

## Review

# Commercial Topical Probiotics for the Skin Microbiome: The Majority Do Not Contain Live Microbes and May Not Satisfy Criteria for Safe and Effective Use

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**Abstract:** In this paper we aim to help topical probiotics research and development achieve its potential as an incredible future solution for skin problems by investigating whether the current products on the market satisfy criteria for safe and effective use on the skin microbiome. As previously defined, this includes whether they use microbes known to be part of a healthy skin microbiome and in healthy amounts. In addition, we evaluate whether they contain live microbes, and therefore can be classified as probiotics according to the WHO's definition. Using recent market analysis at least 84% of products do not contain live microbes. Of the products that appeared to use live microbes, they contained those used in research and development of probiotics for the gut. Due to the varying composition of each person's microbiome, there is not a one size fits all probiotic solution. Personalisation of probiotics products is essential to satisfy the criteria for safe and effective use, but none of the products on the market, understandably, offer this. Upsetting the delicate ecosystem balance of the skin microbiome could have damaging effects and regulation could help to stop a loss of trust between consumers and cosmetics industry. Future work will perform an in-depth evaluation of the topical probiotics on the market in the EU, USA, and Canada. We will also investigate how to move the topic closer to achieving its potential by updating the criteria, including by discussing how to measure the success of a probiotic solution.

**Keywords:** topical probiotics; skin microbiome; probiotics; biodiversity; microbiome; skin allergy; cosmetics

## 1. Introduction

In this paper, we analyse the current commercial topical probiotics on the market to determine whether they pass the criteria for the safe and effective use as defined in previous work [1]. We also discuss whether they contain live microbes, can therefore be called probiotics in accordance with the WHO's definition, and the implications of this. The growth in commercial topical probiotics brings with it the responsibility for companies to develop products that will, at the very least, do no harm. More importantly they should be shown to benefit the skin. Currently, it is a mistaken assumption that anything marketed under the 'probiotics' banner is immediately health giving [2].

But what is the end goal for probiotics? Without this definition, there is no way to objectively determine and improve their efficacy. We believe that the overall aim of probiotics should be to improve the health and diversity of the microbiome because ecosystems across nature exhibit higher biodiversity when healthier [3,4]. A damaged skin microbiome, decreased in biodiversity, has been linked to most common skin problems [3,5–12], however, whether it is a cause or a symptom remains to be determined.

Probiotics in the gut have been linked with beneficial effects, including the prevention of pathogen adherence, antimicrobial properties and controlling illness [13,14]. In comparison, the same research focus the skin is virtually unheard of [15–18]. Topical probiotics, or the application of live microbes to the skin, is a method that has incredible

potential for restoring our skin to levels of health and biodiversity seen on our ancestors and as a treatment for skin diseases linked to a dysbiotic microbiome [1,14]. Recently, their use has been linked to improving skin conditions such as acne, atopic dermatitis, wound and burn healing, psoriasis, and rosacea [15,19,20].

However, it is important to note that probiotics could also potentially disrupt the delicate microbiome balance and reduce biodiversity. The artificial addition of organisms to an ecosystem without understanding the exact numbers and which type to introduce, has produced catastrophic effects across nature throughout human history [1]. For humans, this is made even more complicated by the fact that everyone possesses a 'virtually unique' microbiome that also varies between body sites [21–23].

Previous work has warned against the use of probiotics without proper implementation [1,24], that universal health benefits are a falsehood [2], that side effects remain a concern [16,25], and a growing problem is unsubstantiated therapeutic claims [16,26].

Therefore, we begin the paper with an analysis of current commercial probiotic products.

## **2. Analysis of Commercial Topical Probiotic Products in North America**

Previous work summarised 50 of the products on the market in North America categorised as 'probiotics' using two of the largest cosmetics retailers' databases [27]. As this work was published in 2021, the analysis is recent enough to give an accurate representation of the market. Table 1 is taken from their paper, and we added extra columns to indicate whether products contain live microbes and whether they have been personalised.

The term 'personalised' used in column five of Table 1 is used to indicate whether the probiotics products are tailored to individual consumers' microbiomes. The skin microbiome varies so drastically from person to person that each human is thought to possess a 'virtually unique' microbiome and there is also large variation between body sites [21–23]. Therefore, adding the same microbe(s) to two different microbiomes would not necessarily have the same outcome. Ecosystems are governed by non-linear physics principles and therefore there are no foregone conclusions nor are reproducible results expected [3,28]. To sum up, a successful probiotic solution for one person will not necessarily be a success for another. Therefore, it will be crucial to tailor probiotic solutions to the individual in the future [1].

**Table 1.** A list of commercial topical probiotic products in the EU and UK adapted from previous work [27]. \* “Bifida ferment lysate” is the name given to a lysate from *Bifidobacterium longum reuter* [29].

Product Code	Type	‘Probiotic’ Used	Live/Non-Live	Personal-ised?
1	Balm	<i>Lactococcus</i> ferment lysate	Non-Live	No
2	Balm	<i>Lactobacillus</i> ferment	Non-Live	No
3	Cleanser	Bifida ferment lysate *	Non-Live	No
4	Cleanser	<i>Lactobacillus</i> ferment	Non-Live	No
5	Cleanser	<i>Lactobacillus</i> ferment	Non-Live	No
6	Cleanser	Bifida ferment lysate *	Non-Live	No
7	Cleanser	<i>Lactobacillus</i> ferment	Non-Live	No
8	Cream	<i>Lactobacillus</i> ferment, <i>Lactococcus</i> ferment lysate, Bifida ferment lysate *, <i>Lactobacillus</i> , <i>Streptococcus thermophilus</i> ferment	Live?	No
9	Cream	<i>Lactobacillus</i> ferment	Non-Live	No
10	Cream	<i>Lactobacillus</i> ferment	Non-Live	No
11	Cream	<i>Lactobacillus</i> ferment	Non-Live	No
12	Cream	Bifida ferment lysate *	Non-Live	No
13	Cream	<i>Lactobacillus</i> ferment	Non-Live	No
14	Cream	<i>Bacillus coagulans</i>	Live?	No
15	Cream	<i>Lactococcus</i> ferment lysate	Non-Live	No
16	Cream	<i>Lactobacillus</i> ferment	Non-Live	No
17	Cream	<i>Lactobacillus</i> ferment lysate	Non-Live	No
18	Cream	<i>Lactobacillus</i> ferment	Non-Live	No
19	Cream	Bifida ferment lysate *	Non-Live	No
20	Deodorant	<i>Saccharomyces</i> ferment filtrate	Non-Live	No
21	Foundation	<i>Lactobacillus</i> ferment	Non-Live	No
22	Foundation	<i>Lactobacillus</i>	Live?	No
23	Foundation	<i>Lactococcus</i> ferment lysate	Non-Live	No
24	Gel	<i>Lactococcus</i> ferment lysate	Non-Live	No
25	Gel	<i>Lactobacillus</i> , <i>Lactococcus</i> ferment extract	Non-Live	No
26	Gel	<i>Leuconostoc</i> ferment filtrate	Non-Live	No
27	Gel	<i>Lactococcus</i> ferment lysate	Non-Live	No
28	Gel	<i>Lactobacillus</i> , Greek yogurt, yogurt, yogurt powder	Live?	No
29	Mask	<i>Lactobacillus</i> , Greek yogurt, yogurt, yogurt powder	Live?	No
30	Mask	Bifida ferment lysate *	Non-Live	No
31	Mask	<i>Lactococcus</i> ferment lysate	Non-Live	No
32	Mask	<i>Lactococcus</i> ferment lysate	Non-Live	No
33	Mask	<i>Lactobacillus</i> ferment	Non-Live	No
34	Mask	<i>Lactobacillus</i> ferment, <i>Lactococcus</i> ferment lysate, Bifida ferment lysate *, <i>Lactobacillus</i> , <i>Streptococcus thermophilus</i> ferment	Live?	No
35	Exfoliant	<i>Lactobacillus</i> ferment	Non-Live	No
36	Exfoliant	<i>Lactococcus</i> ferment lysate	Non-Live	No
37	Primer	<i>Saccharomyces</i> ferment filtrate	Non-Live	No
38	Exfoliant	<i>Lactobacillus</i> ferment lysate, <i>Leuconostoc</i> ferment filtrate	Non-Live	No
39	Exfoliant	<i>Saccharomyces</i> ferment filtrate	Non-Live	No
40	Exfoliant	<i>Lactobacillus</i> ferment lysate, <i>Leuconostoc</i> ferment filtrate	Non-Live	No
41	Serum	<i>Lactococcus</i> ferment lysate	Non-Live	No
42	Serum	<i>Lactobacillus</i> ferment, <i>Lactococcus</i> ferment lysate, Bifida ferment lysate *, <i>Lactobacillus</i> , <i>Streptococcus thermophilus</i> ferment	Live?	No
43	Serum	<i>Lactobacillus bulgaricus</i> ferment filtrate	Non-Live	No
44	Serum	Bifida ferment lysate *	Non-Live	No
45	Serum	<i>Lactobacillus</i> ferment extract	Non-Live	No
46	Serum	Bifida ferment lysate *	Non-Live	No
47	Serum	<i>Lactobacillus</i>	Non-Live	No

