Microbial Biosurfactants

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Surface-active molecules also known as surfactants are chemicals that have key impacts on several aspects of our daily products and life. Most of these chemical surfactants originate from petrochemical of oleochemical sources and are ingredients of household laundry cleaning agents, cosmetics, pharmaceutical, environmental cleaning products, petroleum, and agro-food processing industry. Worldwide use of these compounds has been steadily increasing during the past few decades and will be further increasing in the future. Most such chemical surfactants however, have negative effects on the environment, a fact that led to the search for alternatives with less impact and the shift towards a more sustainable environmental friendly biological surfactants (biosurfactants) which was mainly driven by the sustainability agenda by many international players in the field. Most these biosurfactants are produced by microorganisms (bacteria and fungi) and the advantages they bring include much lower toxicity, relative stability at high temperature and in adverse environments in addition to being readily biodegradable when, discharged into the environment. Many chemical surfactants included in cosmetic and pharmaceutical compounds have been reported to have the potential to cause detrimental effects such as allergic reactions and skin irritations to the human skin which encouraged the search for a more suitable replacements with less or no negative effects on skin health. As biosurfactants were known to exhibit skin compatibility, protection and surface moisturizing effects which are key components for an effective skincare routine in addition to lower toxicity. Interest therefore in biosurfactants that have antimicrobial, skin surface moisturizing and low toxicity properties which would make them suitable substitutes for chemical surfactants in current cosmetic and personal skincare and pharmaceutical formulations has been steadily increasing.

biosurfactants cosmetics glycolipids lipopeptides pharmaceutical formulations skincare surfactants

1. Introduction

Microbial biosurfactants are surface-active molecules that are produced by a variety of microorganisms, including bacteria, fungi, and yeast. These compounds are amphiphilic, meaning that they have both hydrophilic and hydrophobic regions, which allows them to lower the surface tension between two immiscible phases, such as oil and water. There are several different types of microbial biosurfactants, including glycolipids, lipopeptides, phospholipids, and fatty acids. Each type of biosurfactant has its own unique chemical structure and properties, which can influence its ability to function as a surfactant. Microbial biosurfactants have several advantages over synthetic surfactants. For example, they are often more environmentally friendly, as they are biodegradable and can be produced from renewable resources. They also tend to have lower toxicity and higher selectivity for specific substrates, which can make them more effective in certain applications.

The skin is a complex structure that constitutes the largest organ of the human body. Its primary function is to serve as a barrier, preventing excessive loss of moisture from the body; while on the outside, it prevents the entry of toxic substances and pathogens [1][2]. Histologically, the human skin is composed of three layers, namely, the epidermis, dermis and hypodermis [3]. Each of these layers contributes significantly to the functioning of the skin [4]. A complex network of interactions exists between epidermal cells and skin microbes, enabling the colonization of skin surfaces by a wide array of microorganisms, both commensal and mutualistic [5][6]. Different niches (moist, dry and sebaceous) of the skin surface selectively facilitate the growth of these diverse groups of microorganisms [7][8]. Many skin-inhabiting microbes offer great benefits to their host; while some help to activate the innate immune system, others produce antimicrobial substances (e.g., bacteriocins), which inhibit the growth of pathogens [7]. It is clear, therefore, that the maintenance of an effective skin microflora is a critical aspect of human health and has to be accommodated within the external challenges applied to the skin in the form of natural environmental contaminants and the optional application of personal care and cleansing products.

Cosmetic and personal care products are often formulated to provide nutrients and protection to the skin, its flora and associated cells, in addition to improving barrier functions, inhibiting the growth of pathogens, cleansing and moisturizing skin surfaces, all of which improve the skin's overall health. In pursuit of the above, researchers and manufacturers of personal skincare products have been actively investigating new and promising ingredients to add to their formulations [9][10][11]. At present, many manufacturers of personal skincare products use chemical surfactants as ingredients in their formulations, particularly as emulsifiers and foaming agents. About 50% of chemical surfactants on the market are of petrochemical origin and are therefore derived from non-sustainable resources [12]. Although these chemical surfactants are extremely effective in formulations, it is suggested that they could be detrimental to the skin and its microbiome [13][14]. It is reported that some of these products often alter the skin flora, causing allergic reactions and skin irritations as they bind to lipids and proteins on the epidermal layer of the skin. Additionally, their prolonged use and high concentration may cause solubilization of the epidermal and intracellular lipids of the skin, thus, affecting the structural integrity and barrier functions of the skin [15]. For these reasons, there has been an impetus for the replacement of chemical surfactants with other compounds that can be produced from cheaper and sustainable resources and, additionally, have properties such as low toxicity, biodegradability and compatibility with the human skin, thereby having less or no negative effects on the health of consumers and the environment [13][16][17][18].

