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Toxicity of Bio-Based Surfactants on Skin: A Systematic Review

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Abstract

The purpose of this paper is to evaluate the toxicity of biosurfactants on the skin using a systematic review approach. Surfactants are widely used in numerous everyday products, from personal care items to cleaning agents, raising questions about their safety and potential adverse effects on users. Conventional surfactants have been found to cause skin irritation and other toxicological issues in some cases, prompting the search for safer, eco-friendly alternatives. Biosurfactants, derived from biological sources, have emerged as a promising substitute due to their potential for reduced toxicity and environmental benefits. This review examines the toxicity profiles of various classes of biosurfactants, including microbial, glycolipids, sugar-based, and other biologically derived surfactants. While most studies indicate that biosurfactants pose minimal irritation and low toxicity to skin cells, isolated findings suggest they may induce cell apoptosis under certain conditions. The systematic review was conducted by analyzing data from PubMed, ScienceDirect, Google Scholar, and Tandfonline using search terms such as "Bio-based surfactant," "Biosurfactant," "Toxicity," and "Skin." The reviewed studies were classified into categories based on biosurfactant characteristics and toxicological findings. This paper provides a comprehensive evaluation of the toxicological, clinical, and pathological effects of biosurfactants on the skin, aiming to bridge the knowledge gap and encourage the development of safer, biologically-derived surfactants for commercial use. Notably, this systematic review highlights novel findings on specific biosurfactants that exhibit enhanced biocompatibility while maintaining effective surfactant properties.

Keywords: Bio-based surfactant, skin, toxicity

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1. Introduction

Surfactants have played an important part in many of the industries today which include cosmetics, pharmaceuticals, detergent and food as stabilizers or enhance penetration of active ingredients [1]. Because of their propensity to absorb at gas-liquid, liquid-liquid, and solid-liquid interfaces, they are also known as surface active agents [2]. This is possible due to their amphipathic nature, which contains both hydrophobic and hydrophilic moieties that help to decrease surface tension [2-3]. Surfactants can also be easily found in our daily household products such as detergents, soaps and gloves. As surfactants are commonly found in everyday items, our skin would very much be the first to be in contact with the surfactants. Unfortunately, most of the surfactants used in the industry today are synthetic, chemical surfactants which have toxic and irritant potential on the skin of the users in the long run [2]. This leads to an increase in demand on searching for a more environmental-friendly, high biodegradability, low toxicity as well as performs better in function to substitute chemical surfactants. This calls for the potential alternative to substitute the harmful synthetic surfactants which are biological surfactants or bio surfactants [4]. Bio-based surfactants are surface-active substances made from sugar or oleo chemicals, which are made from oil and fats. They are acknowledged as being a more environmentally friendly option because they are biodegradable and have an acute affinity compared to the traditional petrochemical-based surfactants.

More studies are being conducted on the creation of novel bio-based surfactants, either from renewable resources or through biological processes such as fermentation [5]. Glycolipids are the most frequently used bio surfactants in cosmetics and personal care products due to their physical-chemical characteristics, biological activity, biocompatibility and biodegradability. They are also utilized as multifunctional components in the formulation of cosmetics. The most popular glycolipids with use in cosmetic and pharmaceutical technologies are sophorolipids, rhamnolipids, and mannosyleryhritol lipids. Lipids have different roles in the composition of cosmetics. They are moisturizing

substances that prevent water loss via a variety of processes [3-6]. Cytotoxicity testing of these biosurfactants would be aimed at skin cells, such as keratinocytes and human fibroblasts. One of the most common methods is the *in vitro* method using skin cell lines [7]. However, there is still limited research on the toxicity effect of biosurfactant on skin. Therefore, this systematic review targets to assess and summaries the published data whether biosurfactants are effective and safe for users to be used compared with chemical surfactants.

2. Materials and Methods

2.1. Protocol

This systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [8].

2.2. Search strategy

The search for original studies was performed on the 18th September 2021 using multiple databases, such PubMed, ScienceDirect, GoogleScholar and Tandfonline. All the databases mentioned followed the search terms: "biosurfactant" OR "bio-based surfactant" AND "skin"; "biosurfactant" OR "bio-based surfactant" AND "skin" AND "toxicity"; "biosurfactant" AND "skin; "biosurfactant" AND "toxicity"; "biosurfactant" AND "skin" AND "toxicity"; "bio-based surfactant" AND "skin"; "bio-based surfactant" AND "toxicity"; "bio-based surfactant" AND "skin" AND "toxicity".

