* RAG-1 and flax seed oil in the production of nanoparticles capable of operating as vehicles for hydrophobic active compounds. The antitumor agent pheophorbide-a was successfully loaded in the hydrophobic core of the nanoparticles as a model drug. The complex has been tested against SCC7 mouse squamous cell carcinoma cells, it showed fast uptake in the tumor cells. Moreover, it was able to kill the tumor cells after activation through laser irradiation due to the photodynamic effect of pheophorbide a.

The complex has been tested through intravenous injection in SCC7 tumor-bearing mice performing better than free pheophorbide a in accumulation in tumor tissue and permanence in blood circulation. These evidences enlarge the potential uses of biosurfactants in innovative drug delivery systems [239].

Liposan

Liposan is an extracellular, water-soluble bioemulsifier prouduced by *Candida lipolytica*. It is composed of 17% protein and 83% carbohydrate; the latter portion consists of an heteropolysaccharide composed of galactose, galactosamine, glucose, and galacturonic acid [5]. Liposan has been effectively

used to stabilize O/W emulsions including a variety of vegetable oils [240]. This biosurfactant is produced by *Candida lipolytica* grown in hexadecane as carbon substrate in the final phase of fermentation [5].

Alasan

Alasan is an anionic alanine-containing bioemulsifier produced by *Acinetobacter radioresistens KA53*. This bioemulsifier is a complex of polysaccharides, alanine and proteins with a total molecular mass of 1MDa [241]. Alasan proteic fraction is composed of three major compounds (of 16, 31, and 45 kDa, respectively) and the Alasan polysaccharide presents uronic acid, *N*-acyl amino sugars and a covalently bound alanine. Each of the three fractionated Alasan proteins showed emulsifying activity: the 45-kDa protein had the most considerable activity, 11% higher than the intact Alasan complex. The *N*-terminal amino acid chain of the 45-kDa protein exhibited high similarity to the OmpA protein of several Gram-negative bacteria. The function of the Alasan polysaccharide in the microorganism is not clear, but it may play a role in releasing proteins into the medium and protecting the protein complex against proteolytic activities. In fact, the purified 45 kDa protein was readily hydrolyzed by trypsin, whereas the protein bound to the polysaccharide resulted more resistant [242].

Alasan can efficiently emulsify various types of hydrocarbons including long chains, alkanes, aromatics, polyaromatic hydrocarbons (PAHs), crude oils, and paraffins. Alasan can facilitate solubilization of PAH by aggregating them into oligomer molecules, and this mechanism increases their solubility by 20-fold, thereby accelerating biodegradation [241].

The increase of temperature in solution of Alasan induce large changes in the viscosity and emulsifying activity of the complex. However, between 30 °C and 50 °C, the viscosity increased 2.6 times with no relevant change in the emulsifying activity of the complex.

Between 50 °C and 90 °C, the viscosity decreased 4.8 times and the emulsifying activity increased five-fold.

Alasan has a CMC of 200 μg/ml and is able to lower interfacial tension from 69 mN/m to 41 mN/m at 20 °C [73].

Biodispersan

Biodispersan is an extracellular, nondialyzable dispersing agent that is produced by *Acinetobacter calcoaceticus A2* [243]. It is an anionic heteropolysaccharide, with an average molecular weight of 51,400. Rosenberg et al. (1988) studied the chemical composition of this biodispersant after concentration by ammonium sulfate precipitation and deprotonation by hot phenol treatment. The active component is an anionic polysaccharide named PS-A2, its activity resulted three times greater than that of the whole complex [244]. Studies regarding the chemical composition evidenced four reducing sugars in the structure of biodispersan: glucosamine, 6-methylaminohexose, galactosamine uronic acid, and an unidentified amino sugar [244].

The biopolymer biodispersan is able to bind to powdered calcium carbonate and change its surface properties allowing a better dispersion in water. Moreover, it effectively disperses titanium dioxide and limestone [245]. Biodispersan can be used also as a surfactantin the limestone grinding process facilitating the fracturing [245].

Polysaccharide Protein Complex

Rodrigues et al. (2006) determined the CMC, surface activity, antimicrobial activity, and antiadhesive activity of a crude biosurfactant composed of protein and polysaccharides containing bound phosphate groups and of three partially purified fractions abundant in glycoproteins. The described biosurfactant is produced by *Lactococcus lactis* 53. In the same study, the most active fraction presented a CMC of 14 g/L similar to that of the crude biosurfactant.

Regarding the antimicrobial activity, the most active fraction of the biosurfactant at a concentration of 40 g/L resulted active against *Staphylococcus epidermidis* GB 9/6, *Streptococcus salivarius* GB 24/9,

Staphylococcus aureus GB 2/1, *Candida albicans* GBJ 13/4A, and *Candida tropicalis* GB 9/9, whereas no antimicrobial activity has been observed against *Rothia dentocariosa* GBJ 52/2B [246].

As concerns the antiadhesive activity, the crude biosurfactant and the most active fraction evidenced inhibition percentages up to 70% against *Staphylococcus epidermidis* GB 9/6 and *Staphylococcus aureus* GB 2/1 even at concentrations of 2.5 g/L. Furthermore, the most active fraction inhibited the adhesion of the tested yeast strains [246].

Gudiña et al. (2015) studied another glycoproteic biosurfactant produced by *Lactobacillus agilis* CCUG31450, showing that it can reduce the surface tension of water to 42.5 mN m^{-1} showing also a strong emulsifying activity. The studied compound evidenced interesting antiadhesive activity against *Staphylococcus aureus* and a consistent antimicrobic activity against *Pseudomonas aeruginosa*, *Streptococcus agalactiae* and *Staphylococcus aureus* at a concentration of 5 g/L [247].

Kaplan et al. (1987) described the mechanism of the emulsifying activity of protein–polysaccharide mixtures [248]. Considering emulsifying agents of bacterial origin both the polysaccharide and the protein components are required, the association of an anionic hydrophilic polysaccharide with proteins is necessary for the activity. Reuniting the protein and polysaccharide fractions after a deproteinization of the extracellular emulsifying complex led to a restoration of the amphipathic properties and to the reappearance of the emulsifying activity [249].

Mannoproteins

Mannoproteins are glycoproteins obtained from the cell wall structures of yeasts. These compounds are catalogued in structural mannoproteins and enzymatic mannoproteins according to their chemical compositions and functions in living organisms. Structural mannoproteins are the most plentiful and are composed of a small protein portion attached to a greater carbohydrate fraction (mannopyranosyl), while in enzymatic mannoproteins, the proteic fraction is more important [241].

Alcantara et al. (2014) evidenced a mannoprotein bioemulsifier obtained from *Saccharomyces cerevisiae* 2031 consisting of 77% carbohydrate and 23% protein [249]. Jagtap et al. (2010) reported a bioemulsifier with 53% protein, 42% polysaccharide, and only 2% lipid from *Acinetobacter* sp. [250]. Mannoproteins are highly soluble in water and can be extracted from the cell wall of *Saccharomyces cerevisiae* in ensuring high yields [251–253]. Thus, Saccharomyces strains represent one of the most important sources of bioemulsifiers produced by low-cost biotechnology methods using water-soluble substrates [254,255]. These sources offer low cost product and a high volume of yeast biomass, which converts into high bioemulsifier yields competitive with synthetic compounds [256].

Hydrophilic mannose polymers covalently bonded to a protein backbone generate an amphiphilic structure that represents the basis of the surface activity and emulsifying activity of mannoproteins. Scientific studies reported the production of large quantities of mannoproteins by *Saccharomyces cerevisiae* that showed excellent emulsifier activity toward several oils, alkanes, and organic solvents. Mannoproteins extracted from *S. cerevisiae* are effective bioemulsifiers [251]. Thus, these proteins are able to form stable emulsions with various hydrocarbons, organic solvents and waste oils, suggesting their potential applications as cleaning agents [241] (Table 4).

Table 4. Polymeric biosurfactants with high molecular weight. N.r. = not reported.

Biosurfactant.	Producing Strain	Properties	Structure	Toxicity
Emulsan	*Acinetobacter calcoaceticus*	Emulsifying agent [238]	Anionic, D-galactosamine-containing, polysaccharide backbone presenting fatty acid side chains and a non-covalently bound protein [231,232]	n.r.
Liposan	*Candida lipolytica*	Water soluble emulsifying agent [240]	Complex of a proteic moiety and a heteropolysaccharide portion composed of galactose, galactosamine, glucose and galacturonic acid [5]	n.r.
Alasan	*Acineto radioresistens*	Anionic emulsifying agent [241,242].	Anionic complex of polysaccharides, alanine and proteins [241]	n.r.
Biodispersan	*Acinetobacter calcoaceticus*	Nondialyzable dispersing agent [243]	Anionic heteropolysaccharide [244]	n.r.
Polysaccharide Protein Complex	*Lactococcus lactis*	Emulsifying activity [246] Antimicrobial activity [246] Antiadhesive activity [248]	Complex of protein and polysaccharides containing phosphate groups [248]	n.r.
Mannoproteins	*Saccharomyces cervisiae*	Emulsifying agent [249,251]	Amphiphilic glycoproteins. Protein moiety attached to a polymeric carbohydrate fraction (mannopyranose) [241,249,250]	n.r.

4. Discussion

Biosurfactants have certain advantages over chemically synthesized surfactants such as better biodegradability, superior environmental compatibility, and in some cases higher foaming property and conserved activity even at high temperature and pH. These molecules present an encouraging low toxicology profile, appropriate for use not only in cosmetics, but also in food and pharmaceutical fields, but they have also some disadvantages like very low production yield, difficulty in obtaining pure and standardized products, and expensive production processes.

In this context it should be emphasized that, to date, there are no complete toxicological studies on many of the biosurfactants presented in this review, especially on polymeric biosurfactants, corynomycolic acids, spiculisporic acid salts, and phosphatidylethanolamines. This fact represents an important missing piece in the study of this very interesting class of compounds, because their natural origin is not sufficient to warrant their safety and stability.