48	Serum	Bifida ferment lysate *	Non-Live	No
49	Soap bar	Bifida ferment lysate *	Non-Live	No
50	Soap bar	Yogurt	Non-Live	No

3. Are These Products Probiotics?

The World Health Organisation (WHO) defines probiotics as “living microorganisms which, when administered in adequate amounts, confer a health effect on the host” [19]. We explain in the subsequent sections, some products on the market call themselves the name without containing live microbes or passing a universal test to determine whether they will confer a health benefit to each individual consumer. This means many products using the title do not qualify as a probiotic and mislead consumers who often immediately associate them with health benefits.

The first and most important prerequisite of probiotics is that they contain live microbes. Therefore, in this section we answer the following two questions regarding the products in Section 2: Do they contain live microbes? Why is this important?

3.1.84%. of Products Do Not Contain Live Microbes

Of the products listed in Table 1, only 16% of products appeared to contain live microorganisms and the other 84% contained ingredients like ferments, lysates and extracts, common in so-called probiotic products [30]. The results are depicted in Figure 1. So, if they don't contain live microbes, what does that classify them as? These ‘probiotic-derived’ compounds all appear to fall under the postbiotics banner. This term means “effector molecules derived from probiotics by bacterial secretion or released after lysis” [31]. They can have similar properties to their parent probiotics [15,32,33] and the idea behind their use is to obtain the benefits of probiotics without the risk of administering living microbes [15]. Lysates contain the products of lysis, which is the breaking down of the membrane of a cell, often using strong detergents, high-energy sound waves or infection with a virus that compromise its integrity [34]. These are contained in a fluid and is classed as a bacterial ‘extract’ [35]. They do not contain live organisms [36]. Future work will elaborate on the different probiotic derived compounds.

There are transparency issues that arise from the issues described here; if the consumer receives a product containing microbes that are dead, it is significantly different to their perception based on the ‘probiotic’ name tag and official definition. Misleading marketing also exists in the ‘natural’ cosmetics industry, where ‘natural’ cosmetics products have been found to contain over 70% synthetic ingredients [11]. Labelling and claims regulation could help prevent a disconnect between consumers and the cosmetics industry. The food industry is ahead in this regard; the European Food Safety Association (EFSA) does not allow health claims attached to probiotic products and the sale of any products called a ‘probiotic’ because it constitutes an “unauthorised health claim” [37].

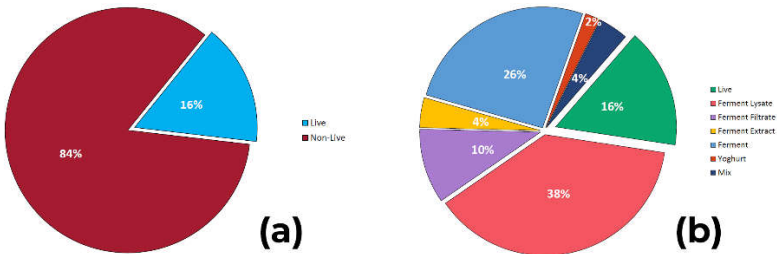


Figure 1. Graph (a) shows the percentage of products summarised in Section 2 which contain live (light blue) and non-live (red). (b) shows the products broken down into what they contain.

3.2. Why is This Important?

While the differentiation between live and non-live microbes may seem pedantic, the difference between live microbes, which have the ability to colonise the skin surface [14],

and dead ones appears significant. Microbes on a healthy skin microbiome live in mutual symbiosis with the host which means that the interactions with the ecosystem are beneficial to both parties [38–40]. Although there have been many beneficial health outcomes associated with their use [41,42], we argue it could be a natural hypothesis to suggest that probiotic-derived substances may not have the long-lasting effects on the ecosystem that live ones would have if introduced correctly [1]. This would need to be investigated in more detail in future work. To offer a perspective on this issue which may aid visualizing the difference, previous work used the re-introduction of the wolves to Yellowstone Park as an example of an incredibly successful ‘probiotic’ solution that transformed the ecosystem [1,3]. Where the wolves represented live microbes being introduced to the skin. Even though the mechanisms are different, the analogy of adding carcasses of dead wolves instead of live ones to Yellowstone Park conveys the idea of postbiotics. It might have some benefit in the short term by providing food for various animals, but in the long term, would dead wolves lead to the systemic and far-reaching ecosystem transformation triggered by the re-introduction of the wolves? When the wolves died out, the Elk were one of the main sources of damage to the park, mainly because their swelling population resulted in overgrazing. Dead wolves would likely do little to curb this, as only living wolves would have been able to keep their numbers at a non-pathogenic level, and keep the ecosystem balance in check.

If the industry is to evolve as is needed, the research that underpins its ideas should lead the way. Just like in the industry, the conflation of probiotics and postbiotics is also apparent in some research. The use of ‘heat-treated’, ‘denatured’, ‘deactivated’, or ‘sonicated’ microbes in topical probiotics studies implies there may be some confusion about the importance of live microbes and their incredible potential for transforming the skin’s ecosystem [15,43–47]. Some studies explicitly define probiotic solutions as those that use ‘inactivated microbial biomass of beneficial bacteria’ [48]. A further study which used a *Lactobacillus* strain as a ‘probiotic’ described the microbes as ‘heat-treated’ and ‘non-replicating’ [43].

Further confusion might arise from the lack of a clear goal. One study stated that probiotics are not intended to take a foothold on the skin [49]. In this case, what is their purpose apart from a small, short-term effect that may require ‘topping up’? The example of the re-introduction of the wolves to Yellowstone Park shows how the colonisation of healthy amounts of known beneficial organisms can transform the health of an ecosystem including the skin microbiome [1,3]. Therefore, it is vital that scientists and companies understand the importance and potential pitfalls of the addition of live microbes.

