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Review

Unlocking the Potential of Mannosylerythritol Lipids: Properties and Industrial Applications

Joana Dias de Almeida [1,2], Miguel Figueiredo Nascimento [1,2], Petar Keković [1,2], Frederico Castelo Ferreira [1,2,*] and Nuno Torres Faria [1,2,*]

[1] Department of Bioengineering, iBB—Institute for Bioengineering and Biosciences, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1049-001 Lisbon, Portugal; joana.d.almeida@tecnico.ulisboa.pt (J.D.d.A.); miguelfnascimento@tecnico.ulisboa.pt (M.F.N.); petarkekovic@tecnico.ulisboa.pt (P.K.)

[2] Associate Laboratory, i4HB—Institute for Health and Bioeconomy, Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisbon, Portugal

* Correspondence: frederico.ferreira@tecnico.ulisboa.pt (F.C.F.); nuno.faria@tecnico.ulisboa.pt (N.T.F.)

Abstract: Mannosylerythritol lipids (MELs), one of the most promising biosurfactants (BS), are glycolipids produced by yeasts or fungi, which have great environmental performance and high compatibility with the human body. MELs, besides working as typical surfactants, can form diverse structures when at or above the critical aggregation concentration (CAC), reduce the surface tension of water and other solutions, and be stable over a wide range of conditions. Among others, MELs present antimicrobial, antitumor, antioxidant and anti-inflammatory activities and skin and hair repair capacity, which opens possibilities for their use in applications from cosmetics and pharmaceutics to bioremediation and agriculture. However, their market share is still low when compared to other glycolipids, due to their less developed production process and higher production cost. This review gathers information on the potential applications of MELs mentioned in the literature since 1993. Furthermore, it also explores the current strategies being developed to enhance the market presence of MELs, in parallel with the ones developed for rhamnolipids and sophorolipids.

Keywords: mannosylerythritol lipids; glycolipids; biosurfactants; cosmetics; biomedical; food; bioremediation

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1. Introduction

Surface active agents, also known as surfactants, are amphiphilic molecules possessing both a hydrophilic head and a hydrophobic tail. Depending on the charge of the hydrophilic domain, surfactants can be categorized as anionic, cationic, amphoteric, or non-ionic [1–3]. Surfactants tend to accumulate at the interface between polar and nonpolar solutions, decreasing repulsive molecular forces and, as a result, decreasing the surface/interface tension, allowing solutions to mix with each other [1,3]. Moreover, the accumulation of surfactants can lead to their aggregation in different structures, such as spherical micelles with hydrophilic groups facing aqueous media, and apolar groups facing a sequestered hydrophobic solution. Surfactants with one polar head group and two hydrophobic tails are also often able to form molecular membrane bilayers, with heads facing the membrane surfaces and tails interacting at its interior. Cylindrical and spherical bilayers can be formed by uni- or multilamellar structures; helical ribbons and tubules are commonly formed by chiral surfactants; and bicelles or disk aggregates can be made by mixing different surfactants in the same solution [1]. Such structures are formed when the surfactant concentration is above the Critical Aggregation Concentration (CAC).

Surfactants can function as wetting, foaming, or coating agents, dispersants, emulsifiers, or de-emulsifiers, and therefore, they are part of and crucial for the efficiency of a wide range of products, such as cleaning products, personal care and cosmetic products,

healthcare products, food and beverages, and paints and coatings [2,3]. In 2023, surfactants' market value was estimated to reach 45.72 billion USD, and it is expected to increase, at a compound annual growth rate (CAGR) of 4.7%, to a value of 69.13 billion USD in 2032 [4].

While extremely useful, 60% (*w*/*w*) of total surfactants produced are estimated to end up in the aquatic environment [5], due to direct product discharge or leakage and inefficient removal from water in wastewater treatment stations. When in the environment, synthetic surfactants persist and accumulate due to their slow biodegradability, and are toxic to microorganisms, aquatic flora and aquatic fauna. In some cases, the degradation products resulting from the biodegradation of surfactants are even more toxic than the parent molecules [2]. Regarding surfactants' safety for human use, several surfactants are classified as irritants; as, above certain concentrations, some are irritant to the skin and eyes, they are classified as dangerous by the European Council, since exposure can cause skin burns and severe damage to the eyes; and some are extremely toxic to aquatic life [6].

Today, consumer awareness of the effects of chemicals on the environment and on human health is increasing, and countries' governments are defining goals and creating new laws to avoid further contamination of the environment and to protect people's health. In 2015, the United Nations developed the Sustainable Development Goals (SDGs) [7]. Among several objectives, the SDGs propose the reduction of air, water and soil pollution by hazardous chemicals (SDG 3 and 6), through better management of the chemicals and wastes during their life cycles and by strengthening the scientific and technological capacity of countries in order to make a transition to more sustainable practices (SDG 12). As a consequence, SDG 3 proposes to yield a substantial reduction in the number of deaths and illnesses from hazardous chemicals pollution by 2030. The European Union went further and created the Green Deal, which aims to reach zero pollution and a toxin-free environment by 2050. As part of that deal, the Regulation on the registration, evaluation, authorization, and restriction of chemicals (REACH) was created [8]. This certification limits or bans the manufacturing, commercialization and use of chemicals that pose unacceptable risks for human and environmental health; at the same time, this regulation stimulates innovation for both the development of alternative substances and the development of alternative methods for chemical testing that do not involve animals.

Surfactants are no exception, and more sustainable alternatives are already being developed. Biosurfactants (BS), defined as surfactants produced by bacteria, yeast, fungi, or archaea [9], have low toxicity and high biodegradability. Their hydrophilic moiety is usually made of amino acids, anionic or cationic peptides, or carbohydrates, whereas the hydrophobic moiety is composed of peptides, proteins, unsaturated or saturated fatty acids. Depending on their structure, BS are divided into different classes: glycolipids, lipopeptides, fatty acids, polymeric and particulate BS [2,3].