2.3. Eligibility criteria

Articles were eligible when reporting in English, had access to full text, original manuscript, reporting on the toxicity of various categories of biosurfactants on skin (i.e. *in vitro*, *in vivo*, human skin models, animal skin models, human and animals cell lines), and a publication year between the range from the year 2000 till present. The year 2000 was determined as the cutoff value in order to retain the reliability of information in the recent decades. Review papers that had access to full text were excluded. Studies that met the above inclusion criteria in terms of language and publication years but had insufficient details on the toxicity of biosurfactants on skin or only reporting on either one of the search terms "bio-based surfactant", "biosurfactant", "toxicity" and "skin" were also excluded.

2.4. Screening

Articles were screened by title and abstract based on the pre-specified inclusion and exclusion criteria. Next, full-text papers were reviewed to assure the eligibility. Results of the search were considered, and any disparities were clarified until an agreement was gained. A flowchart of this selection procedure is shown in Figure 1.

3. Results and discussion

3.1. Results

3.1.1. Search results

There were 4026 likely relevant studies picked out according to the predefined search strategy. A total of 1240 studies remained because of elimination of 2786 duplicates. After screening through abstracts of the articles that remained, 1184 articles were ruled out since they were not fulfilling the inclusion criteria and not eligible for the topic; therefore, 56 studies remained. After a second round of review, 42 were excluded based on exclusion criteria. Thus, 14 studies were suitable for the included criteria in the end.

3.2. Discussion

This systematic review focused on the toxicity of biosurfactant on skin. The main findings revealed that the majority of the biosurfactants showed little to no toxicity when tested on human skin models. Most of included studies demonstrate acceptable toxicity results, with comparative evidence with already commercialized surfactants; either synthetic or biosurfactant used in industries today. From all the articles found, the reported biosurfactants could be divided into several types. Lecithin is a complex combination of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol, as well as varying quantities of triglycerides, fatty acids, carbohydrates. To change qualities of viscosity and crystallization, they utilized in foods as emulsifiers and surfactants. As an emulsifying ingredient for textiles, leather, cosmetics, paints, and plastics as well as a releasing agent for concrete and pesticides, lecithins are utilized in industry [9]. Vater *et al*. used 2 different types of cell viability assays (BrdU and EZ4U) to assess *in vitro* toxicity of lecithin-derived surfactant on primary human keratinocytes and fibroblasts.

When keratinocytes alone were treated with the surfactant, results showed high cell viability of more than 80%. However, when keratinocytes and fibroblasts were treated with sodium lauryl sulfate (SDS) which is a commercialized synthetic surfactant, the cell viability instantly dropped to 0%, thus, displaying how toxic is SDS as a surfactant. Combinational results of the cytotoxicity assays EZ4U and BrdU showed that lecithin-based surfactant performed better than the SDS-based surfactant [10]. This finding is supported in another study of research team where they obtained a mean cell viability of more than 60% when the lecithin-based surfactant was tested on primary fibroblasts and a mean cell viability of 82.43% when tested on primary keratinocytes. The results obtained implies that lecithin-based surfactants possess low cytotoxicity on skin, making them a good candidate to be used for wound healing [11]. On the other hand, according to a study by Sanchez *et al*., it is proven that toxicity and irritancy potential of a lysine-based surfactant was low on human keratinocytes cell line (NCTC 2544) as tested by using MTT assay, and this indicates that surfactant is safe to be used [12].

Biosurfactants could be derived from micro-organisms where they serve as the primary lipids in bacterial and fungal cell walls. In aqueous solution, glycolipids are amphiphilic compounds that form persistent micelles and can provide low interfacial tension [13]. Rhamnolipids is considered one of the most used glycolipids as biosurfactants. Rhamnolipids are generated by a few bacterial species (i.e. *Pseudomonas chlororaphis*, *Pseudomonas aeruginosa*, *Burkholderia pseudomallei*) as one or two rhamnose sugar groups linked to one or two fatty acid chains [14]. According to a study by Voulgaridou *et al*., alamarBlue and propidium iodine assays were used to assess toxicity of surfactants derived from two different bacterial strains, MCTG107b and MCTG214(3bq). Both surfactants reported negligible cytotoxicity when concentrations used were below 0.25 mg/mL. However, cytotoxicity reported when concentrations go beyond 0.25 mg/mL.