### 3.3. Formulation Issues with the Inclusion of Live Microbes in Commercial Products

The regulations for selling cosmetics in the EU state that they must pass microbiological and stability tests [50]. This means products must have effective preservatives and other additives that inhibit the growth of microbes and keep the formulation stable. As a result, it makes the production of a commercially viable cosmetics product that contains live microbes for the duration of its shelf life very difficult. Furthermore, it remains challenging for products containing live microbes to successfully deliver them to the skin.

In the USA, the FDA states “Neither the law nor FDA regulations require specific tests to demonstrate the safety of individual products or ingredients.” [51]. Even though the same regulations as in the EU don’t exist, products often contain many ingredients that would inhibit live microbes, as a way of extending shelf life. Counter-intuitively, the antimicrobial effect may be even more pronounced in some American products because fewer regulations on ingredients may allow the use of harsher preservatives and additives. These reasons highlight why commercial probiotics often contain no live microbes and instead contain ‘denatured’ heat-killed versions, or bacterial lysates and extracts [27].



#### 4. Do Probiotics Products Satisfy the Criteria for Safe and Effective Use?

The addition of organisms can be beneficial or detrimental to an ecosystem depending on how it is implemented [1]. The addition of incorrect numbers or the wrong type of microbe can damage the microbiome. Therefore, in this section we review the products which appear to contain truly live microbes Section 2 to investigate whether they are acceptable under the guidelines of a previous set of criteria for safe and effective use of topical probiotics.

##### 4.1. The Criteria

The re-introduction of wolves to Yellowstone Park is a macro-scale example of an extremely successful probiotics solution to a damaged ecosystem [1]. It was a success because of two reasons. Firstly, the Wolves were known to be an integral part of the ecosystem before being re-introduced. Secondly, the park rangers knew the exact number of wolves that were stable in the ecosystem and that contributed a positive effect to it.

It could also very easily could go the other way and cause significant damage. Examples of this are the introduction of Japanese knotweed (*Fallopia japonica*) and the ash die-back (*Hymenoscyphus fraxineus*) fungus to the UK [1,52,53]. Based on the lessons learned from the two opposing outcomes, the following set of criteria was created which the authors stated should be satisfied to ensure that administering live microbes firstly does no harm, and secondly increases biodiversity and positively impacts skin microbiome health. These are as follows:

1. Make sure that the microbes to be introduced are known to be important constituents of a healthy skin microbiome on the specific person and body site.
2. Make sure that the microbes are introduced in numbers that are known to be stable on a healthy skin microbiome of the individual and specific body site.

In this section, we evaluate whether the products in Section 2 satisfy these criteria.

##### 4.2. Are the Microbes Used in the Products in Section 2 Known to be Important Constituents of a Healthy Skin Microbiome?

According to the previous work the evaluation of commercial probiotics was taken from, 8 of 50 products contained live microbes. This is shown in Figure 1. For the purposes of this study, we take their assessment at face value, despite the difficulties surrounding the inclusion of live microbes in commercial topical probiotics due to formulation issues we described in Section 3. In future work, we will conduct a larger study of the commercial topical probiotics on the market in the UK, EU and USA which will properly evaluate live microbe claims. Table 2 and Figure 3 show that, of the eight products containing live microbes, seven of them, 87.5%, were *Lactobacillus* and one product, 12.5%, contained *Bacillus coagulans*.

##### 4.2.1. Lactobacillus

There is some debate on the topic, with some work stating it is potentially endogenous [54,55] but contrasting research describes how it is thought *Lactobacillus* is rarely found and may not primarily belong on a healthy skin microbiome [56]. An argument for *Lactobacillus* being an important constituent of healthy skin is that, as an integral part of the vaginal microbiome, babies have the bacteria transplanted onto their skin by their mother at birth [57]. However, questions remain around whether it would remain on the skin as children grow up, or it is depleted. It has also been shown that *Lactobacillus* strains were not able to colonise the skin for a long period of time [58]. This could suggest that it may not be an important part of a healthy skin microbiome.

It is the most commonly used microbe in ingestible probiotics for the gut microbiome and has been subject to a large amount of research with many positive study outcomes observed, such as enhancing the integrity of the intestinal barrier, modulating intestinal immunity, improving neurological conditions, sleep quality, diversity of the gut microbiome, and helping alleviate skin problems [59,60]. Therefore, is it used in topical products

because it was used for the gut microbiome? The skin and the gut microbiome, despite being governed by the same non-linear physics principles, are different in composition [61].

Topically applied live *Lactobacillus* strains have been associated with improvements in skin conditions such as reducing acne lesions, improving burn and wound healing and their infections, foot ulcers, and more [19,45,54]. Further work has investigated the effect of topically applied heat-treated, non-live *Lactobacillus johnsonii* NCC 533. The first found “applying the lotion for 3 weeks controlled *S. aureus* colonization and was associated with local clinical improvement” [43], and the second reported a lotion could benefit atopic skin by enhancing the skin’s innate immunity and reducing *S. aureus* colonization [62]. More work is needed; a successful solution should be assessed by its ability to provide lasting beneficial effects, instead of short-term ones which may cover up symptoms instead of deal with the underlying cause.

#### 4.2.2. *Bacillus coagulans*

*Bacillus coagulans* is another example of a microbe that has been used in research and development for ingested probiotics [63]. It is thought to be used due partly to its high tolerance of extreme environmental conditions compared to more conventional probiotics such as *Lactobacillus* spp. [64]. It was found to be stable in static gut model conditions [65]. Research has reported beneficial effects of its use internally, such as the promotion of intestinal digestion, the inhibition of pathogenic bacteria, the boosting of the immune system, and the alleviation of human diseases such as IBS, obesity and depression [66]. However, several studies have reported that it struggles to colonise in the mammalian intestinal tract and therefore has only a transient effect [67,68]. So, if it does not properly take a foothold internally where it is more suited, then would it not encounter the same problem, if not more exaggerated, on the skin?

We only found one study which dealt with topically applied *Bacillus coagulans*; it reported that application with a cream containing the microbe exhibited antimicrobial effects and reduced acne symptoms [69]. However, it was a ‘ferment filtrate extract’ which means it was not in live form.

Its use in topical applications would need to be assessed because of the differences between the skin and gut microbiomes. The pH which allows optimum *Bacillus coagulans* growth is 5.5-6.5 and the optimum temperature is 35 to 50°C [63,70]. The pH of healthy skin is much lower at 4-4.5, so this could signal that *Bacillus coagulans* may not be a part of healthy skin, neither would it be likely to take a foothold if the conditions on the skin are so different to those that promote its growth [11,40]. Maybe the aim is not for it to colonise at all?

#### 4.2.3. What Works in the Gut May Not Benefit the Skin

Decisions on which microbes to use in topical probiotics research and product development appear to be based on results from the gut microbiome. Comparisons between the skin and gut are useful for conveying concepts to a wider audience because the gut microbiome is far more familiar to consumers. However, microbes display different behaviours under different ecosystem conditions and their behaviour depends on the overall health and biodiversity of the microbiome [3,71,72]. Therefore, applying the same microbes used in probiotics for the gut, to the skin, may not be useful, and could be damaging.