As reported in this review, nowadays, a vast knowledge about the chemical characterization and biological activities of biosurfactants is available; the research at this point must focus on issues related to lacking toxicology data and improvement of production yields. Ameliorations in these aspects can lead to the improvement necessary to exploit the use in large-scale sustainable cosmetic production, but also to an extension to other applications, as detergent-like, for the purification of sites contaminated with various types of hydrocarbons (bioremediation) that require non-pollutant agents, low toxicity for environment, adequate quantities, and low production costs. Moreover, this interesting class of molecules is endowed by multiple activities; such are for example the antimicrobial properties that make them interesting multifunctional ingredients. The multifunctional behavior is particularly desired in the sustainable cosmetic field were short INCI are preferred to the respect of the long one, as more the ingredients as more the risk of allergies, intolerance, environmental pollution and or incompatibility between ingredients. In these regards, antimicrobial activity is one of the most appealing properties for a multifunctional ingredient. Beside this not despicable is also the capability to work as penetration enhancer or delivery systems, especially in nanoformulation, participating to particle formation as an alternative to synthetic Tween and Span [257].

Focusing on their cosmetic properties, biosurfactants can be used as active ingredients in skin and hair care products but also as "green" alternative to traditional surfactants. Distinctly, Rincón-Fontán et al. (2018) have been studying a synergic effect between mica minerals and a biosurfactants obtained from corn steep liquor in terms of improved photoprotection against ultraviolet radiation. Interestingly, UV adsorption properties of the formulation has been evaluated through SPF (Sun Protection Factor):

bioactive compound itself registered a SPF value of 2.67, comparable to other natural compound, and gave better adsorption in particular when the mica did not provide it by itself [258].

This innovative and promising activity may be suitable in eco-friendly sunscreen products in which antioxidant property given by biosurfactant represent an additional benefit to provide the photoprotective action.

However, further researches are required toward sustainable processes in terms of industrial costs of production that nowadays are from 3 to 10 times higher than the equivalent traditional one. In this way, it is suggested to approach the possibility of "low-cost biosurfactants" production from agroindustrial by-products. A number of renewable sources (such as crude glycerol from biodiesel refinery, lignocellulose, animal fat, residues from food or oil processing) have been used as raw material in the production processes being an excellent sugar and lipid sources for biosurfactant production.

At the same time, agroindustry by-products can be used as substrate in solid-state fermentation (SSF), rather than in the popular submerged fermentations in stirred tank reactors (STR), to reduce foaming, a negative aspect during fermentation because of reducing bioavailability of nutrients and consequently the yield, with the minimum amount of free water in the system, due to its simplicity and cost [259].

All this aspects gives an added value to the use of biosurfactants as it allows to embrace the concept of "circular economy" and "zero-waste" very popular in this days, to prevent waste generation or otherwise the reuse for bio-economy purposes.

Author Contributions: P.B. was principally responsible for the drafting of the manuscript. H.-R.A.-A. was principally responsible for ideation toghether with S.M., A.B. took care of manuscript revision, merging of contributions by each co-author and re-drafting. E.C., H.S.Z., M.G.G., M.K., S.Z., and P.G. collected, organized, and selected summarized the material from different sources. S.V. was principally responsible for cosmetic application and revision of the final draft. S.M. coordinated and supervised the whole work. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding but we thank the Lamberti Group Spa (Mialn, Italy) and ISTEC-CNR (Faenza, Italy) for providing the PhD scholarship to E.C.

Acknowledgments: The authors would like to thank Elisa Durini for the valuable critical re-reading of the manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Kitamoto, D.; Isoda, H.; Nakahara, T. Functions and potential applications of glycolipid biosurfactants from energy-saving materials to gene delivery carrier. *J. Biosci. Bioeng.* **2002**, *94*, 187. [CrossRef]
2. Vance-Harrop, M.H.; de Gusmão, N.B.; de Campos-Takaki, G.M. New bioemulsifiers produced by *Candida lipolytica* using D-glucose and babassu oil as carbon sources. *Braz. J. Microbiol.* **2003**, *34*, 120–123. [CrossRef]
3. De, S.; Malik, S.; Ghosh, A.; Saha, R.; Saha, B. A review on natural surfactants. *RSC Adv.* **2015**, *5*, 65757–65767. [CrossRef]
4. Coronel León, J.; Manresa Presas, M.Á.; Marqué s Villavecchia, A.M. Lichenysin production and application in the pharmaceutical field. In *Recent Advances in Pharmaceutical Sciences VI*; Muñoz Torrero, D., Domínguez García, À., Manresa Presas, M.Á., Eds.; Research Signpost, 37/661 (2), Fort P.O. Trivandrum-695 023; Research Signpost: Kerala, India, 2016; Volume 9, p. 147. ISBN 978-81-308-0566-5.
5. Vijayakumar, S.; Saravanan, V. Biosurfactants-types, sources and applications. *Res. J. Microbiol.* **2015**, *10*, 181–192.
6. Burger, M.M.; Glaser, L.; Burton, R.M. The enzymatic synthesis of a rhamnose-containing glycolipid by extracts of Pseudomonas aeruginosa. *J. Biol. Chem.* **1963**, *238*, 2595–2602. [PubMed]
7. Guerra-Santos, L.H.; Käppeli, O.; Fiechter, A. Dependence of *Pseudomonas aeruginosa* continous culture biosurfactant production on nutritional and environmental factors. *Appl. Microbiol. Biotechnol.* **1986**, *24*, 443–448. [CrossRef]

8. Ristau, E.; Wagner, F. Formation of novel anionic trehalosetetraesters from *Rhodococcus erythropolis* under growth limiting conditions. *Biotechnol. Lett.* **1983**, *5*, 95–100. [CrossRef]
9. Kilburn, J.O.; Takayama, K. Effects of ethambutol on accumulation and secretion of trehalose mycolates and free mycolic acid in Mycobacterium smegmatis. *Antimicrob. Agents Chemother.* **1981**, *20*, 401–404. [CrossRef]
10. Kretschmer, A.; Bock, H.; Wagner, F. Chemical and physical characterization of interfacial-active lipids from Rhodococcus erythropolis grown on n-alkanes. *Appl. Environ. Microbiol.* **1982**, *44*, 864–870. [CrossRef]
11. Rodrigues, L.R. Microbial surfactants: Fundamentals and applicability in the formulation of nano-sized drug delivery vectors. *J. Colloid Interface Sci.* **2015**, *449*, 304–316. [CrossRef]
12. Satpute, S.K.; Banpurkar, A.G.; Dhakephalkar, P.K.; Banat, I.M.; Chopade, B.A. Methods for investigating biosurfactants and bioemulsifiers: A review. *Crit. Rev. Biotechnol.* **2010**, *30*, 127–144. [CrossRef] [PubMed]
13. Vecino, X.; Cruz, J.M.; Moldes, A.B.; Rodrigues, L.R. Biosurfactants in cosmetic formulations: Trends and challenges. *Crit. Rev. Biotechnol.* **2017**, *37*, 911–923. [CrossRef] [PubMed]
14. Desai, J.D.; Banat, I.M. Microbial production of surfactants and their commercial potential. *Microbiol. Mol. Biol. Rev.* **1997**, *61*, 47–64. [CrossRef]
15. Kruglyakov, P.M. *Hydrophile-Lipophile Balance of Surfactants and Solid Particles: Physicochemical Aspects and Applications*; Elsevier: Amsterdam, The Netherlands, 2000; ISBN 9780444502575.
16. Maneerat, S. Biosurfactants from marine microorganisms. *Songklanakarin J. Sci. Technol.* **2005**, *27*, 1263–1272.
17. Rosen, M.J. Characteristic features of surfactants. In *Surfactants Interfacial Phenom*, 4th ed.; Rosen, M.J., Kunjappu, J.T., Eds.; John Wiley & Sons Ltd.: New York, NY, USA, 2012; Volume 4, pp. 1–37.
18. Cameotra, S.S.; Makkar, R.S. Recent applications of biosurfactants as biological and immunological molecules. *Curr. Opin. Microbiol.* **2004**, *7*, 262–266. [CrossRef] [PubMed]
19. Mohan, P.K.; Nakhla, G.; Yanful, E.K. Biokinetics of biodegradation of surfactants under aerobic, anoxic and anaerobic conditions. *Water Res.* **2006**, *40*, 533–540. [CrossRef]
20. Fakruddin, M. Biosurfactant: Production and application. *J. Pet. Environ. Biotechnol.* **2012**, *3*, 2.
21. Bujaka, T.; Wasilewskib, T.; Nizioł-Łukaszewska, Z. Role of macromolecules in the safety of use of body wash cosmetics. *Colloid Surfaces B* **2015**, *135*, 497–503. [CrossRef]
22. Benincasa, M. Rhamnolipid produced from agroindustrial wastes enhances hydrocarbon biodegradation in contaminated soil. *Curr. Microbiol.* **2007**, *54*, 445–449. [CrossRef]
23. Voet, D.; Voet, J.G.; Pratt, C.W. *Fundamentals of Biochemistry: Life at the Molecular Level*; John Wiley & Sons: New York, NY, USA, 2013; Volume 32, p. 1077.
24. Mnif, I.; Ghribi, D. Glycolipid biosurfactants: Main properties and potential applications in agriculture and food industry. *J. Sci. Food Agric.* **2016**, *96*, 4310–4320. [CrossRef]
25. Lunaa, J.M.; Rufinoa, R.D.; Campos-Takakia, G.M.; Sarubbo, L.A. Properties of the biosurfactant produced by Candida sphaerica cultivated in low-cost substrates. *Chem. Eng.* **2012**, *27*, 67–72.
26. Saimmai, A.; Rukadee, O.; Onlamool, T.; Sobhon, V.; Maneerat, S. Isolation and functional characterization of a biosurfactant produced by a new and promising strain of Oleomonas sagaranensis AT. *World J. Microbiol. Biotechnol.* **2012**, *28*, 2973. [CrossRef]
27. Hayder, N.H.; Alaa, S.; Abdulmalik, H. Optimized conditions for bioemulsifier production by local Streptomyces sp. SS 20 isolated from hydrocarbon contaminated soil. *Rom. Biotechnol. Lett.* **2014**, *19*, 8979–8993.
28. 28. Kim, H.S.; Jeon, J.W.; Kim, S.B.; Oh, H.M.; Kwon, T.J.; Yoon, B.D. Surface and physic-chemical properties of a glycolipid biosurfactant, mannosylerythritol lipid, from *Candida Antarctica*. *Biotechnol. Lett.* **2002**, *24*, 1637–1641. [CrossRef]
29. Lourith, N.; Kanlayavattanakul, M. Natural surfactants used in cosmetics: Glycolipids. *Int. J. Cosmet. Sci.* **2009**, *31*, 255–261. [CrossRef]
30. Fukuoka, T.; Morita, T.; Saika, A.; Habe, H. Application of Glycolipid Biosurfactants as Surface Modifiers in Bioplastics. *J. Oleo Sci.* **2018**, *67*, 1609–1616. [CrossRef] [PubMed]
31. Vedaraman, N.; Venkatesh, N. The effect of medium composition on the production of sophorolipids and the tensiometric properties by Starmerella bombicola MTCC 1910. *Pol. J. Chem. Technol.* **2010**, *12*, 9–13. [CrossRef]
32. Kiran, G.S.; Thomas, T.A.; Selvin, J. Production of a new glycolipid biosurfactant from marine Nocardiopsis lucentensis MSA04 in solid-state cultivation. *Colloids Surf. B Biointerfaces* **2010**, *78*, 8–16. [CrossRef] [PubMed]