Biosurfactants are surface-active agents of biological origin, mainly produced by bacteria, yeast or filamentous fungi as secondary metabolites. Biosurfactants are obtained from these microorganisms through separation processes such as extraction, precipitation and distillation without adding any organic synthesis before, during and after production and as such, biosurfactants are also termed as naturally derived surfactants. Biosurfactants are generally neutral or anionic in nature. However, those that contain amine groups are cationic in nature [19][20][21]. The diverse structure of biosurfactants results from their different microbial origin, the substrate on which they are grown and cultivation conditions used [20]. Examples of biosurfactants that have been extensively studied include rhamnolipids, sophorolipids, mannosylerythritol lipids (MELs) and surfactin [22]. Biosurfactants have several potential advantages over their synthetic counterparts in addition to their wetting, emulsification, surface tension reduction and detergency functions. These potential advantages include lower toxicity, biodegradability, compatibility with the human skin, stability at extreme conditions (pH, temperature and salinity) and production from cheaper and renewable resources [17][21][23][24]. For these reasons, biosurfactants have received considerable attention in recent decades in the food, environmental protection, textile, oil, agriculture, cosmetic, medical and pharmaceutical industries [25].

2. Classification of Biosurfactants

According to the current literature, biosurfactants are generally categorized into low and high molecular weight compounds. The low molecular weight biosurfactants are more effective at reducing surface and interfacial tensions whereas high molecular weight biosurfactants are better emulsifiers [19]. Each of these groups are further categorized into different classes based on their chemical composition [26][27]. The major classes of low molecular weight biosurfactants include glycolipids, lipopeptides, glycopeptides and phospholipids while high molecular weight biosurfactants include lipoproteins, polysaccharide-protein-fatty acid complexes and lipopolysaccharide-protein complexes [19][28][29]. However, for the purpose of this review, we will focus on low molecular weight biosurfactants, specifically glycolipids and lipopeptides.

Glycolipids constitute the most encountered and most promising group of biosurfactants in the cosmetic, pharmaceutical and food industries [30]. Glycolipids are composed of carbohydrate moieties bonded to fatty acid chains of varying lengths. Examples of glycolipids include rhamnolipids (mono- and di-rhamnolipids) of *Pseudomonas* spp., sophorolipids (Lactonic and acidic) and MELs (MELs A-C) of *Candida* spp., and trehalose lipids of *Mycobacterium* and *Rhodococcus* spp. [20][31][32].

Lipopeptides also have been in high demand in the therapeutic and biotechnological industries in recent years owing to their antimicrobial, antitumor and antitoxin potential [33]. Lipopeptides are mainly produced by *Bacillus* spp. The hydrophilic end of lipopeptides is generally composed of 7–10 amino acids and with hydrophobic component of fatty acids arranged in linear or cyclic order [34][35].

3. Biosurfactants as Promising Alternatives to Chemical Surfactants

Chemical surfactants are mainly classified based on the charge present on their hydrophilic heads after dissociation in water. They are therefore classified as cationic, anionic, amphoteric and non-ionic [36][37]. The amphiphilic structure and other unique properties of chemical surfactants allow their wide application in many current cosmetic and personal care products [15]. Examples of commercially available chemical surfactants mostly used in cosmetic and personal cleansing products include sodium dodecyl sulphate (SDS), sodium lauryl sulphate (SLS), cocamidopropyl betaine and cocamide diethanolamide [18][36]. These chemical surfactants are effective in carrying out the following functions: removal of skin and hair dirt; foaming to enhance lather in shampoos, emulsification or solubilization of immiscible liquids; skin and hair conditioning; moisturizing and wetting. Furthermore, they have absorption and surface tension reduction properties [15][36]. Despite these numerous benefits, it is reported that the prolonged use of cosmetic and personal care products formulated with chemical surfactants could have negative effects on the human skin. Paramount among these effects are alterations in the skin microbiome, skin irritations and allergic reactions, which may arise from the interaction of chemical surfactants with the epidermal layer of the skin [15][38].