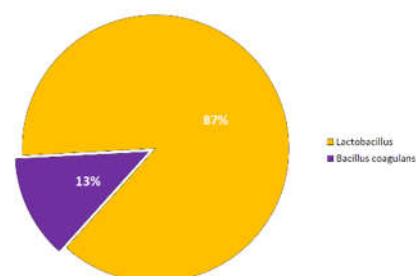
More work would be needed to confirm whether *Lactobacillus* and *Bacillus coagulans* are part of a healthy skin microbiome, and that they are safe. However, if not, it is difficult to predict how the resident microbial communities would react when repeatedly introducing microbes that are not part of a particular region. The assumption that what works for the skin will also work for the gut misunderstands that the two ecosystems are profoundly different in composition [61]. The same is true for the introduction of any organisms that are non-native to an ecosystem. Previous work describes the catastrophic

damage done to ecosystems by the introduction of non-native species, whether it was accidental or intentional [1,3,73,74]. Well-known examples of this ecosystem interference include the introduction of Japanese knotweed (*Fallopia japonica*) to the UK and the cane toad to Australia [52,75]. It is likely that the skin is no different.

Lastly, if these microbes used internally may not be suitable for the skin, which ones could be used? This may depend on the person, body site and particular issue. For example, sebaceous areas of the body such as the glabella (forehead) crease are dominated by *Propionibacterium* species, with *Staphylococcus* second with regards to relative abundance [76]. In moist areas, bacteria that thrive in humid environments, such as *Staphylococcus* and *Corynebacterium* species, were more abundant in moist areas such as the feet [76]. Research for the gut has suggested that, just like in Yellowstone Park, a solution to biodiversity loss and problems could be re-introducing “key bacterial predators” that have been reduced by western lifestyle [77]. Further work would be needed to investigate this novel idea for the skin and identify potential ‘predators’.

**Table 2.** The products from Table 1 which contain live microbes according to the study it was adapted from [27].

Product Code	Microbe
8	<i>Lactobacillus</i>
14	<i>Bacillus coagulans</i>
22	<i>Lactobacillus</i>
28	<i>Lactobacillus</i>
29	<i>Lactobacillus</i>
34	<i>Lactobacillus</i>
42	<i>Lactobacillus</i>
43	<i>Lactobacillus</i>



**Figure 2.** Types of microbes within the products containing live microbes.

#### 4.3. Are the Microbes Within the Products in Section 2 Being Introduced in Healthy Amounts that are Tailored to the Individual?

Understandably, each product described in Table 1 has not been tailored to the skin microbiome and body site of the individual using it. We note it is incredibly difficult to create a mass market product that can be tailored to each individual and the body site being targeted [27].

It remains to be concluded whether the repeated introduction of large numbers of microbes to the skin, especially non-native and potentially invasive ones, would have some transient benefit, or whether in the long run, the biodiversity would be reduced, and its colonisation resistance would break down. The latter is a possibility as the introduction is blind and without careful calculation. Upsetting the delicate balance can have catastrophic effects and could potentially lead to dysbiosis on the skin, a condition linked to many skin ailments [3]. Therefore, future work should investigate what benefit could be achieved by doing this?

Furthermore, at our current level of knowledge the exact composition of a healthy skin microbiome is unknown, which means a safe and effective solution would be difficult



to achieve [1,3,88]. This is because every human has a virtually unique microbiome and high intra-personal variation between body sites [3,21–23,89]. Therefore, it is likely, personalised or not, that the wrong amounts of microbes are being added to the skin from topically applied commercial probiotic products.

#### 4.4. *Preservatives and Other Cosmetic Ingredients*

Another concern is the potential allergic reaction caused by consistent contact with synthetic ingredients that make up the remaining cosmetic formulation [16]. The use of preservatives and other additives in everyday cosmetics are thought to damage the skin microbiome because the human body has not encountered these substances for the majority of our c. 300,000 years of existence, and could interpret them as ‘alien’ [3,11,81,90]. Using synthetic ingredients in ‘probiotic’ cosmetics every day could further upset the delicate skin microbiome balance. For example, they can raise the skin’s pH, which decreases the biodiversity [91] and leads to dispersal of resident bacteria from the skin which allows pathogenic bacterial and fungal growth [3,10].

#### 4.5. *Regulation*

Regulation is needed to make sure consumers know exactly what they are purchasing [16]; a first step could be to mirror the food industry standards [92]. If left unaddressed, it could lead to divide between consumers and the industry.

### 5. **Alternatives to Topical Probiotics and Questions to Answer in Future Work**

#### 5.1. *What are the Alternatives to Topical Probiotics?*

While the knowledge gap regarding the composition of a healthy microbiome is filled in, it could be beneficial to pursue some other skin microbiome enhancing techniques. The main one is very simple. If plants are struggling to grow in a garden, the gardeners often replace the soil to create the right conditions. The ‘probiotic’ route of planting more flowers may not be successful if the conditions are not right for their growth. The same may be possible on the skin, by creating the right conditions for biodiversity to thrive.

A first step could be by stopping exposure to factors in the western world that are thought to be contributing to biodiversity loss on the human microbiome. The overuse of antibiotics and steroids, our hypersanitised indoor living environment and overexposure to everyday cosmetics which contain 21<sup>st</sup> century synthetic chemicals, are all thought to be contributing [3,11,17,23,71,78–85].

Secondly, it may be possible to further recreate the skin’s natural environment through balancing of the skin’s natural pH and electrolyte levels, re-balancing sebum production and regulation (that is crucial to the immune symbiosis), skin cell regeneration and immune system regulation [40,56,86,87].

#### 5.2. *Future Work*

One of our goals is to make scientific research more accessible and easier to read. Research filled with impenetrable scientific jargon is not only off-putting but studies have shown that it receives fewer citations from fellow researchers too [93]. Therefore, we have decided to answer just two questions per review.

In follow-up work we will do a larger evaluation of the commercial topical probiotic products on the market in the EU, USA, and Canada, where there are different regulations. We will also answer the following questions about the topical probiotics research and development. This can assist us in updating the criteria and moving the topic closer towards fulfilling its incredible potential.

How do we measure the success of a topical probiotics solution? Does focusing on one aspect out of thousands to do so, misinterpret the true effect [90]? Are observed ‘beneficial’ effects useful if they are only temporary? As demonstrated in Yellowstone Park, should the long-term effects of probiotics be a priority? Are in vitro studies sufficient to draw conclusions about a complex ecosystem?

Are topical probiotics pointless if there are environmental factors in the western world that will immediately strip the skin microbiome of its biodiversity after application? Would it be like throwing grass seed on a desert? How do we create the right conditions on the skin for biodiversity to thrive, if not through topically applying microbes? Due to the gut-skin axis, would strengthening the gut and skin microbiome together have greater benefits than one in isolation?

## 6. Conclusions

In this review of commercial topical probiotic products for the skin microbiome, we found that the majority, 84%, do not contain live microbes and do not satisfy the WHO's definition to be named probiotics. Furthermore, there is an understandable lack of personalisation due to difficulties with mass market products, and an incomplete understanding of the composition of a healthy skin microbiome. The use of microbes used in probiotics for the gut that could be alien to the skin also means that current topical probiotics products may not fulfill the criteria for safe and effective implementation laid out in previous work. There is not a 'one size fits all' probiotic solution because every human possesses a virtually unique microbiome and solutions appear to work best when tailored to the individual. Regulation could help the development of new products along with protecting consumers and making sure they don't lose trust in the cosmetics industry. Despite it having enormous future potential, there is a long way to go before topical probiotics are an effective solution for skin problems and it is proven to be safe and effective for a mass market. Therefore, in follow-up work we will update the criteria by discussing how to measure the success of a solution, the need to assess long-term effects as well as immediate, and alternative restorative methods for the skin microbiome while science catches up with the idea.