33. Nalini, S.; Parthasarathi, R. Production and characterization of rhamnolipids produced by Serratia rubidaea SNAU02 under solid–state fermentation and its application as biocontrol agent. *Bioresour. Technol.* **2014**, *173*, 231–238. [CrossRef]
34. Abbasi, H.; Sharafi, H.; Alidost, L.; Bodagh, A.; Zahiri, H.S.; Noghabi, K.A. Response surface optimization of biosurfactant produced by *Pseudomonas aeruginosa* MA01 isolated from spoiled apples. *Prep. Biochem. Biotechnol.* **2013**, *43*, 398–414. [CrossRef]
35. Shao, Z. Trehalolipids. *Biosurfactants Microbiol. Monogr.* **2011**, *20*, 121–143.
36. Yuan, X.; Ling, H.; Chengjun, W.; Yiwe, G.; Zhi, J.; Chaoyue, L.; Shaojing, J.; Shanshan, L. *Labrys* sp. Strain for Producing Biosurfactant. Patent CN109022329, 10 September 2018.
37. Kuyukina, M.S. In vitro immunomodulating activity of biosurfactant glycolipid complex from Rhodococcus ruber. *Bull. Exp. Biol. Med.* **2007**, *144*, 326–330. [CrossRef] [PubMed]
38. Gein, S.V.; Kuyukina, M.S.; Ivshina, I.B.; Baeva, T.A.; Chereshnev, V.A. In vitro cytokine stimulation assay for glycolipid biosurfactant from Rhodococcusruber: Role of monocyte adhesion. *Cytotechnology* **2011**, *63*, 559–566. [CrossRef] [PubMed]
39. Saeki, H.; Sasaki, M.; Komatsu, K.; Miura, A.; Matsuda, H. Oil spill remediation by using the remediation agent JE1058BS that contains a biosurfactant produced by *Gordonia* sp. strain JE-1058. *Bioresour. Technol.* **2009**, *100*, 572–577. [CrossRef]
40. Munstermann, B.; Poremba, K.; Lang, S.; Wagner, F. Studies on environmental compatibility: Influence of (bio) surfactants on marine microbial and enzymatic systems. In Proceedings of the International Symposium on Soil Decontamination Using Biological Processes, Karlsruhe, Germany, 6–9 December 1992.
41. Flasz, A.; Rocha, C.A.; Mosquera, B. A comparative study of the toxicity of a synthetic surfactant and one produced by Pseudomonas aeruginosa ATCC. *Med. Sci. Res.* **1998**, *26*, 181–185.
42. Das, K.; Mukherjee, A.K. Characterization of biochemical properties and biological activities of biosurfactants produced by Pseudomonas aeruginosa mucoid and non-mucoid strains isolated from hydrocarbon-contaminated soil samples. *Appl. Microbiol. Biotechnol.* **2005**, *69*, 192–199. [CrossRef]
43. Morita, T.; Fukuoka, T.; Imura, T.; Kitamoto, D. Production of mannosylerythritol lipids and their application in cosmetics. *Appl. Microbiol. Biotechnol.* **2013**, *97*, 4691–4700. [CrossRef] [PubMed]
44. Lang, S.; Wullbrandt, D. Rhamnose lipids-biosynthesis, microbial production and application potential. *Appl. Microbiol. Biotechnol.* **1999**, *51*, 22–32. [CrossRef]
45. Soberon-Chavez, G.; Aguirre-Ramírez, M.; Sanchez, R. The Pseudomonas aeruginosa RhlA enzyme is involved in rhamnolipid and polyhydroxyalkanoate production. *J. Ind. Microbiol. Biotechnol.* **2005**, *32*, 675–677. [CrossRef]
46. Abdel-Mawgoud, A.M.; Lépine, F.; Déziel, E. Rhamnolipids: Diversity of structures, microbial origins and roles. *Appl. Microbiol. Biotechnol.* **2010**, *86*, 1323–1336. [CrossRef]
47. Ochsner, U.A.; Fiechter, A.; Reiser, J. Isolation, characterization, and expression in Escherichia coli of the Pseudomonas aeruginosa rhlAB genes encoding a rhamnosyltransferase involved in rhamnolipid biosurfactant synthesis. *J. Biol. Chem.* **1994**, *26*, 19787–19795.
48. Cabrera-Valladares, N.; Richardson, A.P.; Olvera, C.; Treviño, L.G.; Déziel, E.; Lépine, F.; Soberón-Chávez, G. Monorhamnolipids and 3-(3-hydroxyalkanoyloxy) alkanoic acids (HAAs) production using Escherichia coli as a heterologous host. *Appl. Microbiol. Biotechnol.* **2006**, *73*, 187–194. [CrossRef] [PubMed]
49. Rahim, R.; Ochsner, U.A.; Olvera, C.; Graninger, M.; Messner, P.; Lam, J.S.; Soberon-Chavez, G. Cloning and functional characterization of the Pseudomonas aeruginosa rhlC gene that encodes rhamnosyltransferase 2, an enzyme responsible for di-rhamnolipid biosynthesis. *Mol. Microbiol.* **2001**, *40*, 708–718. [CrossRef] [PubMed]
50. Nguyen, T.T.; Youssef, N.H.; McInerney, M.J.; Sabatini, D.A. Rhamnolipid biosurfactant mixtures for environmental remediation. *Water Res.* **2008**, *42*, 1735–1743. [CrossRef]
51. Nguyen, T.T.; Sabatini, D.A. Formulating alcohol-free microemulsions using rhamnolipid biosurfactant and rhamnolipid mixtures. *J. Surfactants Deterg.* **2009**, *12*, 109–115. [CrossRef]
52. Syldatk, C.; Lang, S.; Wagner, F.; Wray, V.; Witte, L. Chemical and physical characterization of four interfacial-active rhamnolipids from Pseudomonas spec. DSM 2874 grown on n-alkanes. *Z. Für Nat. C* **1985**, *40*, 51–60. [CrossRef]
53. Kosaric, N.; Cairns, W.L.; Gray, N.C.C. *Biosurfactants and Biotechnology*; Surfactant Science Series (USA); Marcel Dekker: New York, NY, USA, 1987.

54. Parra, J.L.; Guinea, J.; Manresa, M.A.; Robert, M.; Mercadé, M.E.; Comelles, F.; Bosch, M.P. Chemical characterization and physicochemical behavior of biosurfactants. *J. Am. Oil Chem. Soc.* **1989**, *66*, 141–145. [CrossRef]
55. Xie, Y.; Li, Y.; Ye, R. Effect of alcohols on the phase behavior of microemulsions formed by a biosurfactant-rhamnolipid. *J. Dispers. Sci. Technol.* **2005**, *26*, 455–461. [CrossRef]
56. Pornsunthorntawee, O.; Wongpanit, P.; Chavadej, S.; Abe, M.; Rujiravanit, R. Structural and physicochemical characterization of crude biosurfactant produced by *Pseudomonas aeruginosa* SP4 isolated from petroleum-contaminated soil. *Bioresour. Technol.* **2008**, *99*, 1589–1595. [CrossRef]
57. Lovaglio, R.B.; dos Santos, F.J.; Jafelicci, J.M.; Contiero, J. Rhamnolipid emulsifying activity and emulsion stability: pH rules. *Colloids Surf. B Biointerfaces* **2011**, *85*, 301–305. [CrossRef]
58. Scheibenbogen, K.; Zytner, R.G.; Lee, H.; Trevors, J.T. Enhanced removal of selected hydrocarbons from soil by Pseudomonas aeruginosa UG2 biosurfactants and some chemical surfactants. *J. Chem. Technol. Biotechnol. Int. Res. Process Environ. Clean Technol.* **1994**, *59*, 53–59.
59. Hirata, Y.; Ryu, M.; Oda, Y.; Igarashi, K.; Nagatsuka, A.; Furuta, T.; Sugiura, M. Novel characteristics of sophorolipids, yeast glycolipid biosurfactants, as biodegradable low–foaming surfactants. *J. Biosci. Bioeng.* **2009**, *108*, 142–146. [CrossRef] [PubMed]
60. Bai, G.; Brusseau, M.L.; Miller, R.M. Biosurfactant–enhanced removal of residual hydrocarbon from soil. *J. Contam. Hydrol.* **1997**, *25*, 157–170. [CrossRef]
61. Piljac, T.; Piljac, G. Use of rhamnolipids in wound healing, treating burn shock, atherosclerosis, organ transplants, depression, schizophrenia and cosmetics. Patent WO1999043334 A1, 2 September 1999.
62. Desanto, K. Rhamnolipid-Based Formulations. World Patent WO2008013899A2, 31 January 2008.
63. Bloomberg, G. Designing proteins as emulsifiers. *Lebensmitteltechnologie* **1991**, *24*, 130–131.
64. Khaje Bafghi, M.; Fazaelipoor, M.H. Application of rhamnolipid in the formulation of a detergent. *J. Surfactants Deterg.* **2012**, *15*, 679–684. [CrossRef]
65. Chrzanowski, Ł.; Dziadas, M.; Ławniczak, Ł.; Cyplik, P.; Białas, W.; Szulc, A.; Lisiecki, P.; Jeleń, H. Biodegradation of rhamnolipids in liquid cultures: Effect of biosurfactant dissipation on diesel fuel/B20 blend biodegradation efficiency and bacterial community composition. *Bioresour. Technol.* **2012**, *111*, 328–335. [CrossRef]
66. Pei, X.; Zhan, X.; Zhou, L. Effect of biosurfactant on the sorption of phenanthrene onto original and H2O2–treated soils. *J. Environ. Sci.* **2009**, *21*, 1378–1385. [CrossRef]
67. Fiebig, R.; Schulze, D.; Chung, J.C.; Lee, S.T. Biodegradation of polychlorinated biphenyls (PCBs) in the presence of a bioemulsifier produced on sunflower oil. *Biodegradation* **1997**, *8*, 67–75. [CrossRef]
68. Poremba, K.; Gunkel, W.; Lang, S.; Wagner, F. Toxicity testing of synthetic and biogenic surfactants on marine microorganisms. *Environ. Toxicol. Water Qual.* **1991**, *6*, 157–163. [CrossRef]
69. Schilling, M.; Hartung, C.; Cabirol, F.; Schafer, S.; Alef, P. Mixture Composition Comprising Rhamnolipids. Patent US10292924B2, 21 May 2019.
70. Siegmund, L.; Philp, J.C. Surface-active lipids in rhodococci. *Antonie Van Leeuwenhoek* **1998**, *74*, 59–70.
71. Kurtzman, C.P.; Price, N.P.J.; Ray, K.J.; Kuo, T.M. Production of sophorolipid biosurfactants by multiple species of the Starmerella (Candida) bombicola yeast clade. *FEMS Microbiol. Lett.* **2010**, *311*, 140–146. [CrossRef] [PubMed]
72. White, D.A.; Hird, L.C.; Ali, S.T. Production and characterization of a trehalolipid biosurfactant produced by the novel marine bacterium *Rhodococcus* sp., strain PML026. *Appl. Microbiol.* **2013**, *115*, 744–755. [CrossRef]
73. Asselineau, C.; Asselineau, J. Trehalose-containing glycolipids. *Prog. Chem. Fats Other Lipids* **1978**, *16*, 59–99. [CrossRef]
74. Rosenberg, E.; Ron, E.Z. High-and low-molecular-mass microbial surfactants. *Appl. Microbiol. Biotechnol.* **1999**, *52*, 154–162. [CrossRef]
75. Franzetti, A.; Gandolfi, I.; Bestetti, G.; Smyth, T.J.P.; Banat, I.M. Production and applications of trehalose lipid biosurfactants. *Eur. J. Lipid Sci. Technol.* **2010**, *112*, 617–627. [CrossRef]
76. Azuma, M.; Suzutani, T.; Sazaki, K.; Yoshida, I.; Sakuma, T.; Yoshida, T. Role of interferon in the augmented resistance of trehalose-6, 6′-dimycolate-treated mice to influenza virus infection. *J. Gen. Virol.* **1987**, *68*, 835–843. [CrossRef] [PubMed]