Among BS, the glycolipids class is the most mature in terms of industrial applications, particularly sophorolipids (SLs) and rhamnolipids (RLs). In fact, multinational companies are increasingly investing in scaling up their research and production. For instance, Evonik and Unilever announced a partnership in 2022 for the construction of a rhamnolipid-producing facility in Slovakia with a three-digit million-euro investment [10]. BASF and Holiferm also announced a partnership for SL production and secured a 21.4 million EUR investment [11], while in 2020 Stepan Company acquired Natsurfact [12], a rhamnolipid-producing company. Besides those, there are more companies producing RLs and SLs on a large scale like Jeneil Biotechnology and Amphistar. Besides glycolipids, other BS are entering the market, as in the case of surfactin, a powerful cyclic lipopeptide produced by *Bacillus subtilis* [13]. Surfactin is commercialized by companies like Kaneka [13] and InventionBio [14] and is already being integrated into personal care products. The investment in companies dedicated to BS production clearly shows the growing market demand for BS.

Mannosylerythritol lipids (MELs) are an emerging glycolipid class, and despite a lower technology readiness level (TRL) of 4 compared with SLs/RLs (8/9), they hold significant potential, as herein explored. This paper highlights MELs' properties and applications that are already described in the literature (summarized in Figure 1) and assesses the advantages

of MELs compared to other surfactants and BSs, as well as the steps MELs must take to thrive in the market.

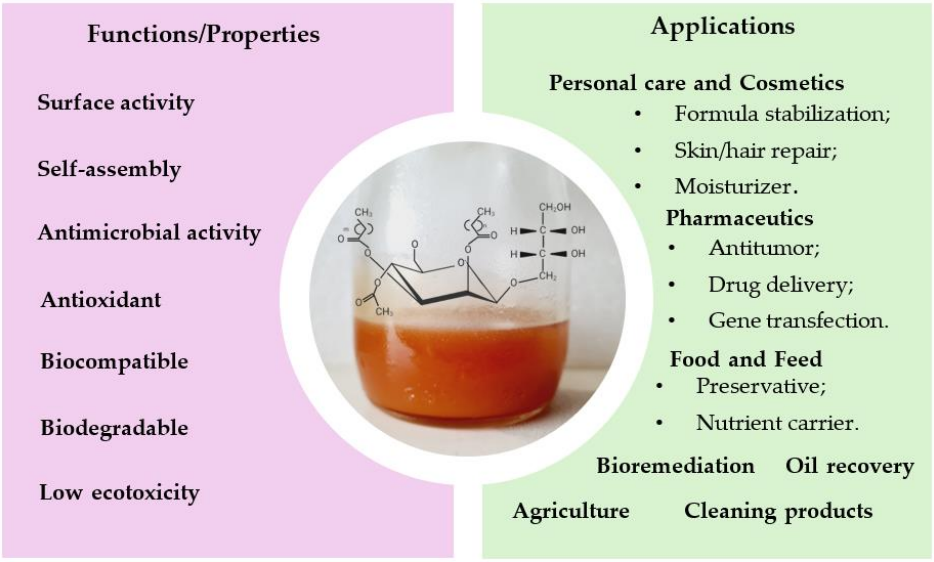

Figure 1. MELs' properties, functionalities and examples of possible applications.

2. Materials and Methods

The Google Scholar, Clarivate Web of Science, and Google Patents platforms were used to search for articles and patents. The words "Mannosylerythritol lipids" were defined as mandatory, while the words "cosmetics", "agriculture", "pharmaceutical", "medical", "food", "feed", "remediation", "detergent", "oil", "fuel" were defined as optional, and papers including "review" were excluded. The search was limited to the years between 1990 and 2024.

3. Mannosylerythritol Lipids: Structure, Properties, and Production

MELs are produced by species of the yeast genera *Moesziomyces* (formerly known as *Pseudozyma)* and *Kurtzmanomyces* and the fungi genera *Schizonella* and *Ustillago* [15]. Although their function is still not clear, it is believed that MELs, similarly to triacylglycerols, act as energy storage material in the cell [15,16] and that their secretion helps in the emulsification of carbon sources, such as oils, facilitating their transport through the microorganism's cell wall [1].

MELs belong to the non-ionic BS category, and are constituted of a 4-O-β-D-mannopyra nosyl-D-erythritol hydrophilic moiety and two fatty acid hydrophobic chains with variable sizes, linked to the mannose. There are different MEL congeners according to the number of carbons on the fatty acid chains and the acetylation of mannose's hydroxyl groups, classified into MEL-A (acetylation at C4 and C6); MEL-B (acetylation at C4); MEL-C (acetylation at C6) and MEL-D (no acetylations) [15].

In this regard, depending on the type and the final concentration, MELs can self-assemble into diverse structures. In 2009, Imura et al. [17], studied this phenomenon, quantifying critical aggregation concentrations (CACs) for MELs and elucidating the types of structures formed. The authors concluded that MEL-A and MEL-B aggregate in large unilamellar vesicles at CACs of 4 μM and 4.5 μM, respectively. However, when MEL-A concentration increases to above 20 μM, they form sponge structures (L3 phase) composed of a randomly connected three-dimensional network of bilayers. MEL-B forms typical multilamellar vesicles above its CAC. Importantly, above their CAC concentrations, MEL-A and MEL-B reduce the surface tension of water from 72 $mN \cdot m^{-1}$ to 28.4 and 28.2 $mN \cdot m^{-1}$, respectively. Regarding MEL-C and MEL-D, both form lamellar phases at CACs of 4 μM and 12 μM, reducing the surface tension of water to 24.4 $mN \cdot m^{-1}$ and 24.6 $mN \cdot m^{-1}$, respectively [18,19]. Although MEL-A and MEL-B, and MEL-C and MEL-D, have very

similar water tension-reducing capacities, they present differences in their structures, as described above, and in their hydrophilic-lipophilic balance (HLB); more specifically, MEL-A has 8.8, MEL-B has 8.7–9.4, MEL-C has 8.5–9.4 and MEL-D has 10.1 HLB [20]. The lower the HLB, the higher the hydrophobicity of the molecule, and vice versa. These differences may affect MEL's potential practical applications, opening new possibilities in many different fields, as explained in the next section.

Moreover, MELs' activity has been reported to be stable in extreme temperatures and pHs, which can be an advantage when applying MELs in accordance with the envisaged applications. However, they are sensitive to salt concentrations above 100 mM [16].