The exact mechanisms underlying the detrimental effects that could be caused by chemical surfactants are not properly understood. However, it is believed that such drawbacks stem from the physical and chemical properties of chemical surfactants, the concentration used and duration of contact with the epidermis [18]. The epidermal layer of the skin is mainly composed of keratinocytes [39]. Keratinocytes undergo terminal differentiation to form corneocytes, which constitute the apical layer of epidermis called stratum corneum [40]. Corneocytes are embedded in a lipid-rich matrix and surrounded by a tough cross-linked cell envelope which confers their rigidity and protection [41]. Corneocytes are tightly connected with intracellular junctions called desmosomes. The intracellular spaces of corneocytes are filled with different types of lipids. These lipids are present in the following proportions: 50% ceramides, 25% free cholesterol, 10% cholesterol esters and 10% free fatty acids. These intracellular lipids together with hygroscopic compounds called natural moisturizing factors (NMFs) control transepidermal water loss (TEWL). The penetration of chemical surfactant unimers (individual monomer of surfactants) through the epidermis and its associated cells could cause a shift in balance of the different intracellular lipids (delipidation) and protein denaturation in the membranes of skin cells [42][43]. Furthermore, the interaction of some chemical surfactants with the skin can cause acute swelling of the stratum corneum which is often followed by deswelling [44]. Additionally, the penetration of chemical surfactants through the epidermis may affect living cells such as keratinocytes and Langerhans cells which form an integral part of the innate immune system, thereby affecting the overall immune responses [15].

The tendency of chemical surfactants to penetrate through skin layers causing protein denaturation, allergic reactions and skin irritations, among other factors, is largely dependent on the state of the surfactants in solution (i.e., monomer or micelle) and their concentration [44][45]. Micelles are formed from the aggregates of surfactant monomers in solution at a specific concentration called the critical micelle concentration (CMC) and temperature [46]. Some proposed theories on monomer, micelle and sub-micelle mechanisms of skin penetration remain debatable [47]. While some researchers claim that there is a reduction in rate of surfactant penetration through skin layers when the CMC is reached, owing to the relatively large size of micelles and their surface activities, others report that both micelles and monomers of chemical surfactants have the tendency to penetrate through skin layers and associated cells; and given that micelles are unstable, they may disintegrate into monomers after coming into contact with the skin. Additionally, micelles smaller than aqueous pore of stratum corneum could penetrate through the skin. Moreover, other small-sized micelles (sub-micelles) emerging during the continuous micelle formation and disintegration also have the potential to penetrate through the skin [18][47].

Some well-known approaches to address the effects of chemical surfactants on the human skin have been to increase the size of the surfactant hydrophilic component, the use of mixed surfactants (e.g., anionic and amphoteric surfactants) in formulations and ultimately, the use of surfactants with low CMC [44]. Moreover, in recent years, developments in the field of microbial biotechnology have expanded research into investigating the production of surfactants from natural sources, which will not only have the potential to overcome the above challenges, but in addition, improve skin health [18][22][25]. As such, a promising alternative has been the use of microbial biosurfactants [12][16]. The potential benefits of microbial biosurfactants to the human skin, its microbiome and associated cells will therefore be discussed in the next sections.

4. Biosurfactants, Human Skin and Its Microbiome

One square centimeter of the human skin has been estimated to contain about a billion microorganisms which include bacteria, fungi, virus and eukaryotic microorganisms [48]. Studies have shown that the human body is sterile before birth but becomes colonized by microbes during and after birth. Neonatal skin microbial diversity is dependent on the mode of birth, either by vaginal or assisted delivery (caesarean section). Vaginal delivery babies have a microbial community similar to that of their mother's birth canal while those delivered by caesarean section have microbiota resembling the microbial community of their mother's skin surfaces. Subsequent exposure to environmental microbes, mediated by a wave of activated immune system modulators called regulatory T lymphocytes (*T-reg* cells) and other host factors such as gender, location, nutrition and the use of cosmetic and personal care products often expand the skin's microbial diversity [38][49][50].