77. Vollbrecht, E.; Rau, U.; Lang, S. Microbial conversion of vegetable oils into surface-active di-, tri-, and tetrasaccharide lipids (biosurfactants) by the bacterial strain *Tsukamurella*spec. *Lipid/Fett* **1999**, *101*, 389–394. [CrossRef]
78. Marqués, A.M.; Pinazo, A.; Farfan, M.; Aranda, F.J.; Teruel, J.A.; Ortiz, A.; Manresa, A.; Espuny, M.J. The physicochemical properties and chemical composition of trehalose lipids produced by Rhodococcus erythropolis 51T7. *Chem. Phys. Lipids* **2009**, *158*, 110–117. [CrossRef]
79. Christova, N.; Lang, S.; Wray, V.; Kaloyanov, K.; Konstantinov, S.; Stoineva, I. Production, Structural Elucidation, and In Vitro Antitumor Activity of Trehalose Lipid Biosurfactant from Nocardia farcinica Strain. *J. Microbiol. Biotechnol.* **2015**, *25*, 439. [CrossRef]
80. De Oliveira, M.R.; Magri, A.; Baldo, C.; Camilios-Neto, D.; Minucelli, T.; Celligoi, M.A.P.C. Sophorolipids a promising biosurfactant and it' s applications. *Int. J. Adv. Biotechnol. Res.* **2015**, *6*, 161–174.
81. Thanomsub, B.; Watcharachaipong, T.; Chotelersak, K.; Arunrattiyakorn, P.; Nitoda, T.; Kanzaki, H. Monoacylglycerols: Glycolipid biosurfactants produced by a thermotolerant yeast, *Candida ishiwadae*. *J. Appl. Microbiol.* **2004**, *96*, 588–592. [CrossRef] [PubMed]
82. Hua, Z.; Chen, Y.; Du, G.; Chen, J. Effects of biosurfactants produced by *Candida antarctica* on the biodegradation of petroleum compounds. *World J. Microbiol. Biotechnol.* **2004**, *20*, 25–29. [CrossRef]
83. Chandran, P.; Das, N. Biosurfactant production and diesel oil degradation by yeast species *Trichosporon asahii* isolated from petroleum hydrocarbon contaminated soil. *Int. J. Eng. Sci. Technol.* **2010**, *2*, 6942–6953.
84. Chandankere, R.; Yao, J.; Cai, M.; Masakorala, K.; Jain, A.K.; Choi, M.M.F. Properties and characterization of biosurfactant in crude oil biodegradation by bacterium *Bacillus methylotrophicus* USTBa. *Fuel* **2014**, *122*, 140–148. [CrossRef]
85. Martinez, V.; Corsini, E.; Mitjans, M.; Pinazo, A.; Vinardell, M.P. Evaluation of eye and skin irritation of arginine-derivative surfactants using different in vitro endpoints as alternatives to the in vivo assays. *Toxicol. Lett.* **2006**, *164*, 259–267. [CrossRef]
86. Cooper, D.G.; Paddock, D.A. Torulopsis petrophilum and surface activity. *Appl. Environ. Microbiol.* **1983**, *46*, 1426. [CrossRef] [PubMed]
87. Van Bogaert, I.N.; Zhang, J.; Soetaert, W. Microbial synthesis of sophorolipids. *Process. Biochem.* **2011**, *46*, 821–833. [CrossRef]
88. De Rienzo, M.A.D.; Banat, I.M.; Dolman, B.; Winterburn, J.; Martin, P.J. Sophorolipid biosurfactants: Possible uses as antibacterial and antibiofilm agent. *New Biotechnol.* **2015**, *32*, 720–726. [CrossRef]
89. Kim, K.J.; Kim, Y.B.; Lee, B.S.; Shin, D.H.; Kim, E.K. Characteristics of sophorolipid as an antimicrobial agent. *J. Microbiol. Biotechnol.* **2002**, *12*, 235–241.
90. Vanittanakom, N.; Loeffler, W.; Koch, U.; Jung, G. Fengycin-a novel antifungal lipopeptide antibiotic produced by *Bacillus subtilis* F-29. *J. Antibiot.* **1986**, *39*, 888–901. [CrossRef]
91. Cox, T.F.; Crawford, R.J.; Gregory, L.G.; Hosking, S.L.; Kotsakis, P. Mild to the skin, foaming detergent composition. U.S. Patent 8,563,490, 22 November 2013.
92. Kulkarni, S.; Choudhary, P. Production and isolation of biosurfactant-sophorolipid and its application in body wash formulation. *Asian J. Microbiol. Biotechnol. Environ. Sci.* **2011**, *13*, 217–221.
93. Inoue, S. Biosurfactants in cosmetic applications. In Proceedings of the World Conference on Biotechnology for the Fats and Oils Industry; American Oil Chemists' Society: Champaign, IL, USA, 1988; pp. 206–210.
94. Brown, M.J. Biosurfactants for cosmetic applications. *Int. J. Cosmet. Sci.* **1991**, *13*, 61. [CrossRef]
95. Marchant, R.; Banat, I.M. Biosurfactants: A sustainable replacement for chemical surfactants? *Biotechnol. Lett.* **2012**, *34*, 1597–1605. [CrossRef] [PubMed]
96. Casas, J.A.; Ochoa, F.G. Sophorolipid production by Candida bombicola: Medium composition and culture methods. *J. Biosci. Bioeng.* **1999**, *988*, 488–494. [CrossRef]
97. Guilmanov, V.; Ballistreri, A.; Impallomeni, G.; Gross, R.A. Oxygen transfer rate and sophorose lipid production by Candida bombicola. *Biotechnol. Bioeng.* **2002**, *77*, 489–494. [CrossRef]
98. Krishnaswamy, M.; Subbuchettiar, G.; Kochupappy, R.T.; Panchaksharam, S. Biosurfactants: Properties, commercial production and application. *Curr. Sci.* **2008**, *94*, 00113891.
99. Varvaresou, A.; Iakovou, K. Biosurfactants in cosmetics and biopharmaceuticals. *Lett. Appl. Microbiol.* **2015**, *61*, 214–223. [CrossRef]
100. Inès, M.; Dhouha, G. Glycolipid biosurfactants: Potential related biomedical and biotechnological applications. *Carbohydr. Res.* **2015**, *416*, 59–69. [CrossRef]