Cell biocompatibility tests using different cell lines, such as human melanocytes, human and mouse fibroblasts and human keratinocytes, and in 3D human skin models show that MELs do not exhibit cytotoxic activity below certain concentrations. A study performed by Kim et al. (2002) [16] shows that the reduction of mouse fibroblast viability to 50% after 48 h requires the presence of 5 g/L of MELs, while the same decrease in cell viability is attained with only 0.05 and 0.01 g/L of SDS or LAS, respectively. For given MEL congeners and cell lines used, MELs can even increase cell viability when below the inhibitory concentrations [16,21–26]. These studies indicate MELs' safety for use under given thresholds in cosmetics and personal care applications. Considering that, after their use, a large percentage of surfactants end up in aquatic bodies, it is crucial to assess their impact on the environment. A fast biodegradation rate in MELs was demonstrated in a study by Kim et al. (2002) [16], with these molecules being fully degraded by microorganisms in activated sludge in four days. Moreover, MELs presented low ecotoxicity to aquatic organisms, as quantified by Keković et al. (2002) [27] using the model marine organism *Artemia franciscana* at an LD50 value of about 1 g/L, outperforming rhamnolipids and sophorolipids, whose LD50s reported in the same study were about 0.5 g/L and 0.7 g/L, respectively.

Regarding MEL production, two different approaches have commonly reported:

(1) Using only hydrophobic carbon sources (such as soybean and rapeseed oil), leading to high titres of MELs (up to 150 g/L), but with low purity (ca. 60%) [28]; or
(2) Using only hydrophilic carbon sources (such as glucose), which leads to high purity (~95%), but with low titres (ca. 6 g/L).

However, a recent study by Faria et al. (2023) [29] showed an alternative strategy, designed to reach both sufficient MEL titres and high purity by co-feeding the microorganisms carbon sources with opposite polarities (glucose and soybean oil). This study explored the carbon equimolar substitution of part of the oil with a hydrophilic carbon source (D-glucose). Such an approach did not compromise MEL production and led to lower final residual lipids, increasing MEL purities compared with cultivations using solely hydrophobic carbon sources (80 vs. 64%). It is suggested that the use of D-glucose, which promoted the induction of extracellular lipases (already reported for *Moesziomyces* spp. [30]), improved the incorporation of lipidic molecules into the cells.

Between fermentation and final application, there is a very important step, which is the MEL's separation from the fermentation broth and subsequent purification. For this purpose, the most common techniques are liquid–liquid extraction and column chromatography, but other techniques such as membrane filtration [29,31], heat exposure and decantation [32], and separation of MEL beads with integrated devices [33] are being explored.

MELs can replace chemical surfactants in many applications due to their similar performance in reducing surface tension. However, considering MELs' unusual properties, such as low toxicity, biocompatibility and self-assembly among others, additional possible applications of these products are envisaged. Over past decades, researchers suggested and tested MELs for various applications, including applications in fields ranging from medicine and cosmetics to agriculture and bioremediation, where MELs could be used as both a specialty and a bulk chemical. These applications of MELs are reviewed in Table 1 and described in the next section.

Table 1. Summary table of MELs' potential applications reported in the literature. MIC—Minimum inhibitory concentration; NA—Not Available.

Application Area	Specification	Brief Description of the Results			MELs Used	References
Biomedical/ Pharmaceutics	Anti-microbial activity	■ Both MELs were strongly active against Gram-positive bacteria (*Bacillus subtilis*, *Micrococcus luteus*, *Mycobacterium rhodoochrous*, *Staphylococcus aureus*).	**MIC (μg/mL)**		MEL-A 99% and MEL-B 99%	[34]
				MEL-A	MEL-B	
			B. subtilis	6.2	2.5	
			M. luteus	3.1	12.5	
			M. rhodoochrous	25	25	
			S. aureus	12.5	25	
		■ MELs had antimicrobial activity against *S. aureus* and biofilm disruption activity.		500		MEL-A, -B, -C and -D mixture	[21]
		■ MEL-A inhibited the germination of *Bacillus cereus* spores.		1250		MEL-A 80%	[35]
		■ MEL-A inhibited planktonic cells and biofilm of *S. aureus.*		625		MEL-A 80%	[36]
		■ MEL-B inhibited the growth of bovine mastitis causative *S. aureus.*		10		MEL-B	[37]
		■ MEL-A inhibited *Listeria monocytogenes* by damaging its cell membrane and morphology. Its combination with hydrostatic pressure led to a higher bactericidal effect than the hydrostatic pressure alone.		32		MEL-A 80%	[38,39]
		■ MELs inhibited the growth of *E. coli* and *P. aeruginosa*. The combination of MELs and antibiotics potentiated antibiotics' efficiency.	*E. coli*	300		NA	[40]
			P. aeruginosa	75			
	Antitumor	■ MELs induced the differentiation of human promyelocytic leukemia cells HL60 and inhibited protein kinase C activity.				MEL-A and -B	[41,42]
		■ MELs inhibited tyrosine kinase activity, inhibiting proliferation and inducing the differentiation of human myelogenous leukemia cells K562.				MEL mixture	[43]
		■ MEL-B reduced cell viability and induced death by apoptosis of B16F10 mouse melanoma cells.				MEL-B 95% Toyobo	[23]
Biomedical/ Pharmaceutics (continuation)		■ MELs stimulated tyrosinase activity and melanin production, leading to apoptosis and cell-differentiation of B16 mouse melanoma cells.				NA	[44]
	Anti-inflammatory	■ MELs inhibited the secretion of inflammatory mediators by rat basophilic leukemia RBL-2H3 cells (a mast cell line).				MEL-A and MEL-B	[45]
	Neural repair	■ MELs induced the outgrowth of neurites from and enhanced the activity of acetylcholinesterase in PC12 pheochromocytoma cells.				MEL-A	[46,47]