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**Conflicts of Interest:** Christopher Wallen-Russell and Samuel Wallen-Russell are employees of research and development company Pavane Consultants Ltd. As license holder for the JooMo Ltd. range of skin health products, Pavane Consultants Ltd. is interested in determining how skin health can be measured and which environmental factors caused the huge increase in skin allergy problems in the past 75 years.

## References

1. Wallen-Russell C, Wallen-Russell S. Topical Probiotics Do Not Satisfy New Criteria for Effective Use Due to Insufficient Skin Microbiome Knowledge. *Cosmet* 2021, Vol 8, Page 90 [Internet]. 2021 Sep 17 [cited 2021 Sep 23];8(3):90. Available from: <https://www.mdpi.com/2079-9284/8/3/90/htm>
2. Kothari D, Patel S, Kim SK. Probiotic supplements might not be universally-effective and safe: A review. *Biomed Pharmacother*. 2019 Mar 1;111:537–47.
3. Wallen-Russell C, Wallen-Russell S. Meta Analysis of Skin Microbiome: New Link between Skin Microbiota Diversity and Skin Health with Proposal to Use This as a Future Mechanism to Determine Whether Cosmetic Products Damage the Skin. *Cosmetics* [Internet]. 2017 May 14 [cited 2017 Dec 19];4(2):14. Available from: <http://www.mdpi.com/2079-9284/4/2/14>
4. Balvanera P, Pfisterer AB, Buchmann N, He J-S, Nakashizuka T, Raffaelli D, et al. Quantifying the evidence for biodiversity effects on ecosystem functioning and services. *Ecol Lett* [Internet]. 2006 Oct [cited 2017 Feb 20];9(10):1146–56. Available from: <http://doi.wiley.com/10.1111/j.1461-0248.2006.00963.x>
5. Kong HH, Oh J, Deming C, Conlan S, Grice EA, Beatson MA, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res* [Internet]. 2012 May [cited 2017 Feb 21];22(5):850–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22310478>

6. Zaidi AK, Spaunhurst K, Sprockett D, Thomason Y, Mann MW, Fu P, et al. Characterization of the facial microbiome in twins discordant for rosacea. *Exp Dermatol* [Internet]. 2018 Mar [cited 2018 Jul 18];27(3):295–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/29283459>
7. Velegraki A, Cafarchia C, Gaitanis G, Iatta R, Boekhout T. *Malassezia* Infections in Humans and Animals: Pathophysiology, Detection, and Treatment. Heitman J, editor. *PLoS Pathog* [Internet]. 2015 Jan 8 [cited 2018 Nov 12];11(1):e1004523. Available from: <http://dx.plos.org/10.1371/journal.ppat.1004523>
8. Prescott SL, Larcombe D-L, Logan AC, West C, Burks W, Caraballo L, et al. The skin microbiome: impact of modern environments on skin ecology, barrier integrity, and systemic immune programming. *World Allergy Organ J* [Internet]. 2017 Dec 22 [cited 2018 Jul 18];10(1):29. Available from: <http://waojournal.biomedcentral.com/articles/10.1186/s40413-017-0160-5>
9. Manasson J, Reddy SM, Neimann AL, Segal LN, Scher JU. Cutaneous Microbiota Features Distinguish Psoriasis from Psoriatic Arthritis [abstract]. *Arthritis Rheumatol* [Internet]. 2016;68. Available from: <https://acrabstracts.org/abstract/cutaneous-microbiota-features-distinguish-psoriasis-from-psoriatic-arthritis/>
10. Wallen-Russell C, Wallen-Russell S. A new benchmark to determine what healthy western skin looks like in terms of biodiversity using standardised methodology. *Cosmetics* [Internet]. 2020 Dec 1 [cited 2021 May 20];7(4):1–19. Available from: [www.mdpi.com/journal/cosmetics](http://www.mdpi.com/journal/cosmetics)
11. Wallen-Russell C. The Role of Every-Day Cosmetics in Altering the Skin Microbiome: A Study Using Biodiversity. *Cosmetics* [Internet]. 2018 Dec 27 [cited 2020 Jan 8];6(1):2. Available from: <http://www.mdpi.com/2079-9284/6/1/2>
12. Baviera G, Leoni MC, Capra L, Cipriani F, Longo G, Maiello N, et al. Microbiota in healthy skin and in atopic eczema. *Biomed Res Int* [Internet]. 2014 [cited 2018 Jul 18];2014:436921. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25126558>
13. Kechagia M, Basoulis D, Konstantopoulou S, Dimitriadi D, Gyftopoulou K, Skarmoutsou N, et al. Health Benefits of Probiotics: A Review. *ISRN Nutr* [Internet]. 2013 Jan 2 [cited 2021 Sep 6];2013:1–7. Available from: [/pmc/articles/PMC4045285/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4045285/)
14. Sharma G, Khanna G, Sharma P, Deol PK, Kaur IP. Mechanistic Role of Probiotics in Improving Skin Health. *Probiotic Res Ther* [Internet]. 2022 [cited 2021 Nov 27];27–47. Available from: [https://link.springer.com/chapter/10.1007/978-981-16-5628-6\\_2](https://link.springer.com/chapter/10.1007/978-981-16-5628-6_2)
15. Knackstedt R, Knackstedt T, Gatherwright J. The role of topical probiotics in skin conditions: A systematic review of animal and human studies and implications for future therapies. *Exp Dermatol* [Internet]. 2020 Jan 1 [cited 2021 Sep 6];29(1):15–21. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1111/exd.14032>
16. Lee GR, Maarouf M, Hendricks AJ, Lee DE, Shi VY. Topical probiotics: The unknowns behind their rising popularity. *Dermatol Online J* [Internet]. 2019 May 1 [cited 2021 Jul 16];25(5):5–6. Available from: <https://escholarship.org/uc/item/2v83r5wk>
17. Bustamante M, Oomah BD, Oliveira WP, Burgos-Díaz C, Rubilar M, Shene C. Probiotics and prebiotics potential for the care of skin, female urogenital tract, and respiratory tract. *Folia Microbiol (Praha)* [Internet]. 2020 Apr 1 [cited 2021 Aug 10];65(2):245. Available from: [/pmc/articles/PMC7090755/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC7090755/)
18. Knackstedt R, Knackstedt T, Gatherwright J. The role of topical probiotics on wound healing: A review of animal and human studies. *Int Wound J* [Internet]. 2020 Dec 1 [cited 2021 Sep 20];17(6):1687–94. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1111/iwj.13451>
19. França K. Topical Probiotics in Dermatological Therapy and Skincare: A Concise Review. *Dermatology Ther* 2020 111 [Internet]. 2020 Dec 19 [cited 2021 Sep 6];11(1):71–7. Available from: <https://link.springer.com/article/10.1007/s13555-020-00476-7>
20. Habeebuddin M, Karnati RK, Shiroorkar PN, Nagaraja S, Asdaq SMB, Anwer MK, et al. Topical Probiotics: More Than a Skin Deep. *Pharm* 2022, Vol 14, Page 557 [Internet]. 2022 Mar 3 [cited 2022 Aug 30];14(3):557. Available from: <https://www.mdpi.com/1999-4923/14/3/557/htm>
21. Ley RE, Lozupone CA, Hamady M, Knight R, Gordon JI. Worlds within worlds: evolution of the vertebrate gut microbiota. *Nat Rev Microbiol* [Internet]. 2008 Oct [cited 2017 Feb 20];6(10):776–88. Available from: <http://www.nature.com/doi/10.1038/nrmicro1978>
22. Pei Z, Bini EJ, Yang L, Zhou M, Francois F, Blaser MJ. Bacterial biota in the human distal esophagus. *Proc Natl Acad Sci U S A* [Internet]. 2004 Mar 23 [cited 2017 Feb 20];101(12):4250–5. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15016918>
23. Costello EK, Lauber CL, Hamady M, Fierer N, Gordon JI, Knight R. Bacterial Community Variation in Human Body Habitats Across Space and Time. *Science* (80- ). 2009;326(5960).
24. Zmora N, Zilberman-Schapira G, Suez J, Mor U, Dori-Bachash M, Bashirdes S, et al. Personalized Gut Mucosal Colonization Resistance to Empiric Probiotics Is Associated with Unique Host and Microbiome Features. *Cell* [Internet]. 2018 Sep 6 [cited 2021 Sep 6];174(6):1388–1405.e21. Available from: <http://www.cell.com/article/S0092867418311024/fulltext>
25. Boyle RJ, Bath-Hextall FJ, Leonardi-Bee J, Murrell DF, Tang ML. Probiotics for treating eczema. *Cochrane Database Syst Rev* [Internet]. 2008 [cited 2021 Sep 20];(4). Available from: <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006135.pub2/full>
26. Great Healthworks, Inc. - 611686 - 06/23/2021 | FDA [Internet]. [cited 2021 Oct 12]. Available from: <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/great-healthworks-inc-611686-06232021>
27. Puebla-Barragan S, Reid G. Probiotics in Cosmetic and Personal Care Products: Trends and Challenges. *Molecules* [Internet]. 2021 Mar 1 [cited 2021 Sep 30];26(5). Available from: [/pmc/articles/PMC7956298/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC7956298/)
28. Hooper DU, Chapin FS, Ewel JJ, Hector A, Inchausti P, Lavorel S, et al. Effects of biodiversity on ecosystem functioning: a consensus of current knowledge. *Ecol Monogr* [Internet]. 2005 Feb [cited 2017 Feb 20];75(1):3–35. Available from: <http://doi.wiley.com/10.1890/04-0922>