101. Lee, Y.J.; Choi, J.K.; Kim, E.K.; Youn, S.H.; Yang, E.J. Field experiments on mitigation of harmful algal blooms using a Sophorolipid Yellow clay mixture and effects on marine plankton. *Harmful Algae* **2008**, *7*, 154–162. [CrossRef]
102. Klosowska-Chomiczewska, I.; Medrzycka, K.; Karpenko, E. Biosurfactants-biodegradability, toxicity, efficiency in comparison with synthetic surfactants. In Proceedings of the Polish-Swedish-Ukrainian Seminar "Research and Application of New Technologies in Wastewater Treatment and Municipal Solid Waste Disposal in Ukraine, Sweden, and Poland", Krakow, Poland, 17–19 October 2011.
103. Cavalero, D.A.; Cooper, D.G. The effect of medium composition on the structure and physical state of sophorolipids produced by *Candida bombicola* ATCC. *J. Biotechnol.* **2003**, *103*, 31–41. [CrossRef]
104. Peng, S.; Li, Z.; Zou, L.; Liu, W.; Chengmei, O.; David, L.; McClements, J. Enhancement of Curcumin Bioavailability by Encapsulation in Sophorolipid–Coated Nanoparticles: An in Vitro and in Vivo Study. *J. Agric. Food Chem.* **2018**, *66*, 1488–1497. [CrossRef] [PubMed]
105. Morita, T.; Kitagawa, M.; Suzuki, M.; Yamamoto, S.; Sogabe, A.; Yanagidani, S.; Imura, T.; Fukuoka, T.; Kitamoto, D. Characterization of the genus *Pseudozyma* by the formation of glycolipid biosurfactants, mannosylerythritol lipids. *FEMS Yeast Res.* **2007**, *7*, 286–292. [CrossRef] [PubMed]
106. Morita, T.; Fukuoka, T.; Imura, T.; Kitamoto, D. Production of glycolipid biosurfactants by basidiomycetous yeasts. *Biotechnol. Appl. Biochem.* **2009**, *53*, 39–49. [CrossRef]
107. Arutchelvi, J.I.; Bhaduri, S.; Uppara, P.V.; Doble, M. Mannosylerythritol lipids: A review. *J. Ind. Microbiol. Biotechnol.* **2008**, *35*, 1559–1570. [CrossRef]
108. Fukuoka, T.; Morita, T.; Konishi, M.; Imura, T.; Sakai, H.; Kitamoto, D. Structural characterization and surface-active properties of a new glycolipid biosurfactant, mono-acylated mannosylerythritol lipid, produced from glucose by *Pseudozyma antarctica*. *Appl. Microbiol. Biotechnol.* **2007**, *76*, 801–810. [CrossRef]
109. Kitamoto, D.; Yanagishita, H.; Shinbo, T.; Nakane, T.; Kamisawa, C.; Nakahara, T. Surface active properties and antimicrobial activities of mannosylerythritol lipids as biosurfactants produced by *Candida Antactica*. *J. Biotechnol.* **1993**, *29*, 91–96. [CrossRef]
110. Takahashi, M.; Morita, T.; Fukuoka, T.; Imura, T.; Kitamoto, D. Glycolipid biosurfactants, mannosylerythritol lipids, show antioxidant and protective effects against H2O2-induced oxidative stress in cultured human skin fibroblasts. *J. Oleo Sci.* **2012**, *61*, 457–464. [CrossRef]
111. Schelges, H.; Tretyakova, M. Exfoliant with biosurfactants. Patent GB2544384, 16 March 2017.
112. Tomotake, M.; Masaru, K.; Michiko, S.; Shuhei, Y.; Atsushi, S.; Shusaku, Y.; Tomohiro, I.; Tokuma, F.; Dai, K. A yeast glycolipid biosurfactant, mannosylerythritol lipid, shows potential moisturizing activity toward cultured human skin cells: The recovery effect of MEL-A on the SDS-damaged human skin cells. *J. Oleo Sci.* **2009**, *58*, 639–642.
113. Shen, L.J.; Zhu, J.; Lu, Q.; Gong, M.; Jin, X. Long Isolation and purification of biosurfactant mannosylerythritol lipids from fermentation broth with methanol/water/n-hexane. *Sep. Purif. Technol.* **2019**, *219*, 1–8. [CrossRef]
114. Morita, T.; Ishibashi, Y.; Fukuoka, T.; Imura, T.; Sakai, H.; Abe, M.; Kitamoto, D. Production of glycolipid biosurfactants, cellobiose lipids, by *Cryptococcus humicola* JCM 1461 and their interfacial properties. *Biosci. Biotechnol. Biochem.* **2011**, *75*, 1597–1599. [CrossRef]
115. Kulakovskaya, T.; Shashkov, A.; Kulakovskaya, E.; Golubev, W.; Zinin, A.; Tsvetkov, Y.; Grachev, A.; Nifantiev, N. Extracellular cellobiose lipid from yeast and their analogues: Structures and fungicidal activities. *J. Oleo Sci.* **2009**, *58*, 133–140. [CrossRef]
116. Teichmann, B.; Linne, U.; Hewald, S.; Marahiel, M.A.; Bölker, M. A biosynthetic gene cluster for a secreted cellobiose lipid with antifungal activity from Ustilago maydis. *Mol. Microbiol.* **2007**, *66*, 525–533. [CrossRef]
117. Fuhrhop, J.H.; Wang, T. Bolaamphiphiles. *Chem. Rev.* **2004**, *104*, 2901–2938. [CrossRef]
118. Hamley, I.W. Lipopeptides: From self-assembly to bioactivity. *Chem. Commun.* **2015**, *51*, 8574–8583. [CrossRef] [PubMed]
119. Jonas, A. Lipoprotein structure. *New Compr. Biochem.* **2002**, *36*, 483–504.
120. Lukic, M.; Pantelic, I.; Savic, S. An overview of novel surfactants for formulation of cosmetics with certain emphasis on acidic active substances. *Tenside Surfactants Deterg.* **2016**, *53*, 7–19. [CrossRef]
121. Förster, T.H.; Waldmann-Laue, M.; Both, W.; Jassoy, C. Lipoprotein creams: Utilization of multifunctional ingredients for the preparation of cosmetic emulsions with excellent skin compatibility. *Int. J. Cosmet. Sci.* **1999**, *21*, 253–264. [CrossRef]

122. Rincón-Fontán, M.; Rodríguez-López, L.; Vecino, X.; Cruza, J.M.; Moldes, A.B. Adsorption of natural surface active compounds obtained from corn on human hair. *RSC Adv.* **2016**, *6*, 63064–63070. [CrossRef]
123. Hajfarajollah, H.; Mokhtarani, B.; Noghabi, K.A. Newly antibacterial and antiadhesive lipopeptide biosurfactant secreted by a probiotic strain, Propionibacterium freudenreichii. *Appl. Biochem. Biotechnol.* **2014**, *174*, 2725–2740. [CrossRef]
124. Gallot, B.; Douy, A. Lipopeptides, Their Preparation and Their Application as Emulsifiers. U.S. Patent 460,015, 4 July 1986.
125. Guglielmo, M.; Montanari, D. Cosmetic Preparation with Anti-Wrinkle Action. Patent WO03000222, 9 January 2001.
126. Montanari, D.; Guglielmo, M. Cosmetic Composition for the Treatment and/or Prevention of Skin Stretch Marks. World Patent 80443, 7 October 2008.
127. Ogawa, Y.; Kawahara, H.; Yagi, N.; Kodaka, M.; Tomohiro, T.; Okada, T.; Konakahara, T.; Okuno, H. Synthesis of a novel lipopeptide with α-melanocyte-stimulating hormone peptide ligand and its effect on liposome stability. *Lipids* **1999**, *34*, 387–394. [CrossRef] [PubMed]
128. Kato, E.; Tsuzuki, T.; Ogata, E. Tocopherol Derivative, Ascorbic Acid Derivative and Skin Preparation for External Use Comprising Surfactant Having Lipopeptides Structure. Japanese Patent JP2005336171, 19 April 2005.
129. Fardis, M.; Cameron, D.R.; Boyd, V.A. Dab9 derivatives of lipopeptide antibiotics and methods of making and using the same. U.S. Patent 712,524, 24 October 2006.
130. Cameron, D.R.; Boyd, V.A.; Leese, R.A. Compositions of lipopeptides antibiotic derivatives and methods of use thereof. World Patent WO2005000878 A, 1 June 2005.
131. Hill, J.; Parr, I.; Morytko, M. Lipopeptides as Antibacterial Agents. US Patent 7335725, 26 February 2008.
132. Alonso, C.; Lucas, R.; Barba, C.; Marti, M.; Rubio, L.; Comelles, F.; Morales, J.C.; Coderch, L.; Parra, J.L. Skin delivery of antioxidant surfactants based on gallic acid and hydroxytyrosol. *J. Pharm. Pharm.* **2015**, *67*, 900–908. [CrossRef] [PubMed]
133. Hwang, Y.H.; Park, B.K.; Lim, J.H.; Kim, M.S.; Song, I.B.; Park, S.C.; Yun, H.I. Evaluation of genetic and developmental toxicity of surfactin C from *Bacillus subtilis* BC1212. *J. Health Sci.* **2008**, *54*, 101–106. [CrossRef]
134. Sanchez, L.; Mitjans, M.; Infante, M.R.; Vinardell, M.P. Potential irritation of lysine derivative surfactants by hemolysis and HaCaT cell viability. *Toxicol. Lett.* **2006**, *161*, 53–60. [CrossRef]
135. Tadashi, Y. Cosmetic composition comprising a and a lipopeptide. World Patent WO2005020950, 26 August 2004.
136. Chen, W.C.; Juang, R.S.; Wei, Y.H. Applications of a lipopeptide biosurfactant, surfactin, produced by microorganisms. *Biochem. Eng. J.* **2015**, *103*, 158–169. [CrossRef]
137. Kumar, M.; León, V.; Materano, A.D.S.; Ilzins, O.A. A halotolerant and thermotolerant *Bacillus* sp. degrades hydrocarbons and produces tension-active emulsifying agent. *World J. Microbiol. Biotechnol.* **2007**, *23*, 211–220. [CrossRef]
138. Makkar, R.S.; Cameotra, S.S. Biosurfactant production by a thermophilic Bacillus subtilis strain. *J. Ind. Microbiol. Biotechnol.* **1997**, *18*, 37–42. [CrossRef]
139. Arima, K.; Kakinuma, A.; Tamura, G. Surfactin, a crystalline peptidelipid surfactant produced by Bacillussubtilis: Isolation, characterization and its inhibition of fibrin clot formation. *Biochem. Biophys. Res. Commun.* **1968**, *31*, 488–494. [CrossRef]
140. Haferburg, D.; Hommel, R.; Claus, R.; Kleber, H.P. Extracellular microbial lipids as biosurfactants. In *Bioproducts*; Springer: Berlin/Heidelberg, Germany, 1986; pp. 53–93.
141. Coronel León, J.; Presas, M.M.; Marqués Villavecchia, A.M. Lichenysin production and application in the pharmaceutical field. *Recent Adv. Pharm. Sci.* **2016**, *9*, 147–163.
142. Bonmatin, J.M.; Labbé, H.; Grangemard, I.; Peypoux, F.; Maget-Dana, R.; Ptak, M.; Michel, G. Production, isolation and characterization of [Leu 4]-and [Ile 4] surfactins from Bacillus subtilis. *Lett. Pept. Sci.* **1995**, *2*, 41–47. [CrossRef]
143. Tsan, P.; Volpon, L.; Besson, F.; Lancelin, J.M. Structure and dynamics of surfactin studied by NMR in micellar media. *J. Am. Chem. Soc.* **2007**, *129*, 1968–1977. [CrossRef] [PubMed]
144. Vollenbroich, D.; Pauli, G.; Ozel, M.; Vater, J. Antimycoplasma properties and application in cell culture of surfactin, a lipopeptide antibiotic from Bacillus subtilis. *Appl. Environ. Microbiol.* **1997**, *63*, 44–49. [CrossRef] [PubMed]