Table 1. *Cont.*

Application Area	Specification	Brief Description of the Results	MELs Used	References
Biomedical/ Pharmaceutics (continuation)	Genetic material transfection or drug-carrying	■ MEL-A increased the efficiency of gene transfection by cationic liposomes with a cholesterol derivative or DC-Chol.	MEL-A	[48–50]
		■ MEL-A-containing cationic liposome was able to deliver siRNA rapidly and directly.	MEL-A	[51]
		■ MELs were used as stabilizing agents for silver and zinc oxide nanocomposites, gold nanoparticles and synthesis of silver and magnetic iron oxide nanocomposites, to be used in human liver cancer cell inhibition (HepG2).	NA	[52–54]
		■ Nanoliposomes made of soybean lecithin and cholesterol, when incorporated with MEL-B, had enhanced stability at pH 3–7 and delivered amoxicillin for *Helicobacter pylori* infection treatment in vivo.	MEL-B, Toyobo	[55]
		■ MEL-B nanomicelles successfully carried berberine for *H. pylori* biofilm disintegration and infection eradication.	MEL-B, Toyobo	[56]
	Drug delivery	■ Preparation of MEL nanomiceles for drug delivery (clarithromycin). It was shown that, by varying the pH, it is possible to control clarithromycin delivery (in 2 h, at pH 1.2 37.1% of the drug was delivered, while, at pH 7.4, only 9.7% was released).	MEL-A	[57]
	Immunoglobulin purification	■ MEL-A showed high binding affinity towards HIgG, HIgA and HIgM.	MEL-A	[58,59]
Cosmetics and personal care	Formulation stabilization	■ Nanoemulsification of pseudo-ceramide was stabilized by molecular association with MELs.	Damy Chemicals	[60]
		MELs stabilized the foaming, emulsification, and wetting properties of sodium lauryl sulphate.	MEL-B	[61]
		■ Coating cosmetic pigments (lip primer, foundation and sunscreen) with MELs enhanced their skin adhesion.	NA	[62]
	Skin whitening	■ MELs inhibited melanogenesis via suppressing ERK–CREB–MiTF–tyrosinase signalling in human melanocytes and a three-dimensional human skin equivalent.	MEL-B 85%, DK BIO	[25]
	Hair growth promotion	■ MEL-A produced from soybean oil increased cultured fibroblast cells and 3D human skin model cell viability and activated human papilla cells.	MEL-A 80.1%	[63]
Cosmetics and personal care (continuation)	Damaged hair repair	■ MEL-A and MEL-B showed similar activity to ceramides for hair damage repair, and increased hair flexibility.	MEL-A 99% MEL-B 90%	[64]
	Skin repair and moisturization	■ MELs ameliorated UVA-induced aquaporin-3 downregulation by suppressing c-Jun N-terminal kinase phosphorylation in cultured human keratinocytes.	MELs from DKBIO	[26]

Table 1. *Cont.*

Application Area	Specification	Brief Description of the Results	MELs Used	References
Cosmetics and personal care (continuation)	Skin repair and moisturization	■ MEL-A had a recovery effect on SDS-damaged skin cells	MEL-A	[65]
		■ MEL-A and MEL-B produced with olive oil showed activities similar to natural ceramides on the cell viability of cultured human skin cells and repaired SDS-induced damage; MEL-B increased the water content in the stratum corneum and reduced water loss through perspiration.	MEL-A 100% MEL-B 100%	[66]
		■ MELs with carbon chains with 10 or more carbons exhibited better cell damage repair than a natural C18 ceramide, particularly MEL-D C10 (MELs purified by acetylation level and carbon chain size; see original paper)	Purified MELs	[67]
		■ MEL-B protected both HaCaT and 3D skin cell models from UVB- and SDS-induced damage by upregulating the expression of the key skin barrier damage-associated mRNA genes and proteins LOR, FLG, and TGM1.	Purified MEL-A, -B and -C	[22]
		■ MEL-B liposomes increased skin permeability to water-soluble compounds (calcein) in mice.	MEL-B, Toyobo	[68]
	Antioxidant	■ MEL-C had antioxidant activity through DPPH radical and superoxide anion scavenging and protection of cultured human fibroblast cells against H2O2-induced oxidative stress	MEL-C 80.7–92.5%	[24]
	Anti microbial	■ MELs had antimicrobial activity against Malassezia furfur, the yeast that causes dandruff. A shampoo formulated with MELs and SLS had increased anti-dandruff activity	NA	[69]
Bioremediation/ Environmental responses	Oil spills	■ MELs increased the bioavailability and biodegradation rate of n-alkanes, diesel, kerosene and crude oil (MEL mixture: 68% MEL-A, 28% -B and -C and 4% -D).	NA MEL mixture	[70–72]
		■ Patent using MELs as petroleum demulsifier agents	NA	[73]
	Biodegradtion control	■ Biodegradation of an agricultural biodegradable plastic composed of poly(butylene succinate-co-adipate) by cutinase-like esterases and microorganisms was inhibited by MELs.	MEL-A, -B, and -C	[74]
Food	Nutrient carriers	■ MEL-A was used in the formulation of a stable anthocyanin nutrient carrier. Compared with free anthocyanins, the encapsulated anthocyanins had higher retention rates when exposed to storage and simulated gastrointestinal fluid conditions; their antioxidant capacity after simulated intestinal digestion was enhanced.	MEL-A >95%	[75,76]
	Food functionality	MEL-A reduced aggregation from β-lactoglobulin aggregates, creating microscale MEL-A-β-lg complexes. The foaming stability and emulsion properties were enhanced in the presence of MEL-A, improving food texture.	MEL-A	[77]
Food (continuation)	Food preservation	■ MEL-A enhanced the rheological properties and water holding capacity of frozen dough, minimizing the freezable water content, while killing *B. cereus* cells and spores.	MEL-A 80%	[35,78,79]
		■ Emulsification of essential oils (EO) (*Thymus vulgaris*, *Lippia sidoides* and *Cymbopogon citratus*) with MEL-B led to an enhancement of essential oils' antioxidant activity and preservation of antimicrobial activity.	MEL-B	[61]

	MIC (μg/mL)	
	1250	
B. subtilis	Only MEL 500	MEL + EO 120
Penicillium sp.	250	62.23