29. Guéniche A, Bastien P, Ovigne JM, Kermici M, Courchay G, Chevalier V, et al. Bifidobacterium longum lysate, a new ingredient for reactive skin. *Exp Dermatol* [Internet]. 2010 Aug 1 [cited 2021 Sep 20];19(8):e1–8. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1111/j.1600-0625.2009.00932.x>
30. Dréno B, Araviiskaia E, Berardesca E, Gontijo G, Viera MS, Xiang LF, et al. Microbiome in healthy skin, update for dermatologists. *J Eur Acad Dermatology Venereol* [Internet]. 2016 Dec 1 [cited 2021 Jul 22];30(12):2038–47. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1111/jdv.13965>
31. Patel RM, Myers LS, Kurundkar AR, Maheshwari A, Nusrat A, Lin PW. Probiotic Bacteria Induce Maturation of Intestinal Claudin 3 Expression and Barrier Function. *Am J Pathol* [Internet]. 2012 Feb 1 [cited 2021 Sep 21];180(2):626–35. Available from: <http://ajp.amjpathol.org/article/S0002944011010157/fulltext>
32. Yan F, Cao H, Cover TL, Whitehead R, Washington MK, Polk DB. Soluble Proteins Produced by Probiotic Bacteria Regulate Intestinal Epithelial Cell Survival and Growth. *Gastroenterology* [Internet]. 2007 Feb 1 [cited 2021 Sep 21];132(2):562–75. Available from: <http://www.gastrojournal.org/article/S0016508506024772/fulltext>
33. Mazmanian SK, Round JL, Kasper DL. A microbial symbiosis factor prevents intestinal inflammatory disease. *Nat* 2008 453:195 [Internet]. 2008 May 29 [cited 2021 Sep 21];453(7195):620–5. Available from: <https://www.nature.com/articles/nature07008>
34. Suárez N, Ferrara F, Rial A, Dee V, Chabalgoity JA. Bacterial Lysates as Immunotherapies for Respiratory Infections: Methods of Preparation. *Front Bioeng Biotechnol*. 2020 Jun 5;0:545.
35. Didovyk A, Tonooka T, Tsimring L, Hasty J. Rapid and scalable preparation of bacterial lysates for cell-free gene expression. *ACS Synth Biol* [Internet]. 2017 Dec 15 [cited 2021 Oct 10];6(12):2198. Available from: [/pmc/articles/PMC6038143/](https://pubs.acs.org/doi/10.1021/acssynbio.7b00143)
36. Coviello S, Wimmenauer V, Polack FP, Irusta PM. Bacterial lysates improve the protective antibody response against respiratory viruses through Toll-like receptor 4. *Hum Vaccin Immunother* [Internet]. 2014 Oct 1 [cited 2021 Oct 10];10(10):2896. Available from: [/pmc/articles/PMC5443103/](https://pubs.acs.org/doi/10.1021/acs.nanolett.7b00143)
37. MB K. Why the European Food Safety Authority was right to reject health claims for probiotics. *Benef Microbes* [Internet]. 2012 Jun [cited 2021 Sep 2];3(2):85–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/22683835/>
38. Noble WC. Staphylococci on the skin. In: *The Skin Microflora and Microbial Skin Disease* (Noble, W C, ed). London: Cambridge University Press; 2004. p. 135–52.
39. Katsuyama M, Ichikawa H, Ogawa S, Ikezawa Z. A novel method to control the balance of skin microflora: Part 1. Attack on biofilm of *Staphylococcus aureus* without antibiotics. *J Dermatol Sci*. 2005;38(3):197–205.
40. Lambers H, Piessens S, Bloem A, Pronk H, Finkel P. Natural skin surface pH is on average below 5, which is beneficial for its resident flora. *Int J Cosmet Sci*. 2006;28(5):359–70.
41. Nataraj BH, Ali SA, Behare P V., Yadav H. Postbiotics-parabiotics: The new horizons in microbial biotherapy and functional foods. *Microb Cell Fact* [Internet]. 2020 Aug 20 [cited 2021 Dec 10];19(1):1–22. Available from: <https://microbialcellfactories.biomedcentral.com/articles/10.1186/s12934-020-01426-w>
42. Nam Y, Kim JH, Baek J, Kim W. Improvement of Cutaneous Wound Healing via Topical Application of Heat-Killed *Lactococcus chungangensis* CAU 1447 on Diabetic Mice. *Nutrients* [Internet]. 2021 Aug 1 [cited 2022 Oct 7];13(8):2666. Available from: [/pmc/articles/PMC8401197/](https://pubs.acs.org/doi/10.1021/acs.nanolett.7b00143)
43. Blanchet-Réthoré S, Bourdès V, Mercenier A, Haddar CH, Verhoeven PO, Andres P. Effect of a lotion containing the heat-treated probiotic strain *Lactobacillus johnsonii* NCC 533 on *Staphylococcus aureus* colonization in atopic dermatitis. *Clin Cosmet Investig Dermatol* [Internet]. 2017 Jul 3 [cited 2021 Jul 22];10:249–57. Available from: <https://www.dovepress.com/effect-of-a-lotion-containing-the-heat-treated-probiotic-strain-lactob-peer-reviewed-fulltext-article-CCID>
44. Marzio L Di, Centi C, Cinque B, Masci S, Giuliani M, Arcieri A, et al. Effect of the lactic acid bacterium *Streptococcus thermophilus* on stratum corneum ceramide levels and signs and symptoms of atopic dermatitis patients. *Exp Dermatol* [Internet]. 2003 Oct 1 [cited 2021 Sep 20];12(5):615–20. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1034/j.1600-0625.2003.00051.x>
45. Muizzuddin N, Maher W, Sullivan M, Schnittger S, Mammone T. Physiological effect of a probiotic on skin. *J Cosmet Sci* [Internet]. [cited 2018 Jul 30];63(6):385–95. Available from: [http://www.ncbi.nlm.nih.gov/pubmed/23286870](https://pubmed.ncbi.nlm.nih.gov/23286870/)
46. Marzio L Di, Cinque B, Simone C De, Cifone MG. Effect of the Lactic Acid Bacterium *Streptococcus thermophilus* on Ceramide Levels in Human Keratinocytes In Vitro and Stratum Corneum In Vivo. *J Invest Dermatol* [Internet]. 1999 Jul 1 [cited 2021 Sep 20];113(1):98–106. Available from: [http://www.jidonline.org/article/S0022202X15405408/fulltext](https://www.jidonline.org/article/S0022202X15405408/fulltext)
47. Dimarzio L, Cinque B, Cupelli F, Simone C De, Cifone MG, Giuliani M. Increase of Skin-Ceramide Levels in Aged Subjects following a Short-Term Topical Application of Bacterial Sphingomyelinase from *Streptococcus Thermophilus*: <https://doi.org/10.1177/039463200802100115> [Internet]. 2008 Jan 1 [cited 2021 Sep 20];21(1):137–43. Available from: <https://journals.sagepub.com/doi/10.1177/039463200802100115>
48. Simmering R, Breves R. Prä- und probiotische Kosmetik. *Der Hautarzt* [Internet]. 2009 Oct 27 [cited 2018 Jul 30];60(10):809–14. Available from: [http://www.ncbi.nlm.nih.gov/pubmed/19711025](https://pubmed.ncbi.nlm.nih.gov/19711025/)
49. Boxberger M, Cenizo V, Cassir N, La Scola B. Challenges in exploring and manipulating the human skin microbiome. *Microbiome* 2021 91 [Internet]. 2021 May 30 [cited 2021 Sep 20];9(1):1–14. Available from: <https://microbiomejournal.biomedcentral.com/articles/10.1186/s40168-021-01062-5>
50. THE SCCP'S NOTES OF GUIDANCE FOR THE TESTING OF COSMETIC INGREDIENTS AND THEIR SAFETY EVALUATION 6 TH REVISION.



