

Review

Topical Probiotics Do Not Satisfy New Criteria for Effective Use Due to Insufficient Skin Microbiome Knowledge

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Abstract: We propose a set of criteria for topical probiotics to adhere to for safe and effective use for the skin microbiome. To form the basis of the criteria, we redefine the term “probiotics” and discuss successful and unsuccessful high-profile examples of the artificial addition of organisms to ecosystems in nature to understand what worked and what did not. Probiotics are often immediately assumed to have health benefits. However, as ecologists are aware, interfering with ecosystems is potentially catastrophic. The addition or removal of just one organism can significantly upset the delicate ecosystem balance. If our criteria are not met, we argue that topical probiotics could also cause damage and will not be beneficial. Due to the large intra- and inter-personal variation of the skin microbiome, our current knowledge of a healthy skin microbiome composition is not complete enough to fully satisfy the criteria. In follow-up work, we will investigate whether current topical probiotics research and commercial products meet our new criteria. We will also discuss problems with how to measure their effectiveness and suggest alternative solutions to replacing the lost biodiversity of the skin microbiome that was stripped away by environmental factors in the Western world.



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1. Introduction: Redefining Probiotics and Microbiome Basics

1.1. A New Definition of Probiotics

To propose a new set of criteria for topical probiotics to be administered safely and effectively, we first need to understand what the word “probiotic” means. This means introducing a new definition of probiotics because they have predominantly been associated with the gut. The World Health Organisation defines the term as “living microorganisms which, when administered in adequate amounts, confer a health effect on the host” [1]. However, the term “probiotics” explains something extremely simple that can be done to any ecosystem; we re-define it as “the artificial addition of one or more types of living organism to an ecosystem”. In fact, this has been done in many ecosystems across nature and throughout human existence, whether inadvertently or consciously. In Sections 2 and 3, we describe examples of real-world use of “probiotics” where organisms have been added to ecosystems in nature. In some cases, they have benefitted the ecosystem, but in many, they had the opposite effect, depending on how they were implemented.

Probiotics in the gut and, more recently, the skin have been linked with improvements in certain aspects of health [1–3]. They have been used with the intention of causing a health benefit. The word “intention” is important here. Consumers often subconsciously associate the term with a beneficial health effect, in part due to large marketing campaigns for probiotic drinks and supplements. However, the European Food Safety Association (EFSA) has banned the sale of any product named “probiotic” because it is an “unauthorised health claim” [4]. According to the EU guidelines, the term “probiotic” implies a health benefit that could mislead consumers because the science surrounding them remains largely inconclusive. In America, the FDA has not approved any probiotic products [2].

In addition, a study concluded in 2018 that probiotics were ineffective and could potentially cause harm if not implemented correctly [5]. This echoed previous research that warned against the use of probiotics for the immunocompromised and that, because of the very inconclusive science, extensive research is needed to be able to safely administer different strains, which have different effects depending on the person [6]. Other studies showed that probiotics had no effects on helping eczema [7] or diarrhoea [8] that was caused by infection or antibiotics. Finally, a review by the Agency for Healthcare Research and Quality (AHRQ) concluded that the available literature is not sufficiently equipped to determine the safety of probiotic use with confidence [9].

As a much under-researched topic, it is emerging that strengthening the skin microbiome could have great potential in treating many health problems [10]. To mitigate against the inconclusive science, the focus of this study is to find a set of criteria for the safe and effective implementation of topical probiotic solutions. We use examples from other ecosystems in nature to try to answer some of the biggest questions surrounding their future potential.

1. Is our current knowledge at a level where we can understand the skin microbiome and what makes it healthy?
2. What are the criteria for being confident that topical probiotics would work?

A recurring theme throughout our work is that we feel that researchers miss out on solutions by failing to take inspiration from areas outside of their own fields of research. It is for this reason that we explain concepts regarding probiotics by using examples of other more well-known ecosystems, so our research is universally accessible. As Einstein famously said, “If you cannot explain something to a six-year-old, you do not understand it yourself”.