The launching of the Human Microbiome Project (HMP) in 2008 in the United States of America (USA), and the use of advanced molecular biology approaches such as 16S rRNA and whole genome shotgun metagenomic sequencing, have revolutionized our understanding of the skin microbial community [49]. It has been further understood that bacteria are the predominant skin microbes at the kingdom level of microbial classification, having approximately equal interpersonal and intrapersonal variations [51]. Using 16S rRNA phenotyping, Grice et al. [52] detected 19 bacteria phyla from a study of 20 diverse skin sites of 10 healthy individuals. Most of the sequences were assigned to four phyla as follows: *Actinobacteria* (52%), *Firmicutes* (24%), *Proteobacteria* (17%) and *Bacteroidetes* (6%). They also found that *Cutibacterium* spp. and *Staphylococci* spp. were dominant in sebaceous areas and although *Staphylococci* spp. were present in moist areas, *Corynebacteria* spp. were the predominant. Moreover, dry areas of the skin such as volar forearm, hypothenar and the buttocks had mixed populations of bacterial cells [52]. More recently, Cosseau et al. [53] also detected the four major phyla abovementioned from the volar forearm of two healthy donors using both culture dependent (traditional method of bacterial identification) and culture independent (16S gene sequencing) methods of bacterial identification. Although Gram negative cells were present, they occupied a very small percentage (approximately 9.7%). Moreover, those Gram negative bacterial cells were mainly detected by gene sequencing [53]. The skin is an ecosystem on its own and it has a very responsive immune system modulating both pathogenic and commensal microbes [1][54]. Notwithstanding, the idea to incorporate bioactive compounds such as microbial biosurfactants into cosmetic and personal care products to encourage a balanced skin microbiome has long been postulated [13][21][31].

Biosurfactants have important potential physiochemical properties which are valuable for the maintenance of skin health. For instance, their fatty acid ends are effective for moisturizing rough and dry skin surfaces. Furthermore, *Cutibacterium acnes* (*C. acnes*) (formerly known as *Propionibacterium acnes*) hydrolysis of triglycerides in the fatty acid chain of microbial biosurfactants could help maintain the acidic pH of the skin, thereby encouraging the adherence of resident skin flora and discouraging the growth of pathogenic skin microbes to maintain a healthy skin microbiome. Additionally, the fatty acids could act as antioxidants to prevent the generation of free radicals by UV light [8][31][55][56].

Unlike chemical surfactants, the components of biosurfactants (sugars, lipids and proteins) are similar to those found in the membrane of skin cells (phospholipids and proteins). Moreover, the movement of compounds across the membrane of skin cells is dependent on their lipophilicity and surface activity, therefore, the unique structure of biosurfactants offers them a high rate of permeability through the membrane of skin cells to regulate protein and skin barrier functions, and trigger beneficial effects relating to hair repair and skin protection mechanisms [9][31][57]. Additionally, several in vitro studies have demonstrated that rhamnolipids, sophorolipids, MELs and surfactin are compatible with the human skin [21][31][58]. Furthermore, their emulsification, foaming, wetting and solubilizing functions, which are dependent on their chemical structure, make them desirable for use as ingredients in creams, lotions, powder, shampoos and other essential cosmetic products applied on the skin [59]. Current commercial cosmetic and skincare products containing microbial biosurfactants include Relipidium™ (body and face moisturizer, produced by BASF, Monheim, Germany) [60], Sopholiance™ S (deodorant, face cleaner and shower gel, produced by Givaudan Active Beauty, Paris, France) [61], Kanebo skincare (moisturizer, cleansing and UV filter, produced by Kanebo Cosmetics, Tokyo, Japan) [28], etc.

Natural inhibitory substances such as bacteriocins, enzymes, and alpha and beta defensins present on the skin surfaces help to keep its microbiome in constant check against pathogens [13][31]. In addition to the skin compatibility features of microbial biosurfactants, their potential to be effective in skin treatment therapies have been reported. Several biosurfactants have been demonstrated to have effective inhibitory mechanisms against skin pathogens such as *Pseudomonas aeruginosa* (*P. aeruginosa*), *Staphylococcus aureus* (*S. aureus*), *Streptococcus pyogenes* and *C. acnes.* For this reason, biosurfactants have been suggested for use as an alternative to conventional antibiotics, although the biocidal activity of biosurfactants is often slight and variable from one compound to another and their overall congener profile [59][62].

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