51. FDA Authority Over Cosmetics: How Cosmetics Are Not FDA-Approved, but Are FDA-Regulated | FDA [Internet]. [cited 2021 Oct 11]. Available from: <https://www.fda.gov/cosmetics/cosmetics-laws-regulations/fda-authority-over-cosmetics-how-cosmetics-are-not-fda-approved-are-fda-regulated>
52. SHAW RH, TANNER R, DJEDDOUR D, CORTAT G. Classical biological control of *Fallopia japonica* in the United Kingdom – lessons for Europe. *Weed Res* [Internet]. 2011 Dec 1 [cited 2021 Sep 5];51(6):552–8. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-3180.2011.00880.x>
53. Pautasso M, Aas G, Queloz V, Holdenrieder O. European ash (*Fraxinus excelsior*) dieback – A conservation biology challenge. *Biol Conserv*. 2013 Feb 1;158:37–49.
54. Lebeer S, Oerlemans EFM, Claes I, Henkens T, Delanghe L, Wuyts S, et al. Selective targeting of skin pathobionts and inflammation with topically applied lactobacilli. *Cell Reports Med*. 2022 Feb 15;3(2):100521.
55. Delanghe L, Spacova I, Van Malderen J, Oerlemans E, Claes I, Lebeer S. The role of lactobacilli in inhibiting skin pathogens. *Biochem Soc Trans* [Internet]. 2021 Apr 30 [cited 2021 Dec 10];49(2):617–27. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1002/biot.4280>
56. Grice EA, Segre JA. The skin microbiome. *Nat Rev Microbiol* [Internet]. 2011;9(4):244–53. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21407241> <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3535073>
57. Thursby E, Juge N. Introduction to the human gut microbiota. *Biochem J* [Internet]. 2017 Jun 1 [cited 2021 Oct 7];474(11):1823. Available from: <https://pubmed.ncbi.nlm.nih.gov/27412261/>
58. Callewaert C, Lambert J, Wiele T Van de. Towards a bacterial treatment for armpit malodour. *Exp Dermatol* [Internet]. 2017 May 1 [cited 2021 Sep 21];26(5):388–91. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1111/exd.13259>
59. Wang X, Zhang P, Zhang X. Probiotics Regulate Gut Microbiota: An Effective Method to Improve Immunity. *Molecules* [Internet]. 2021 Oct 1 [cited 2022 Oct 4];26(19). Available from: <https://pubmed.ncbi.nlm.nih.gov/35812487/>
60. Hemarajata P, Versalovic J. Effects of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. *Therap Adv Gastroenterol* [Internet]. 2013 [cited 2022 Oct 4];6(1):39. Available from: <https://pubmed.ncbi.nlm.nih.gov/23539293/>
61. Coates M, Lee MJ, Norton D, MacLeod AS. The Skin and Intestinal Microbiota and Their Specific Innate Immune Systems. *Front Immunol*. 2019 Dec 17;0:2950.
62. Rosignoli C, Thibaut de Ménonville S, Orfila D, Béal M, Bertino B, Aubert J, et al. A topical treatment containing heat-treated *Lactobacillus johnsonii* NCC 533 reduces *Staphylococcus aureus* adhesion and induces antimicrobial peptide expression in an in vitro reconstructed human epidermis model. *Exp Dermatol* [Internet]. 2018 Apr 1 [cited 2022 Oct 7];27(4):358–65. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1111/exd.13504>
63. Konuray G, Erginkaya Z. Potential Use of *Bacillus coagulans* in the Food Industry. *Foods* [Internet]. 2018 Jun 1 [cited 2021 Oct 12];7(6). Available from: <https://pubmed.ncbi.nlm.nih.gov/3025323/>
64. Keller D, Verbruggen S, Cash H, Farmer S, Venema K. Spores of *Bacillus coagulans* GBI-30, 6086 show high germination, survival and enzyme activity in a dynamic, computer-controlled in vitro model of the gastrointestinal tract. *Benef Microbes*. 2019;10(1):77–87.
65. Maity C, Kumar Gupta A, Saroj DB, Biyani A, Bagkar P, Kulkarni J, et al. Impact of a Gastrointestinal Stable Probiotic Supplement *Bacillus coagulans* LBSC on Human Gut Microbiome Modulation. 2020 [cited 2022 Oct 7]; Available from: <https://www.tandfonline.com/action/journalInformation?journalCode=ijds20>
66. Cao J, Yu Z, Liu W, Zhao J, Zhang H, Zhai Q, et al. Probiotic characteristics of *Bacillus coagulans* and associated implications for human health and diseases. *J Funct Foods*. 2020 Jan 1;64:103643.
67. Casula G, Cutting SM. *Bacillus* probiotics: Spore germination in the gastrointestinal tract. *Appl Environ Microbiol* [Internet]. 2002 [cited 2022 Oct 4];68(5):2344–52. Available from: <https://journals.asm.org/doi/10.1128/AEM.68.5.2344-2352.2002>
68. Abhari K, Shekarforoush SS, Sajedianfard J, Hosseinzadeh S, Nazifi S. The effects of probiotic, prebiotic and synbiotic diets containing *Bacillus coagulans* and inulin on rat intestinal microbiota. *Iran J Vet Res* [Internet]. 2015 [cited 2022 Oct 4];16(3):267. Available from: <https://pubmed.ncbi.nlm.nih.gov/2682696/>
69. Majeed M, Majeed S, Nagabhushanam K, Mundkur L, Rajalakshmi HR, Shah K, et al. Novel Topical Application of a Postbiotic, LactoSporin®, in Mild to Moderate Acne: A Randomized, Comparative Clinical Study to Evaluate its Efficacy, Tolerability and Safety. *Cosmet* 2020, Vol 7, Page 70 [Internet]. 2020 Sep 15 [cited 2022 Oct 4];7(3):70. Available from: <https://www.mdpi.com/2079-9284/7/3/70/html>
70. Aşan Özusağlam M. Importance of *Bacillus coagulans* bacterium as probiotic in animal nutrition. *Süleyman Demirel Üniv Ziraat Fak Derg*. 2010;5:50–7.
71. Cogen AL, Nizet V, Gallo RL. Skin microbiota: a source of disease or defence? *Br J Dermatol*. 2009;158:442–55.
72. Grice EA, Kong HH, Renaud G, Young AC, Bouffard GG, Blakesley RW, et al. A diversity profile of the human skin microbiota. *Genome Res*. 2008;18(7):1043–50.
73. Pyšek P, Hulme PE, Simberloff D, Bacher S, Blackburn TM, Carlton JT, et al. Scientists' warning on invasive alien species. *Biol Rev* [Internet]. 2020 Dec 1 [cited 2021 Oct 12];95(6):1511–34. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1111/brv.12627>
74. Nunes AL, Fill JM, Davies SJ, Louw M, Rebelo AD, Thorp CJ, et al. A global meta-analysis of the ecological impacts of alien species on native amphibians. *Proc R Soc B* [Internet]. 2019 Feb 27 [cited 2021 Oct 12];286(1897). Available from: <https://royalsocietypublishing.org/doi/abs/10.1098/rspb.2018.2528>