145. Kracht, M.; Rokos, H.; Özel, M.; Kowall, M.; Pauli, G.; Vater, J. Antiviral and hemolytic activities of surfactin isoforms and their methyl ester derivatives. *J. Antibiot.* **1999**, *52*, 613–619. [CrossRef] [PubMed]
146. Sheppard, J.D.; Jumarie, C.; Cooper, D.G.; Laprade, R. Ionic channels induced by surfactin in planar lipid bilayer membranes. *Biochim. Biophys. Acta (BBA)-Biomembr.* **1991**, *1064*, 13–23. [CrossRef]
147. Heerklotz, H.; Seelig, J. Leakage and lysis of lipid membranes induced by the lipopeptide surfactin. *Eur. Biophys. J.* **2007**, *36*, 305–314. [CrossRef]
148. Chen, H.L.; Juang, R.S. Recovery and separation of surfactin from pretreated fermentation broths by physical and chemical extraction. *Biochem. Eng. J.* **2008**, *38*, 39–46. [CrossRef]
149. Chang, C.C.; Chen, W.C.; Ho, T.F.; Wu, H.S.; Wei, Y.H. Development of natural anti-tumor drugs by microorganisms. *J. Biosci. Bioeng.* **2011**, *111*, 501–511. [CrossRef]
150. Seydlová, G.; Svobodová, J. Review of surfactin chemical properties and the potential biomedical applications. *Cent. Eur. J. Med.* **2008**, *3*, 123–133. [CrossRef]
151. Kim, S.D.; Cho, J.Y.; Park, H.J.; Lim, C.R.; Lim, J.H.; Yun, H.I.; Park, S.C.; Kim, S.K.; Rhee, M.H. A comparison of the anti-inflammatory activity of surfactin A, B, C, and D from *Bacillus subtilis*. *J. Microbiol. Biotechnol.* **2006**, *16*, 1656–1659.
152. Wu, Y.S.; Ngai, S.C.; Goh, B.H.; Chan, K.G.; Lee, L.H.; Chuah, L.H. Anticancer Activities of Surfactin and Potential Application of Nanotechnology Assisted Surfactin Delivery. *Front. Pharmacol.* **2017**, *26*, 761. [CrossRef]
153. Mireles, J.R.; Toguchi, A.; Harshey, R.M. *Salmonella enterica* serovar Typhimurium swarming mutants with altered biofilm-forming abilities: Surfactin inhibits biofilm formation. *J. Bacteriol.* **2001**, *183*, 5848–5854. [CrossRef] [PubMed]
154. Sen, R. Surfactin: Biosynthesis, genetics and potential applications. In *Biosurfactants*; Advances in Experimental Medicine and Biology Book Series; Spinger: Berlin/Heidelberg, Germany, 2010; Volume 672, pp. 316–323.
155. Maget–Dana, R.; Thimon, L.; Peypoux, F.; Ptak, M. Surfactin/iturin A interactions may explain the synergistic effect of surfactin on the biological properties of iturin A. *Biochimie* **1992**, *74*, 1047–1051. [CrossRef]
156. Lai, C.C.; Huang, Y.C.; Wei, Y.H.; Chang, J.S. Biosurfactant-enhanced removal of total petroleum hydrocarbons from contaminated soil. *J. Hazard. Mater.* **2009**, *167*, 609–614. [CrossRef] [PubMed]
157. Whang, L.M.; Liu, P.W.G.; Ma, C.C.; Cheng, S.S. Application of biosurfactants, rhamnolipid, and surfactin, for enhanced biodegradation of diesel-contaminated water and soil. *J. Hazard. Mater.* **2008**, *151*, 155–163. [CrossRef]
158. Debois, D.; Fernandez, O.; Franzil, L.; Jourdan, E.; de Brogniez, A.; Willems, L.; Clément, C.; Dorey, S.; De Pauw, E.; Ongena, M. Plant polysaccharides initiate underground crosstalk with bacilli by inducing synthesis of the immunogenic lipopeptide surfactin. *Environ. Microbiol. Rep.* **2015**, *7*, 570–582. [CrossRef]
159. Razafindralambo, H.; Paquot, M.; Baniel, A.; Popineau, Y.; Hbid, C.; Jacques, P.; Thonart, P. Foaming properties of surfactin, a lipopeptide biosurfactant from *Bacillus subtilis*. *J. Am. Oil Chem. Soc.* **1996**, *73*, 149–151. [CrossRef]
160. Razafindralambo, H.; Paquot, M.; Baniel, A.; Popineau, Y.; Hbid, C.; Jacques, P.; Thonart, P. Foaming properties of a natural cyclic lipoheptapeptide belonging to a special class of amphiphilic molecules. *Food Hydrocoll.* **1997**, *11*, 59–62. [CrossRef]
161. Reddy, A.S.; Chen, C.Y.; Chen, C.C.; Jean, J.S.; Fan, C.W.; Chen, H.R.; Wang, J.C.; Nimje, V.R. Synthesis of gold nanoparticles via an environmentally benign route using a biosurfactant. *J. Nanosci. Nanotechnol.* **2009**, *9*, 6693. [CrossRef]
162. Reddy, A.S.; Chen, C.-Y.; Baker, S.C.; Chen, C.-C.; Jean, J.-S.; Fan, C.-W.; Chen, H.R.; Wang, J.C. Synthesis of silver nanoparticles using surfactin: A biosurfactant as stabilizing agent. *Mater. Lett.* **2009**, *63*, 1227. [CrossRef]
163. Singh, B.R.; Dwivedi, S.; Al-Khedhairy, A.A.; Musarrat, J. Synthesis of stable cadmium sulfide nanoparticles using surfactin produced by Bacillus amyloliquifaciens strain KSU-109. *Colloids Surf. B Biointerfaces* **2011**, *85*, 207. [CrossRef]
164. Krishnan, N.; Velramar, B.; Pandiyan, R.; Velu, R.K. Anti-pseudomonal and anti-endotoxic effects of surfactin-stabilized biogenic silver nanocubes ameliorated wound repair in streptozotocin induced diabetic mice. *Artif. Cells Nanomed. Biotechnol.* **2017**, *14*, 1. [CrossRef] [PubMed]

165. Hwang, Y.-H.; Kim, M.-S.; Song, I.-B.; Park, B.-K.; Lim, J.-H.; Park, S.-C.; Yun, H.I. Subacute (28 day) toxicity of Surfactin C, a lipopeptide produced by Bacillus subtilis, in rats. *J. Health Sci.* **2009**, *55*, 351. [CrossRef]
166. Duarte, C.; Gudina, E.J.; Lima, C.F.; Rodrigues, L.R. Effects of biosurfactants on the viability and proliferation of human breast cancer cells. *AMB. Express* **2014**, *4*. [CrossRef] [PubMed]
167. Wu, Q.; Zhia, Y.; Xu, Y. Systematically engineering the biosynthesis of a green biosurfactant T surfactin by *Bacillus subtilis*. *Metab. Eng.* **2019**, *52*, 87–89. [CrossRef] [PubMed]
168. Maget-Dana, R.; Peypoux, F. Iturins, a special class of pore-forming lipopeptides: Biological and physicochemical properties. *Toxicology* **1994**, *87*, 151–174. [CrossRef]
169. Peypoux, F.; Guinand, M.; Michel, G.; Delcambe, L.; Das, B.C.; Varenne, P.; Lederer, E. Isolement de l'acide 3-amino 12-methyl tetradecanoique et de l'acide 3-amino 12-methyl tridecanoique a partir de l'iturine, antibiotique de *Bacillus subtilis*. *Tetrahedron* **1973**, *29*, 3455–3459. [CrossRef]
170. Lichtenberg, D.; Robson, R.J.; Dennis, E.A. Solubilization of phospholipids by detergents structural and kinetic aspects. *Biochim. Biophys. Acta (BBA)-Rev. Biomembr.* **1983**, *737*, 285–304. [CrossRef]
171. Nitschke, M.; Pastore, G.M. Production and properties of a surfactant obtained from *Bacillus subtilis* grown on cassava wastewater. *Bioresour. Technol.* **2006**, *97*, 336–341. [CrossRef]
172. Besson, F.; Peypoux, F.; Michel, G.; Delcambe, L. Characterization of iturin A in antibiotics from various strains of *Bacillus subtilis*. *J. Antibiot.* **1976**, *29*, 1043–1049. [CrossRef]
173. Singh, P.; Cameotra, S.S. Potential applications of microbial surfactants in biomedical sciences. *Trends Biotechnol.* **2004**, *22*, 142–146. [CrossRef]
174. Dang, Y.; Zhao, F.; Liu, X.; Fan, X.; Huang, R.; Gao, W.; Wang, S.; Yang, C. Enhanced production of antifungal lipopeptide iturin A by *Bacillus amyloliquefaciens* LL3 through metabolic engineering and culture conditions optimization. *Microb Cell Fact.* **2019**, *18*. [CrossRef] [PubMed]
175. Steller, S.; Vollenbroich, D.; Leenders, F.; Stein, T.; Conrad, B.; Hofemeister, J.; Jacques, P.; Thonart, P.; Vater, J. Structural and functional organization of the fengycin synthetase multienzyme system from Bacillus subtilis b213 and A1/3. *Chem. Biol.* **1999**, *6*, 31–41. [CrossRef]
176. Schneider, J.; Taraz, K.; Budzikiewicz, H.; Deleu, M.; Thonart, P.; Jacques, P. The structure of two fengycins from *Bacillus subtilis* S499. *Zeitschrift für Naturforschung* **1999**, *54*, 859–866. [CrossRef] [PubMed]
177. Bonmatin, J.M.; Laprévote, O.; Peypoux, F. Diversity among microbial cyclic lipopeptides: Iturins and surfactins. Activity-structure relationships to design new bioactive agents. *Comb. Chem. High. Throughput Screen.* **2003**, *6*, 541–556. [CrossRef]
178. Lang, S. Biological amphiphiles (microbial biosurfactants). *Curr. Opin. Colloid Interface Sci.* **2002**, *7*, 12–20. [CrossRef]
179. Meena, K.R.; Dhima, R. Applications of Lipopeptide (s) from a *Bacillus* sp.: An Overview. *Res. J. Recent Sci.* **2016**, *5*, 50–54.
180. Ongena, M.; Jacques, P. Bacillus lipopeptides: Versatile weapons for plant disease biocontrol. *Trends Microbiol.* **2008**, *16*, 115–125. [CrossRef]
181. Guo, Q.; Dong, L.; Wang, P.; Li, S.; Zhao, W.; Lu, X.; Zhang, X.; Ma, P.J. The PhoR/PhoP two-component system regulates fengycin production in *Bacillus subtilis* NCD-2 under low-phosphate conditions. *J. Integr. Agric.* **2018**, *17*, 149–157. [CrossRef]
182. Cheng, Y.; Ke, W.; Liu, S. Inactivation of phoR or phoP genes has been shown to significantly decrease fengycin production. *J. Microbiol. Immunol. Infect.* **2017**, *50*, 755. [CrossRef]
183. Neu, T.R.; Poralla, K. Emulsifying agents from bacteria isolated during screening for cells with hydrophobic surfaces. *Appl. Microbiol. Biotechnol.* **1990**, *32*, 521–525. [CrossRef]
184. Kochi, M.; Weiss, D.W.; Pugh, L.H.; Groupé, V. Viscosin, a new antibiotic. *Bacteriol. Proc.* **1951**, *1*, 29–30.
185. Groupé, V.; Pugh, L.H.; Weiss, D.; Kochi, M. Observations on antiviral activity of viscosin. *Proc. Soc. Exp. Biol. Med.* **1951**, *78*, 354–358. [CrossRef] [PubMed]
186. Bourinbaiar, A.S.; Coleman, C.F. The effect of gramicidin, a topical contraceptive and antimicrobial agent with anti-HIV activity, against herpes simplex viruses type 1 and 2 in vitro. *Arch. Virol.* **1997**, *142*, 2225–2235. [CrossRef] [PubMed]
187. Anuradha, S.N. Structural and molecular characteristics of lichenysin and its relationship with surface activity. In *Biosurfactants*; Advances in Experimental Medicine and Biology Book Series; Spinger Nature: Cham, Switzerland, 2010; Volume 672, pp. 304–315.