Table 1. *Cont.*

Application Area	Specification	Brief Description of the Results	MELs Used	References
Agriculture	Agro-spreader	■ MELs were used as agrochemical spreader for biopesticides for hydrophobic plant surfaces (MEL mixture: 58% MEL-A, 25% MEL-B and 10% MEL-D).	MEL mixture	[80]
	Wetting agent	■ MEL solutions showed good wetting ability on poorly wettable Gramineae plant surfaces.	MEL-A, -B, and -C	[80]
	Biocide	■ MEL-Ag nanoparticles displayed activity against mosquito larvae and pupae	MEL mixture	[81]
		Powdery mildew was suppressed on MEL-treated leaves.	MEL-A	[82]
		■ MELs, combined with other ingredients, were used for nematodes control.	NA	[83]
		■ MEL-B had a biostimulant and phytotoxic effect on lettuce plant germination and growth for given concentrations.	MEL-B 95% Toyobo	[84]
Others	Fuel additive	■ MEL-A enhanced the fluidity of fuels at low temperatures.	MEL-A	[85]
	Jet biofuel	■ MELs were used as precursors for fuel with lipid chains comprising 6 to 14 carbons production.	NA	[86]
	Enhanced oil recovery	■ MEL-B could create emulsions with heavy oils.	MEL-B	[87]
	Detergent	■ MELs had stability over wide pH and temperature ranges and improved detergent efficiency in removing stains from fabric in a proportion of 1:1 (w detergent/w MELs)	Crude MEL-A, -B and -C mixture	[88,89]
	Ice prevention	Suppression of agglomeration and growth of ice particles	MEL-A	[90]

4. Mannosylerythritol Applications Described in the Literature

Until 1993, the only known function of MELs was their surface tension-reducing capacity; since then, new functions such as antimicrobial activity, nanostructure formation capacity and interaction with certain cell types and molecules have been discovered and, consequently, new applications have been proposed.

4.1. Biomedical/Pharmaceutical Industries

In the field of medicine, MELs' proposed applications are based on their beneficial interactions with various cell types, antimicrobial properties, and nanostructure formation capabilities (e.g., liposome structures to more effectively transport drugs to their site of action).

In this regard, one of the first functions to be explored was antimicrobial activity, in which Kitamoto et al. (1993) [34] tested the activity of MEL-A and MEL-B on Gram-positive bacteria (*Bacillus subtilis*, *Micrococcus luteus*, *Mycobacterium rhodochrous*, *Staphylococcus aureus*), Gram-negative bacteria (*Pseudomonas aeruginosa*, *Pseudomonas rivoflavina*, *Escherichia coli*), and fungi (*Candida albicans*, *Aspergillus niger*). The researchers concluded that MELs exhibit a robust inhibitory effect on Gram-positive bacteria, along with some sensitivity towards *Pseudomonas* strains. Antimicrobial activity was further studied in the food-borne pathogens *S. aureus*, *Bacillus cereus* and *Listeria monocytogenes* [35–38,78]. It was observed that MELs' antimicrobial effect was linked to their capacity to damage the integrity of cell membranes. Additionally, it was observed that MELs interfere with the adhesive capacity of bacteria, inhibiting biofilm formation. Due to these properties, MELs have the potential to be used by the pharmaceutical or biomedical industries in equipment treatment and medical implants, and by the food and feed industries as food preservatives and in the treatment of diseases in farms. Additionally, in a recent conference paper [40] it was pointed out that MELs can potentiate the activity of antibiotics.

Regarding the field of medicine, different studies have determined the use of MELs for anticarcinogenic applications, based on their ability to damage cancer cells, namely leukemia and melanoma cells, and cause their differentiation [23,41–44]. Isoda et al. (1999) [46] reported that MELs induce neurite outgrowth, opening the possibility of applications for neural damage repair. Morita et al. (2011) [45] observed MELs to display anti-inflammatory capabilities by inhibiting the secretion of inflammatory mediators by mast cells. The capacity to form liposomes opens a new range of possibilities for MELs. Inoh et al. (2001 and 2011) [50,51], Ueno et al. (2007) [49] and Igarashi et al. (2016) [48] generated liposomes containing 1,2-Dioleoyl-sn-glycero-3-phosphatidylethanolamine, cholesterol derivatives and MELs, and studied their effectiveness in gene and siRNA transfection in host cells. MELs were able to increase the efficiency of liposome-mediated gene transfection through enhancement of the interaction between the liposome and the host cell and a reduction in the immune response and cytotoxicity, having a rapid and direct delivery. Thus, MELs have potential as effective vectors in gene therapy.

Liposomes were further explored by Wu et al. (2022) [55], who designed a drug delivery complex liposome for antibiotic delivery using MEL-B, soybean lecithin (SL) and cholesterol (LipoSC-MELB). These liposomes loaded with amoxicillin, an antibiotic, were tested against *Helicobacter pylori* (responsible for gastritis and peptic ulcer disease in humans). Similarly, Cheng et al. (2023) [56] loaded MEL nanomicelles with berberin and tested them in vivo. Remarkably, the authors showed that these liposomes and nanomicelles can be used for treatment of *H. pylori* infection, a disease that affects most of the world population. Similarly, MELs can possibly be used for drug delivery in the form of nanoparticles formed with metals [52–54]. MEL-A was also found to have a high binding affinity towards immunoglobulins [58,59], opening up the possibility of its application in purification processes.

Overall, due to the complexity and pre-requirements needed for in-vivo tests for medical applications, only some reports have results based on tests performed in realistic conditions, namely the ones that relate to MELs' antimicrobial properties and drug carrying

for *H. pylori* treatment. Nevertheless, more studies are required (clinical trials) to really enhance the use of MELs in pharmaceutical applications.

4.2. Personal Care and Cosmetics

Due to MELs' biocompatibility and positive interaction with the human body, many cosmetic applications were proposed. In fact, there are already companies (Kao Corporation, DKBIO, Kanebo Cosmetics) commercializing cosmetics containing MELs.

In this field, the use of MELs is focused on improving formulation bulk properties, where MELs can act as emulsifiers, foam stabilizers or enhancers of pigments' adhesion to skin; in addition, MELs have been used in the fabrication and stabilization of nanoemulsions improving dispersion stability, avoiding the formation of molecular crystals and alteration of particles sizes over long storage times [60], or to provide higher value functions, where MELs are used in formulations as active compounds.