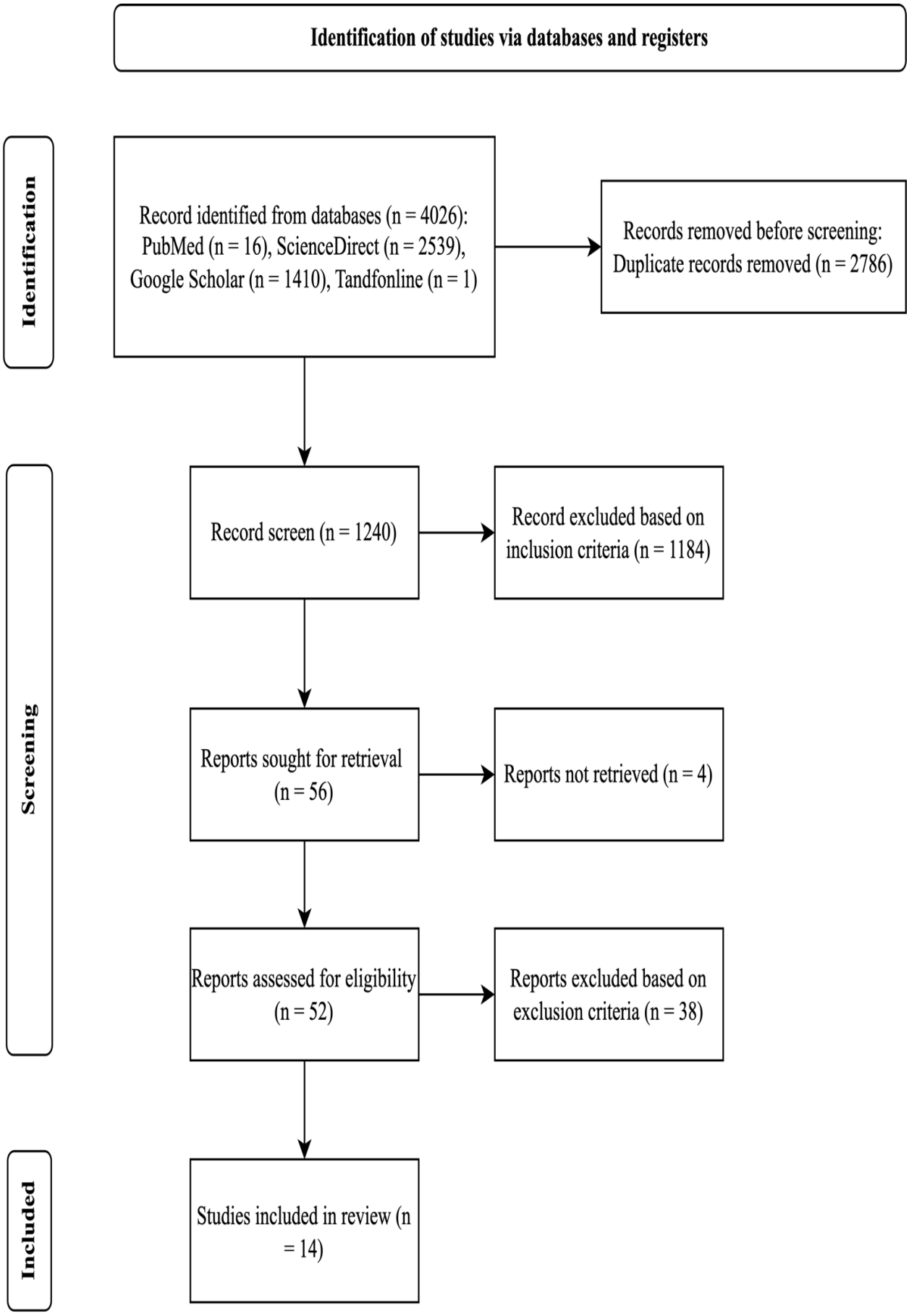

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

Table 1: Types of biosurfactants, their functions and toxicity on skin**.**

Biosurfactants	Applications/ functions	Findings	References
Lecithin derivatives	Emulsifier	Viability of keratinocytes > 80%	[10]
		Mean fibroblast viability > 60%; mean keratinocyte viability of 82.43%	[11]
Lysine derivatives	Emulsifier	Inversed correlation between MTT values and maximum amount of IL-1α	[12]
Rhamnolipid-based	Stabilizer	MCTG107b and MCTG214(3b1) showed negligible cytotoxicity (concentration < 0.25 mg/mL)	[2]
		RL-1 and -2 were tested to be non-toxic	[15]
Sugar-based	Stabilizer/ emulsifier	Sucrose stearate and sucrose oleate biosurfactants showed no toxicity to the cells but sucrose laurate biosurfactant had toxicity.	[19]
		Glucose or maltose-based surfactants show lower cytotoxicity compared to Tween 20 and Hecameg when tested on 3D dermal model	[1]
Sophorolipid-derived	Stabilizer	Low cytotoxicity of surfactant towards human keratinocytes cell line HPK II and human fibroblasts (96% cell viability)	[20]
		Surfactant does not affect cell viability of human endothelial (HUVEC& HDMVEC) cells and keratinocytes (HaCaT)	[21]
Mannosylerythritol lipid (MEL)	Emulsifier	MEL-A solution of 5 wt% and 10 wt% ; recovery rate of 73% and 91% respectively, cell viability of 91.3%	[22]
		MEL-C had no toxicity towards skin fibroblasts at concentration less than 10 µg/mL	[23]
		MEL-B is cytotoxic towards cancer cells at concentration over 20 µg/mL	[25]
Buriti oil-based	Moisturizer	Low toxicity on HaCat and 3T3 cells	[24]
Di-rhamnolipid-based	Moisturizer	Cytotoxic towards myofibroblasts but not keratinocytes and dermal fibroblasts	[24]

At concentration of 1 mg/ml, cell viability was markedly seen to drop below than 50% after treated for 2 and 3 days [2]. On the other hand, Müller *et al*. used alamarBlue cell proliferation assay to prove that rhamnolipids RL-1 and RL-2 biosurfactants that are derived from the bacteria *Pseudomonas aeruginosa* were non-toxic and safe to be used. The non-toxic property of the