188. Saini, H.S.; Barragán-Huerta, B.E.; Lebrón-Paler, A.; Pemberton, J.E.; Vázquez, R.R.; Burns, A.M.; Marron, M.T.; Seliga, C.J.; Gunatilaka, A.A.L.; Maier, R.M. Efficient Purification of the Biosurfactant Viscosin from Pseudomonas libanensis Strain M9-3 and Its Physicochemical and Biological Properties. *J. Nat. Prod.* **2008**, *71*, 1011–1015. [CrossRef]
189. McInerney, M.J.; Javaheri, M.; Nagle, D.P. Properties of the biosurfactant produced by *Bacillus licheniformis* strain JF-2. *J. Ind. Microbiol.* **1990**, *5*, 95–101. [CrossRef]
190. Yakimov, M.M.; Timmis, K.N.; Wray, V.; Fredrickson, H.L. Characterization of a new lipopeptide surfactant produced by thermotolerant and halotolerant subsurface *Bacillus licheniformis* BAS50. *Appl. Environ. Microbiol.* **1995**, *61*, 1706–1713. [CrossRef]
191. Grangemard, I.; Wallach, J.; Maget-Dana, R.; Peypoux, F. Lichenysin. A more efficient cation chelator than surfactin. *Appl. Biochem. Biotechnol.* **2001**, *90*, 199–210. [CrossRef]
192. Zhu, C.; Xiao, F.; Qiu, Y.; Wang, Q.; He, Z.; Chen, S. Lichenysin production is improved in codY null Bacillus licheniformis by addition of precursor amino acids. *Appl. Microbiol. Biotechnol.* **2017**, *101*, 6375. [CrossRef]
193. Burkhart, B.M.; Gassman, R.M.; Langs, D.A.; Pangborn, W.A.; Duax, W.L.; Pletnev, V. Gramicidin D conformation, dynamics and membrane ion transport. *Pept. Sci.* **1999**, *51*, 129–144. [CrossRef]
194. Krauss, E.M.; Sunney, I.C. Complexation and phase transfer on nucleotides by gramicidin S. *Biochemistry* **1983**, *22*, 4280–4291. [CrossRef] [PubMed]
195. Ainsworth, G.C.; Brown, A.M.; Brownlee, G. Aerosporin, an antibiotic produced by *Bacillus aerosporus* Greer. *Nature* **1947**, *160*, 263. [CrossRef] [PubMed]
196. Satlin, M.J.; Jenkins, S.G. Polymyxins. In *Infectious Diseases*, 4th ed.; Elsevier: Amsterdam, The Netherlands, 2016; pp. 1285–1288.
197. Brownlee, G.; Bushby, S.R.M.; Short, E.I. The chemotherapy and pharmacology of the polymyxins. *Br. J. Pharmacol. Chemother.* **1952**, *7*, 170–188. [CrossRef] [PubMed]
198. Landman, D.; Georgescu, C.; Martin, D.A.; Quale, J. Polymyxins revisited. *Clin. Microbiol. Rev.* **2008**, *21*, 449–465. [CrossRef]
199. Suzuki, T.; Hayashi, K.; Fujikawa, K.; Tsukamoto, K. The chemical structure of polymyxin E: The identities of polymyxin E1 with colistin A and of polymyxin E2 with colistin B. *J. Biochem.* **1965**, *57*, 226–227. [CrossRef]
200. Zavascki, A.P.; Goldani, L.Z.; Li, J.; Nation, R.L. Polymyxin B for the treatment of multidrug–resistant pathogens: A critical review. *J. Antimicrob. Chemother.* **2007**, *60*, 1206–1215. [CrossRef]
201. Peterson, A.A.; Fesik, S.W.; McGroarty, E.J. Decreased binding of antibiotics to lipopolysaccharides from polymyxin-resistant strains of *Escherichia coli* and *Salmonella typhimurium*. *Antimicrob. Agents Chemother.* **1987**, *31*, 230–237. [CrossRef]
202. Gerth, K.; Irschik, H.; Reichenbach, H.; Trowitzsch, W. The myxovirescins, a family of antibiotics from *Myxococcus virescens* (Myxobacterales). *J. Antibiot.* **1982**, *35*, 1454–1459. [CrossRef]
203. Takayama, S.; Yamanaka, S.; Miyashiro, S.; Yokokawa, Y.; Shibai, H. Novel Macrocyclic Antibiotics: Megovalicins, A.; B.; C.; D.; G. and H. *J. Antibiot.* **1988**, *41*, 433–438. [CrossRef]
204. Onishi, N.; Izaki, K.; Takahashi, H. A macrocyclic antibiotic M–230B produced by *Myxococcus xanthus*. *J. Antibiot.* **1984**, *37*, 13–19. [CrossRef]
205. Rosenberg, E.; Vaks, B.; Zuckerberg, A. Bactericidal action of an antibiotic produced by *Myxococcus xanthus*. *Antimicrob. Agents Chemother.* **1973**, *4*, 507–513. [CrossRef] [PubMed]
206. Xiao, Y.; Gerth, K.; Müller, R.; Wall, D. Myxobacterium-produced antibiotic TA (myxovirescin) inhibits type II signal peptidase. *Antimicrob. Agents Chemother.* **2012**, *56*, 2014–2021. [CrossRef] [PubMed]
207. Kaur, R.; Singh, S.K.; Kaur, R.; Kumari, A.; Kaur, R. Myxococcus xanthus: A source of antimicrobials and natural bio-control agent. *Pharma Innov. J.* **2017**, *6*, 260–262.
208. Rosenberg, E.; Porter, J.M.; Nathan, P.N.; Manor, A.; Varon, M. Antibiotic TA: An adherent antibiotic. *Bio/Technol.* **1984**, *2*, 796–799. [CrossRef]
209. Eli, I.; Judes, H.; Varon, M.; Manor, A.; Rosenberg, E. Antibiotic TA—-a new adherent agent for the treatment of periodontal disease. *Refu'at Ha-Shinayim* **1998**, *6*, 14–15.
210. Manor, A.; Eli, I.; Varon, M.; Judes, H.; Rosenberg, E. Effect of adhesive antibiotic TA on plaque and gingivitis in man. *J. Clin. Periodontol.* **1989**, *16*, 621–624. [CrossRef]
211. Schierholz, J.M.; Beuth, J. Implant infections: A haven for opportunistic bacteria. *J. Hosp. Infect.* **2001**, *49*, 87–93. [CrossRef]