75. Shine R. The Ecological Impact of Invasive Cane Toads (*Bufo Marinus*) in Australia. <https://doi.org/10.1086/655116> [Internet]. 2015 Jul 19 [cited 2021 Sep 1];85(3):253–91. Available from: <https://www.journals.uchicago.edu/doi/abs/10.1086/655116>
76. Byrd AL, Belkaid Y, Segre JA. The human skin microbiome [Internet]. Vol. 16, *Nature Reviews Microbiology*. Nature Publishing Group; 2018 [cited 2020 Sep 25]. p. 143–55. Available from: [www.nature.com/nrmicro](http://www.nature.com/nrmicro)
77. Mosca A, Leclerc M, Hugot JP. Gut Microbiota Diversity and Human Diseases: Should We Reintroduce Key Predators in Our Ecosystem? *Front Microbiol*. 2016 Mar 31;0(MAR):455.
78. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The Human Microbiome Project. *Nature* [Internet]. 2007 Oct 18 [cited 2018 Jan 8];449(7164):804–10. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17943116>
79. Staudinger T, Pipal A, Redl B. Molecular analysis of the prevalent microbiota of human male and female forehead skin compared to forearm skin and the influence of make-up. *J Appl Microbiol* [Internet]. 2011 Jun [cited 2018 Jan 8];110(6):1381–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21362117>
80. Martínez I, Stegen JC, Maldonado-Gómez MX, Eren AM, Siba PM, Greenhill AR, et al. The Gut Microbiota of Rural Papua New Guineans: Composition, Diversity Patterns, and Ecological Processes. *Cell Rep* [Internet]. 2015;11(4):527–38. Available from: <http://www.sciencedirect.com/science/article/pii/S221112471500340X>
81. Rocha LA, Ferreira de Almeida e Borges L, Gontijo Filho PP. Changes in hands microbiota associated with skin damage because of hand hygiene procedures on the health care workers. *Am J Infect Control* [Internet]. 2009 Mar [cited 2018 Jan 8];37(2):155–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19249642>
82. Blaser MJ, Falkow S. What are the consequences of the disappearing human microbiota? *Nat Rev Microbiol* [Internet]. 2009;7(12):887–94. Available from: <http://dx.doi.org/10.1038/nrmicro2245>
83. Holland KT, Bojar R a. Cosmetics: what is their influence on the skin microflora? *Am J Clin Dermatol*. 2002;3(7):445–9.
84. Belkaid Y, Segre JA. Dialogue between skin microbiota and immunity. *Science* (80- ) [Internet]. 2014 Nov 21 [cited 2018 Jan 8];346(6212):954–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25414304>
85. Stingley RL, Zou W, Heinze TM, Chen H, Cerniglia CE. Metabolism of azo dyes by human skin microbiota. *J Med Microbiol* [Internet]. 2010 Jan 1 [cited 2018 Jan 8];59(1):108–14. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19729456>
86. Nakatsuji T, Kao MC, Zhang L, Zouboulis CC, Gallo RL, Huang C-M. Sebum free fatty acids enhance the innate immune defense of human sebocytes by upregulating  $\beta$ -defensin-2 expression. *J Invest Dermatol* [Internet]. 2010 Apr [cited 2017 Feb 21];130(4):985–94. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20032992>
87. Fluhr JW, Kao J, Ahn SK, Feingold KR, Elias PM, Jain M. Generation of free fatty acids from phospholipids regulates stratum corneum acidification and integrity. *J Invest Dermatol*. 2001;117(1):44–51.
88. Findley K, Grice EA. The skin microbiome: A focus on pathogens and their association with skin disease. *PLoS Pathog*. 2014;10(11).
89. Scholz CFP, Jensen A, Lomholt HB, Brüggemann H, Kilian M. A Novel High-Resolution Single Locus Sequence Typing Scheme for Mixed Populations of *Propionibacterium acnes* In Vivo. *PLoS One* [Internet]. 2014 Aug 11 [cited 2021 Sep 15];9(8):e104199. Available from: <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0104199>
90. Wallen-Russell C. Is There a Relationship between Transepidermal Water Loss and Microbial Biodiversity on the Skin? *Cosmetics* [Internet]. 2019 Mar 9 [cited 2019 Dec 17];6(1):18. Available from: <https://www.mdpi.com/2079-9284/6/1/18>
91. Ying S, Zeng D-N, Chi L, Tan Y, Galzote C, Cardona C, et al. The Influence of Age and Gender on Skin-Associated Microbial Communities in Urban and Rural Human Populations. Badger JH, editor. *PLoS One* [Internet]. 2015 Oct 28 [cited 2018 Jan 9];10(10):e0141842. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26510185>
92. FSA. Criteria for the use of the terms fresh, pure, natural etc. in food labelling [Internet]. 2017. Available from: <https://admin.food.gov.uk/sites/default/files/multimedia/pdfs/markcritguidance.pdf>
93. Martínez A, Mammola S. Specialized terminology reduces the number of citations of scientific papers. *Proc R Soc B* [Internet]. 2021 Apr 14 [cited 2021 Sep 23];288(1948). Available from: <https://royalsocietypublishing.org/doi/abs/10.1098/rspb.2020.2581>