microbial-derived biosurfactants suggests that compounds are safe and compatible for future applications [15]. Sugar-based surfactants are surface active agents that consist of sugar group in their structure. Sugar raw ingredients appearing in the monomeric form (i.e. glucose, fructose), polymeric (i.e. starch cellulose) or dimeric (i.e. lactose) are used to make these sugar-based surfactants [16-17]. In contrast with synthetic surfactants, these surfactants that contain sugars as polar component heads are more stable when used. Furthermore, they are also non-irritating, gentle on the skin, mucous membranes and eyes. Thus, this makes sugar-based biosurfactants to be appealing in the use for personal care items, particularly face skin care and those used on children's sensitive skin [18].

These surfactants have started gaining popularity and have been widely applied and used due to their availability. In a study by Lémery *et al.*, the viability of epidermal cells was tested through MTT and LDH tests using different sugar-derived (sucrose stearate, and sucrose oleate and sucrose laurate) surfactants and effect of these biosurfactants was compared with the commonly used synthetic surfactants, sodium lauryl sulphate (SLS). The findings suggested that all the sugar-based biosurfactants

showed no toxicity to the cells except sucrose laurate, which induced the release of interleukin-1∝ and interleukin-8 three times higher than the control. In return, the cell viability dropped to 50% and lower. The most toxic surfactant is SLS, showing the smallest MTT value which was 0.05 while poly(ethylene glycol)-100 stearate showed the largest MTT value of 1.12, showing that it is a very mild and gentle surfactant. When the MTT value is high, it indicates that the substance tested has low toxicity. Hence, the results obtained by Lémery *et al.* suggested that SLS was highly toxic while sugar-derived biosurfactant was less toxic. The synthetic surfactants containing SLS, cethyltrimethylammonium chloride, and Ceteth-10 exhibited 80-100% cell death, indicating the toxicity of synthetic surfactants [19].