212. Simhi, E.; van der Mei, H.C.; Ron, E.Z.; Rosenberg, E.; Busscher, H.J. Effect of the adhesive antibiotic TA on adhesion and initial growth of *E. coli* on silicone rubber. *FEMS Microbiol. Lett.* **2000**, *192*, 97–100. [CrossRef]
213. Cirigliano, M.C.; Carman, G.M. Purification and characterization of liposan, a bioemulsifier from *Candida lipolytica*. *Appl. Environ. Microbiol.* **1985**, *50*, 846–850. [CrossRef]
214. Zajic, J.; Seffens, E.W.; Panchal, C. Biosurfactants. *Crit. Rev. Biotechnol.* **1983**, *1*, 87–107. [CrossRef]
215. Shaw, N. Lipid composition as a guide to the classification of bacteria. In *Advances in Applied Microbiology*; Academic Press Elsevier: Amsterdam, The Netherlands, 1974; Volume 17, pp. 63–108.
216. Asselinean, J. *The Bacterial Lipids*; Holden-Day Inc.: San Francisco, CA, USA, 1966; p. 190.
217. Kates, M. Techniques of lipidology; isolation, analysis and identification of lipids. *Lab. Tech. Biochem. Mol. Biol.* **1972**, *3*, 347–353.
218. Cooper, D.G.; Zajic, J.E. Surface-active compounds from microorganisms. In *Advances in Applied Microbiology*; Academic Press Elsevier: Amsterdam, The Netherlands, 1980; Volume 26, pp. 229–253.
219. Macdonald, C.R.; Cooper, D.G.; Zajic, J.E. Surface-active lipids from Nocardia erythropolis grown on hydrocarbons. *Appl. Environ. Microbiol.* **1981**, *41*, 117–123. [CrossRef] [PubMed]
220. Kiuru, P.; D'Auria, M.V.; Muller, C.D.; Tammela, P.; Vuorela, H.; Yli-Kauhaluoma, J. Exploring marine resources for bioactive compounds. *Planta Med.* **2014**, *80*, 1234–1246. [CrossRef] [PubMed]
221. Wang, R.; Guo, Z.K.; Li, X.M.; Chen, F.X.; Zhan, X.F.; Shen, M.H. Spiculisporic acid analogues of the marine-derived fungus, *Aspergillus candidus* strain HDf2, and their antibacterial activity. *Antonie Van Leeuwenhoek* **2015**, *108*, 215–219. [CrossRef]
222. Tabuchi, T.; Nakamura, I.; Kobayashi, T. Accumulation of the open-ring acid of spiculisporic acid by *Penicillium spiculisporum* in shake culture. *J. Ferment. Technol.* **1977**, *55*, 37.
223. Tabuchi, T.; Nakamura, I.; Kobayashi, T. Factors affecting the production of the open-ring acid of spiculisporic acid by *Penicillium spiculisporum*. *J. Ferment. Technol.* **1977**, *55*, 43–49.
224. Ishigami, Y.; Yamazaki, S.; Gama, Y. Surface active properties of biosoap from spiculisporic acid. *J. Colloid Interface Sci.* **1983**, *94*, 131–139. [CrossRef]
225. Wellner, N.; Diep, T.A.; Janfelt, C.; Hansen, H.S. N-acylation of phosphatidylethanolamine and its biological functions in mammals. *Biochim. Et Biophys. Acta (BBA)-Mol. Cell Biol. Lipids* **2013**, *1831*, 652–662. [CrossRef]
226. Käppeli, O.; Finnerty, W.R. Partition of alkane by an extracellular vesicle derived from hexadecane–grown Acinetobacter. *J. Bacteriol.* **1979**, *140*, 707–712. [CrossRef]
227. Santos, D.K.F.; Rufino, R.D.; Luna, J.M.; Santos, V.A.; Sarubbo, L.A. Biosurfactants: Multifunctional biomolecules of the 21st century. *Int. J. Mol. Sci.* **2016**, *17*, 401. [CrossRef]
228. Casem, M.L. *Case Studies in Cell Biology*; Academic Press Elsevier: Amsterdam, The Netherlands, 2016; Volume 7, pp. 157–192.
229. Van Oss, C.J. *Phagocytic Engulfment and Cell Adhesiveness as Cellular Surface Phenomena*; Marcel Dekker: New York, NY, USA, 1975; ISBN 0824762843.
230. Neufeld, R.J.; Zajic, J.E.; Gerson, D.F. Cell surface measurements in hydrocarbon and carbohydrate fermentations. *Appl. Environ. Microbiol.* **1980**, *39*, 511–517. [CrossRef] [PubMed]
231. Neufeld, R.J.; Zajic, J.E. The surface activity of Acinetobacter calcoaceticus sp. 2cabiotechnology. *Bioengineering* **1984**, *26*, 1108–1113.
232. Zuckerberg, A.; Diver, A.; Peeri, Z.; Gutnick, D.L.; Rosenberg, E. Emulsifier of Arthrobacter RAG-1: Chemical and physical properties. *Appl. Environ. Microbiol.* **1979**, *37*, 414–420. [CrossRef] [PubMed]
233. Belsky, I.; Gutnick, D.L.; Rosenberg, E. Emulsifier of Arthrobacter RAG-1: Determination of emulsifier-bound fatty acids. *FEBS Lett.* **1979**, *101*, 175–178. [PubMed]
234. Rosenberg, E. Surface-Active properties of Acinetobacter exopolysaccharides. In *Bacterial Outer Membranes as Model Systems*; John Wiley & Sons: New York, NY, USA, 1986.
235. Zosim, Z.; Gutnick, D.; Rosenberg, E. Properties of hydrocarbon-in-water emulsions stabilized by Acinetobacter RAG-1 emulsan. *Biotechnol. Bioeng.* **1982**, *24*, 281–292. [CrossRef]
236. Pines, O.; Gutnick, D.L. Relationship between phage resistance and emulsan production, interaction of phages with the cell-surface of *Acinetobacter calcoaceticus*. *RAG Arch. Microbiol.* **1981**, *130*, 129–133. [CrossRef]
237. Kaplan, N.; Rosenberg, E. Exopolysaccharide distribution of and bioemulsifier production by *Acinetobacter calcoaceticus* BD4 and BD413. *Appl. Environ. Microbiol.* **1982**, *44*, 1335–1341. [CrossRef]
238. Gautam, K.K.; Tyagi, V.K. Microbial surfactants: A review. *J. Oleo Sci.* **2006**, *55*, 155–166. [CrossRef]

239. Yi, G.; Son, J.; Yoo, J.; Park, C.; Koo, H. Emulsan-based nanoparticles for in vivo drug delivery to tumors. *Biochem. Biophys. Res. Commun.* **2019**, *508*, 326–331. [CrossRef]
240. Chakrabarti, S. Bacterial Biosurfactant: Characterization, Antimicrobial and Metal Remediation Properties. Ph.D. Thesis, National Institute of Technology, Rourkela, India, 2012.
241. Uzoigwe, C.; Burgess, J.G.; Ennis, C.J.; Rahman, P.K.S.M. Bioemulsifiers are not biosurfactants and require different screening approaches. *Front. Microbiol.* **2015**, *6*, 245. [CrossRef]
242. Rosenberg, E.; Ron, E.Z. Bioemulsans: Surface-active Polysaccharide-containing Complexes. *Biopolym. Online Biol. Chem. Biotechnol. Appl.* **2005**, *5*. [CrossRef]
243. Rosenberg, E.; Rubinovitz, C.; Gottlieb, A.; Rosenhak, S.; Ron, E.Z. Production of biodispersan by *Acinetobacter calcoaceticus* A2. *Appl. Environ. Microbiol.* **1988**, *54*, 317–322. [CrossRef] [PubMed]
244. Rosenberg, E.; Rubinovitz, C.; Legmann, R.; Ron, E.Z. Purification and chemical properties of Acinetobacter calcoaceticus A2 biodispersan. *Appl. Environ. Microbiol.* **1988**, *54*, 323–326. [CrossRef] [PubMed]
245. Ron, E.Z.; Rosenberg, E. Natural roles of biosurfactants: Minireview. *Environ. Microbiol* **2001**, *3*, 229–236. [CrossRef] [PubMed]
246. Rodrigues, L.R.; Teixeira, J.A.; van der Mei, H.C.; Oliveira, R. Physicochemical and functional characterization of a biosurfactant produced by *Lactococcus lactis* 53. *Colloids Surf. B Biointerfaces* **2006**, *49*, 79–86. [CrossRef]
247. Gudiña, E.J.; Fernandes, E.C.; Teixeira, J.A.; Rodrigues, L.R. Antimicrobial and anti-adhesive activities of cell–bound biosurfactant from *Lactobacillus agilis* CCUG31450. *RSC Adv.* **2015**, *5*, 90960–90968. [CrossRef]
248. Kaplan, N.; Zosim, Z.; Rosenberg, E. Reconstitution of emulsifying activity of Acinetobacter calcoaceticus BD4 emulsan by using pure polysaccharide and protein. *Appl. Environ. Microbiol.* **1987**, *53*, 440–446. [CrossRef]
249. Alcantara, V.A.; Pajares, I.G.; Simbahan, J.F.; Edding, S.N. Downstream recovery and purification of a bioemulsifier from *Sacchromyces cerevisiae* 2031. *Phil. Agric. Sci.* **2014**, *96*, 349–359.
250. Jagtap, S.; Yavankar, S.; Pardesi, K.; Chopade, B. Production of bioemulsifier by *Acinetobacter* sp. from healthy human skin of tribal population. *Ind. J. Expt. Biol.* **2010**, *48*, 70–76.
251. Ballou, C. Structure and biosynthesis of the mannan component of the yeast cell envelope. In *Advances in Microbial Physiology*; Academic Press: New York, NY, USA, 1976; Volume 14, pp. 93–158.
252. Cabib, E.; Roberts, R.; Bowers, B. Synthesis of the yeast cell wall and its regulation. *Annu. Rev. Biochem.* **1982**, *51*, 763–793. [CrossRef]
253. Torabizadeh, H.; Shojaosadati, S.A.; Tehrani, H.A. Preparation and characterisation of bioemulsifier from *Saccharomyces cerevisiae* and its application in food products. *LWT Food Sci. Technol.* **1996**, *29*, 734–737. [CrossRef]
254. Barriga, J.A.T.; Cooper, D.G.; Idziak, E.S.; Cameron, D.R. Components of the bioemulsifier from *S. cerevisiae*. *Enzym. Microb. Technol.* **1999**, *25*, 96–102. [CrossRef]
255. Dikit, P.; Maneerat, S.; Musikasang, H.; Kittikun, A.H. Emulsifier properties of the mannoprotein extract from yeast isolated from sugar palm wine. *Sci. Asia* **2010**, *36*, 312–318. [CrossRef]
256. Casanova, M.; Lopez-Ribot, J.L.; Martinez, J.P.; Sentandreu, R. Characterization of cell wall proteins from yeast and mycelial cells of *Candida albicans* by labelling with biotin: Comparison with other techniques. *Infect. Immun.* **1992**, *60*, 4898–4906. [CrossRef]
257. Haque, F.; Sajid, M.; Cameotra, S.S.; Battacharyya, M.S. Anti-biofilm activity of a sophorolipid-amphotericin B niosomal formulation against *Candida albicans*. *Biofouling* **2017**, *33*, 768. [CrossRef]
258. Rincón–Fontán, M.; Rodríguez-López, L.; Vecino, X.; Cruz, J.M.; Moldes, A.B. Design and characterization of greener sunscreen formulations based on mica powder and a biosurfactant extract. *Powder Technol.* **2018**, *327*, 442–448. [CrossRef]
259. Franco-Marcelino, P.R.; Gonçalves, F.; Muñoz Jimenez, I.; Curry Carneiro, B.; Bosquiroli Santos, B.; Silvério da Silva, S. Sustainable Production of Biosurfactants and Their Applications. *Lignocellul. Biorefining Technol.* **2020**. [CrossRef]