Several studies show that MELs have repairing and moisturizing effects on skin comparable with those of natural ceramides. Ceramides are precursor molecules for sphingolipid formation in cell membranes and are present in large amounts in the skin stratum corneum, providing the barrier property of the epidermis and playing a crucial role in the water retention capacity of the skin [91]. Research shows that ceramides have beneficial effects on skin disorder treatment, and currently, ceramides are becoming more commonly found in dermatological products.

Yamamoto et al. (2012) [66], Morita et al. (2009) [65] and Kondo et al. (2022) [67], in different studies, induced cell damage to cultured human skin with the surfactant SDS and then treated it with MELs. The cells treated with MELs had high recovery rates, similar to the ceramide-treated cells, and increased the water content of skin and its water-holding capacity. MELs recovered damaged cells, increasing cell viability from approximately 20% to 89%, while ceramides increased cell viability to approximately 30% [67].

The effect of MELs on UV-damaged cells is also protective; in fact, Bae et al. (2019) [26] indicated that MELs suppress UVA-induced phosphorylation of JNK, therefore alleviating the downregulation of the expression of aquaporin-3, a membrane protein that contributes to the water homeostasis of the epidermis. Thus, MELs can be used to modulate aquaporin-3 expression to improve skin moisturization following UVA irradiation-induced damage.

As an attempt to understand MELs' action mechanism on damaged skin, Jing et al. [22] explored the effects of MEL-B on two skin damage models: UVB-irradiated human epidermal keratinocyte cells and SDS-exposed 3D human skin cells. Skin barrier damage and dysfunction is frequently associated with the reduced production of transglutaminase-crosslinked proteins (such as filaggrin and loricrin) that are crosslinked by an enzyme (endoenzyme transglutaminase-1, TGM1). These proteins are essential for cornified envelope generation and maintenance. Therefore, to explore MELs' effect on damaged skin, the authors assessed cellular FLG, LOR, and TGM1 mRNA genes and protein expression levels. The authors concluded that MEL-B treatment increases the levels of these proteins in damaged cells, pointing out the protective effect of MEL-B in UVB- and SDS-damaged skin cells.

Two reports from Morita et al. (2010) tested MELs' interaction with hair and hair-growth cells. The results show that MELs have a similar reparative effect on hair damage to ceramides and a stimulation effect on papilla cells, crucial for hair growth [63,64]. More specifically, the tensile strength of the damaged hair was increased by treatment with MEL-A, MEL-B and a natural ceramide (approximately 122.0, 119.4 and 100.7 gf/p, respectively) compared with lauryl glucoside (approx. 96.7 gf/p). The average friction coefficient was maintained after treatment with MEL-A, MEL-B and the ceramide (0.108, 0.107 and 0.111, respectively) and increased by lauryl glucoside treatment (0.126), and the increase in bending rigidity caused by treatment with lauryl glucoside (0.204) was prevented by MEL-A, MEL-B and the ceramide (0.129, 0.176 and 0.164, respectively) [63,64]. In the same research group, the potential of MELs as antioxidant agents was assessed using fibroblasts

in oxidative stress. MEL-C showed a protective effect, increasing cell viability, suggesting the potential of MELs as anti-aging ingredients [24].

A study by Mawani et al. (2022) [69] showed that, by adding MELs to anti-dandruff shampoo, antimicrobial activity against *Malassezia furfur*, the microorganism that causes dandruff, is enhanced.

Bae et al. (2018) [25] observed that MELs inhibit melanogenesis in human melanocytes and in a 3D human skin model through the inhibition of ERK phosphorylation, which leads to the suppression of melanogenic gene expression. This opens the possibility for the development of new skin-whitening products containing MELs as active ingredients. In fact, there is a patent filed in 2017 for a skin-whitening composition containing MELs as whitening agents [92].

4.3. Agriculture

Agricultural applications of MELs are mostly based on their surface tension reduction activity and bioactivity. Fukuoka et al. (2015) [80] tested MELs' applicability as an agro-spreading agent due to their beneficial interaction with hydrophobic plant surfaces, where MELs had the best performance among several conventional surfactants in spreading and fixing the biopesticide on plant surfaces. Similarly, MELs applied to wheat leaf surfaces were shown to prevent conidial germination of the pathogenic fungus *Blumeria graminis* [82]. Thus, MELs have the potential to be used as wetting and spreading agents and as pesticides in agriculture.

Moreover, MELs' toxicity against mosquito larvae and pupae was tested and an LC50 between 30–60 μg/mL was obtained, depending on the stage of the larvae, which is a moderate degree of toxicity. On the other hand, MEL-synthesised silver nanoparticles were shown to be highly toxic, with an LC50 of approximately 1 μg/mL. The authors propose that nanoparticles with silver increase the bioactivity of MELs against mosquito larvae and pupae [81]. Still in the insecticide field, MELs are being applied in compositions for nematode control [83]. A recent study by Matosinhos et al. (2023) [84] studied the effect of MELs in lettuce seed germination, plant growth and root development, concluding that MELs can have both a biostimulant and a phytotoxic effect depending on their concentration.

4.4. Food and Feed Industry

As referenced in Section 4.1, the antimicrobial activity of MELs against food-borne pathogens opens possibilities for MELs to be applied in food and beverage preservation and in the treatment of diseases in farms. In fact, regarding the latter topic, a patent application claims the use of MELs as feed additives to prevent and treat infectious diseases caused by Gram-positive bacteria in livestock, avoiding the use of antibiotics, as well as reducing the methane emissions associated with digestion [93].

Zanotto et al. (2023) [61] evaluated the effect of MELs in essential oil activity stabilization and solubilization. Essential oils are natural and effective agents for controlling microorganisms that cause biodeterioration and disease, and therefore are good alternatives to chemical food preservatives. However, essential oils are immiscible in water and are highly volatile, so they are frequently mixed with surfactants for stabilization. MELs were able to create stable oil in water emulsions, preserving the antimicrobial activity of the essential oils and increasing their antioxidant activity.