This was also supported by another study by Lu *et al*., where the sugar-based surfactants (with an eight-carbon alkyl chain bound to a glucose or a maltose head group through an amide linkage) showed lower cytotoxicity than standard surfactants (Tween® 20 and Hecameg®) when tested on a 3D skin model with no appearance of irritation after 2 days of application [1]. Another widely used biosurfactant is derived from glycolipids. Hirata *et al*. investigated sophorolipids-derived biosurfactants on human keratinocytes cell line HPK II and human fibroblasts. MTT results showed an extremely high cell viability of 96% and the cytotoxicity was even lower than a commonly used surfactant in cosmetic materials, surfactin [20]. The data obtained from Lydon *et al.* further support the non-cytoxicity of sophorolipids where the findings showed that sophorolipid-based surfactant did not affect cell viability when tested in an *in vitro* human endothelial (HUVEC and HDMVEC) cells and keratinocytes. In short, sophorolipids are suitable to be used in wound healing or treatment of bacterial infections [21]. There have been a few studies conducted on mannosylerythirol lipids (MEL), which are also classified under glycolipids.

A study on MEL-A was conducted to examine its recovery effect on skin that was damaged by SDS. MEL-A shows cell viability of 91.3% on skin with recovery rate of 73% and 91% when used at 5 wt% and 10 wt%, respectively. The findings indicate that MEL-A is a suitable compound for novel skincare as it also displays moisturizing effects towards keratinocytes [22]. Another study on MEL-C by Takahashi *et al*. found that the biosurfactant did not exhibit any toxicity towards skin fibroblasts if concentration used was less than 10 µg/mL [23]. Study by Zanatta *et al*. was done using the neutral red release assay to investigate the cytotoxicity of buriti oil-based surfactant on two cell lines, HaCat and 3T3. Results indicated that the biosurfactant presented low cytotoxicity to the cells even at high concentrations [24]. Biosurfactants have been known as being less toxic, highly biodegradable and environmentally friendly in general, and the above studies have enhanced the idea of biosurfactants as being safe for users. Interestingly, there are a few studies that oppose the concept of biosurfactants as safe and low cytotoxicity compounds and rather using the biosurfactants to target cell apoptosis.

Feuser *et al*. investigated the cytotoxic effect of MEL-B on tumour (B16F10) and non-tumour (NIH3T3) cells. The results revealed that MEL-B was cytotoxic to the tumour cells when used at a concentration of more than 20 µg/mL which would decrease cell viability by 65%. The drop in cell viability was more pronounced when concentration increased to 40 and 80 µg/mL. Aside from concentration being an important key factor in cytotoxicity of cell, incubation period is also important. In same study, death of B16F10 cell was more obvious at 40 µg/mL after 48 and 72 hours than 24 hours of incubation. About NIH3T3 cells, cytotoxicity of cells seen at concentrations 40 and 80 µg/mL but no cytotoxicity when the concentration was between 5 to 20 µg/mL [25]. Another study that presented findings on cell killing capability of biosurfactants was by Shen *et al*. where they tested di-rhamnolipid (RHA) which is a glycolipid-type biosurfactant on myofibroblasts. Results illustrated that RHA was effective in killing myofibroblasts. Fortunately, there was no significant toxicity to human keratinocytes as well as dermal fibroblasts [26]. The important findings from systematic review are summarized in Table 1.

4. Conclusion

In conclusion, the present systematic review found that majority of the different types of biosurfactants displayed little to no toxicity to the skin with the exception of a few studies that supported the notion of biosurfactants having cytotoxic effect on the cells. This systematic review also supports and highly encourages the use of biosurfactants in industries in the future. Additionally, this systematic review highlights novel findings on specific biosurfactants that demonstrate enhanced skin compatibility while retaining their surfactant efficacy, paving the way for safer alternatives in consumer products. This paper provides an overall perspective on the toxicity of different types of bio-based surfactants on the skin. Due to the heterogeneity of the included papers, a meta-analysis was not carried out. The current challenges in the medical field are the insufficient testing of biosurfactants on skin and limited reports addressing the safety use of biosurfactants on products that comes in contact with the skin and the lack of clinical data of it. Hence, more efforts in the testing of a variety of surfactants are encouraged. The use of animal models and human volunteers should be expanded and implemented for testing.

Conflict of interests

None to declare.

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