Moreover, in two different studies, Shu et al. (2019, 2022) [35,78] observed that MEL-A has strong antimicrobial activity against *Bacillus cereus*, killing 99.97% of vegetative cells and 75.54% of spores. Besides that, MELs improved the rheological properties of frozen dough by strengthening the gluten network, enhancing the water-holding capacity of the frozen dough and reducing the free water content. In the presence of MELs, the dough had the largest volume and a more uniform and porous crumb structure [79]. These results suggest that MELs could potentially be used for the storage of flour products and in the baking industry. In another study [77], MEL-A contributed to an improvement in food texture,

namely through emulsification and enhancement of the foaming ability of heat-induced β-lactoglobulin aggregates, a key ingredient in milk whey proteins.

A paper by Fan et al. (2021) [76] and a patent application [75] describe the use of MELs for the construction of nutrient carriers, together with L-α-phosphatidylcholine or lactoglobulins, respectively. These carriers have high encapsulation efficiency for anthocyanin, maintaining their activity when exposed to storage or simulated gastrointestinal fluid conditions. Their antioxidant capacity was improved by 3–3.5 times after simulated intestinal digestion because of the protection provided by the vesicle encapsulation.

4.5. Environmental Responses

Applications within the field of bioremediation were proposed based mainly on MELs' capacity to interact with specific pollutant molecules. MELs interact positively with hydrocarbons, creating emulsions and making them more bioavailable for hydrocarbon-consuming microorganisms to biodegrade the oils; this effect was observed with n-alkanes, kerosene, diesel, petrol and light crude oil [27,70,71,94]. More recently, a formulation for an oil spill dispersant comprising MELs was developed [72]. This formulation exhibits excellent interfacial properties and dispersibility effectiveness under different mechanical energy and temperature conditions, comparable to those of commercial chemical dispersants. On the other hand, a submitted patent claims the use of MELs as demulsifying agents to separate water and petroleum emulsions, which can also be considered a bioremediation method, allowing the recovery of petroleum and treated water in separate streams [73]. Therefore, MELs could be applied as novel and eco-friendly solutions for the bioremediation of hydrocarbon-contaminated water or soil.

In a study by Fukuoka et al. (2016) [74], the pre-treatment of a biodegradable plastic with MELs inhibited the enzymatic degradation of the plastic polymers, and after removing the MELs, this biodegradability was recovered. This application is very relevant, as the performance of biodegradable plastics can be enhanced through MEL treatment without resorting to chemical modifications, and it is reversible, allowing for control of the biodegradability.

4.6. Others

Although there are only a few reports assessing MELs' potential to be used in detergents, it is one of their potential applications. Like other surfactants, MELs have surface tension-reducing properties and emulsifying activity; therefore, they have detergent activity. Moreover, MELs are stable at high temperatures and pH, and, in a 1:1 mixture with a commercial detergent, they improve the efficiency of stain removal [88].

MELs have possible applications in the petrochemical industry and could be a promising agent for enhanced oil recovery, especially because they maintain stability and activity under extreme temperatures, pH and salt concentration values [87,95]. In addition, MEL-A improves the fluidity of biodiesel and hydrocarbon fuels at low temperatures, opening the possibility for MELs to be applied as fuel additives [85]. The use of MELs as precursors for fuel production, through transesterification or hydrogenation reactions, for fuel used in air, marine or land transportation has been patented [86]. Moreover, Kitamoto et al. (2001) [90] concluded that MELs prevent ice particle growth, making them a promising ice agglomeration control agent.

The diversity of applications in which MELs can be used suggests that there could be additional, yet undiscovered, potential uses for this BS. The studies here highlight and position MELs as multifunctional molecules with exceptional properties, with the potential to provide technical advantages over chemical agents and other BS in the envisaged applications mentioned above. All these properties open possibilities for MELs, not only as substitutes for existing compounds, but also in the development of novel products where multiple features of this biomolecule can be utilized.

5. Current and Future Perspectives on MELs in the Market

Undoubtedly, MELs present advantages over other surfactants, from their environmental performance and biocompatibility with the human body to the effectiveness conferred by their low CAC and surface activity stability, which are summarized in Table 2. Moreover, unlike chemical surfactants, MELs present several different bioactivities as described in the previous chapter, such as antioxidant, antimicrobial, cell repair and antitumor activity, widening their potential applications and fitting into areas where chemical surfactants and even BS do not. However, MELs still occupy a small share of the BS glycolipids market, with a market value estimated at 3.3 million USD in 2022 [96], and this may be attributed to several factors.

Table 2. Comparative table of MELs, other biosurfactants and a synthetic surfactant. NA—Not Available.

		CMC/CAC (mM)	Surface Activity (mN/m)	Stability			Environmental Impact		Antimicrobial Activity
				pH	T (°C)	Salt (NaCl)	IC50 [1] (mg/L)	Biodegradability	MIC [4] (µg/mL)
MELs	-A	0.004 [17]	28.4 [17]	4–10 [16]	Up to 90 [16]	Up to 100 mM (~0.6%) [16]	999.95 [27]	Readily biodegradable [16]	32 [39]
	-B	0.0045 [17]	28.2 [17]						NA
Rhamnolipids	Mono-	0.4 [97]	27.4 [97]	4–10 [97]	Up to 120 [97]	50–1000 mM (~0.3–5.5%) [97]	545.65 [27]	Readily biodegradable [98]	78.1–2500 [99]
	Di-	0.46 [97]	31.3 [97]						
Sophorolipids		0.04–0.4 [100]	38.5–40 [100]	2–12 [101]	Up to 100 [101]	Up to 10–13% [101]	722.90 [27]	Readily biodegradable [102]	470 [103]
Surfactin		0.0094 [104]	30 [104]	5–13 [105]	Up to 100 [105]	Up to 6% [105]	>500 [2] [106]	Readily biodegradable [107]	10 [108]
Triton x-100		0.4 [109]	30.6 [109]	NA	NA	NA	26 [3] [106]	Not readily biodegradable [110]	NA

[1] Values for 50% inhibitory concentration against *Artemia francsicana*, [2] Value for 50% effective concentration against *Artemia salina*, [3] Value for 50% effective concentration against *Daphnia magna*, [4] Minimum inhibitory concentration against *Listeria monocytogenes*.

Compared to other surfactants and BS, MELs are relatively recently-studied molecules. The first studies on MELs are from the beginning of the 1990s [111], while for RLs and SLs, the first studies are from 1949 [112] and 1961 [113], respectively. Chemical and bio-based chemically synthesized surfactant production is very well established. Historically, the earliest evidence of soap manufacturing is as old as 2800 BC [114]. Consequently, there remains a limited understanding of MELs, as evidenced by the relatively few companies producing them, including Toyobo Corporation, Biotopia, Damy Chemicals, Sollice Biotech, and the most recent addition, SurfACTinnov. However, identifying companies utilizing MELs can be challenging due to sparse public information and difficulty in discerning MELs within product ingredient lists.

Concerning bioprocess development, of which a detailed review is outside the scope of this manuscript, while the reported maximum productivities of SLs and RLs are 3.7 and 1.54 g/L/h, respectively, MELs' maximum productivities are significantly lower at values of 0.59 g/L/h [115]. In addition to lower productivity and consequent needs for CAPEX investment, other important cost-drivers are related to the use of pure substrates and the downstream process, which represents approximately 60% of the total production cost [3]. These factors contribute to MEL production costs that are not low enough to facilitate their commercialization. An economic analysis on MEL production is not yet available in the literature. However, considering titres of 100 g/L, SL and RL production cost is estimated to be 2.95 USD/kg [116] and 20–25 USD/kg [117], respectively. It is expected that MELs have an even higher production cost than these two glycolipids. Despite the efforts to reduce glycolipid production costs, the costs of BS production are still higher than those

for chemical surfactants (US$1–3/kg) [117]. However, recent reports have demonstrated the scalability of MEL production up to 1 m^3 [118], marking a significant advancement in scalability validation. Concurrently, there is a need to assess the disparity between current production capacities and market demands, which are still under development as the markets and possible applications are still being explored. Furthermore, addressing technical, economic and logistical challenges will provide valuable insights into overall production costs and the feasibility of MEL implementation in identified markets.

Therefore, lowering manufacturing costs and scaling up the processes are necessary strategies to increase MELs' market share. In this regard, there are already studies aiming to reduce MEL production costs from the substrate point of view by replacing the carbon and nitrogen sources with industrial byproducts. Glycerol [119], lignocellulosic materials [120], sweetwater from the fat-splitting industry [121], cassava wastewater [122] and cheese whey [122] are some of the substrates that have been used to replace hydrophilic carbon sources; as for hydrophobic carbon sources, studies with waste cooking oils have been performed [123–125]. Contributing to cost reductions, Nascimento et al. (2022) [123] successfully replaced the use of yeast extract and mineral supplementation in the fermentation medium with cheese whey.

Increasing productivity is an important strategy to decrease production costs, which relies on optimization of the fermentation conditions, namely the quantities and types of nitrogen and hydrophilic and hydrophobic carbon sources; air supply and agitation; and microorganism strain used, as different organisms have different productivities [126]. The fermentation modes currently reported for MEL production are batch, fed-batch and repeated fed-batch fermentations [126]. However, other fermentation modes could be explored, such as solid-state fermentations, which are being used for SL production [127]. The choice of microorganism is relevant not only for increasing productivity, but also to define the MEL congener mixtures obtained. A review paper by Saika et al. (2018) [128] compiles the studies that have resorted to genetic engineering to modify MEL producers, with some of the strains described being capable of more selective production of specific MEL congeners and other strains being able to produce novel derivatives of MELs. Additional studies may result in increasing MEL productivity and expansion of MELs' possible industrial applications. Such studies can take a process approach or focus on the genetic modification of MEL producers and the creation of recombinant strains with hosts other than the original species, as is being performed for RLs [129]. On the other hand, the fermentation conditions used can also affect the final product purity and downstream process intensity, namely concerning the steps needed to remove hydrophobic carbon sources when used in excess. It is worth noting that many studies utilize high concentrations of vegetable oils as substrates, resulting in the accumulation of unconsumed or residual lipids and thereby reducing MEL purity [28,29]. For some high-grade applications, like pharmaceuticals, the high downstream costs are justified, since a highly pure product is required [3,29]. However, for applications at lower grades like bioremediation or agriculture, the purity of the product is not as important, and the crucial factor is to ensure that the product is cost-effective without compromising the final performance. For example, in most cosmetic formulations, lipids are also used, so the impurities present in crude MEL extracts can be a benefit.

One strategy to decrease downstream costs is through solvent recycling. Most of the techniques described resort to solvents such as ethyl acetate, chloroform, and n-hexane. When some of these solvents are mixed, they may form azeotropes, and thus make efficient solvent recycling by distillation more challenging [130]. Careful selection of the solvents used, or the use of a single solvent rather than mixtures, may avoid this problem [131]. In addition, the downstream processes can be time-consuming; depending on the solvent, liquid–liquid extraction and evaporation are estimated to take 2 h per 100 mL and silica-gel column chromatography can take from 1 day to 2 weeks [132]. However, other downstream processes have been suggested based on heat differences [32], physical separation of MEL beads with integrated devices [33] or membrane filtration [29,31], which can pro-

vide alternative routes for the cost-efficient harvesting and purification of MELs from the fermentation broth.

In summary, the reports presented illustrate the potential of MELs in terms of their properties and applications. Such features may foster MELs' possible ability to capture interesting market shares and create global traction, in particular using niche sectors willing to pay premium prices as entry markets, where there is a particular fit between MELs' properties and activities and envisaged product features, as is the case in the cosmetics market. In particular, due to environmental concerns and rising awareness of the dangers of hazardous compounds present in cosmetic products, the personal care market is increasingly searching for biological and organic products with similar performance to chemical ingredients [133]. Namely, in 2023, the market size for natural beauty products was estimated to be 37.9 billion USD, and is expected to reach 58.8 billion USD in 2032, growing at a 5.1% CAGR [133]. However, to increase MELs' market share, it is important to strengthen actions towards: (1) scaling and improving productivity, which is essential to lowering production costs, to compete with SLs or RMs; (2) using residual raw materials as substrates, fostering circular economy approaches and optimizing downstream processes for value-added applications, and (3) validating target applications leveraging the specific properties of given mixtures of MEL congeners, thus enabling the creation of demand for MEL production.

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