1.2. Loss of Skin Microbiome Biodiversity

For the majority of the c. 300,000 years of the *Homo sapien's* existence and for the total 6 million years over which our direct ancestors can be traced back [11,12], they have lived in peaceful co-existence with the ecosystems in nature. It is only very recently that humans have dominated the landscape. The introduction of modern, “Western” civilisation, accelerated by scientific and societal advances such as the Industrial Revolution, has meant that humans have become increasingly isolated from nature [13]. The exposure of the body to 21st-century soaps, cosmetics, pollution, medicine, and drugs has caused significant microbiome alterations [10,14–16].

Our previous work discovered that biodiversity was the only reliable indicator of microbiome health—a phenomenon that is replicated throughout all other ecosystems in nature [10,17]. Just like in the gut, the biodiversity of the skin microbiome has decreased dramatically in recent years, and people who live in communities that are not exposed to Western practices, such as isolated tribespeople, display far greater microbial biodiversity than humans living in Western civilisation [10,18]. This catastrophic diversity loss has been attributed to Western practices and is linked to many skin problems, including the rapid increase in skin allergies in the last 75 years [10,17,19].

Consequently, there has been increased research interest in finding methods of restoring the lost biodiversity to the microbiome, which was stripped away by the Western environment [20]. Restoring our skin to the “caveman” state of our ancestors, who are thought to have had the highest biodiversity, remains the holy grail [17]. There are thought to be multiple ways of doing this, including reducing exposure to man-made substances in cosmetics, cleaning products, and pollution with which the body has not evolved to cope, exposing our bodies more frequently to the natural environment, and stopping the overuse of medicines and drugs for chronic problems [15]. Just like in the gut, a popular idea is the use of probiotics [21]. The idea is similar to that of replacing the lost plants in a garden that has been damaged by an environmental disaster, such as a flood.

2. Successful Example of Probiotics: The Re-Introduction of the Wolves to Yellowstone Park

Is there potential for topical probiotics to be used as a future solution for skin ailments? To answer this question, we use a well-known example from another macro-scale ecosystem. We remind our readers of our definition of probiotics, which describes the artificial addition of one or more types of live organisms to an ecosystem. Some people may think that the concept of probiotics has only been around for the last couple of decades due to an explosion of interest in digestive health. However, humans have been experimenting with this idea in other ecosystems for hundreds of years.

The re-introduction of wolves into Yellowstone Park was so successful it that gained worldwide publicity, and it shows that the use of topical probiotics to treat skin microbiome problems has remarkable future potential [22]. Adding the wolves to the ecosystem is the same as adding a type of microbe to the skin, but it is more relatable.

Wolves were a natural part of Yellowstone Park until the last official killing in 1926 [23,24]. After they died out, Yellowstone Park became extremely damaged, and the park rangers were at a loss about what to do. The elk population had increased dramatically because there were no wolves to keep their numbers in check, and they started over grazing and grazing in areas of the park in which they previously had not [10,25,26].

In 1995, the park rangers re-introduced the wolves because they wanted to keep down the swelling elk numbers. They only introduced an amount that they knew would be sustainable according to the park's records. There were dramatic changes in the landscape, many of which could not have been predicted and were not thought possible by scientists. Most importantly, the biodiversity was hugely increased [27]. Rivers changed direction; eagle, raven, and grizzly bear populations increased, elk populations decreased, and shrubs grew taller and richer [22,28,29].

Just by re-introducing one type of organism into the park, the biodiversity and health of the ecosystem was transformed. This effect could have been exaggerated due to the wolves' status as a top predator; the addition or removal of these could have a greater impact compared to that of organisms lower down the food chain [30]. There were far-reaching effects that impacted the park in ways that could not be linearly explained or predicted. If this can be done in Yellowstone Park, then the same must be achievable on the skin. This is a great example of the potential power of topical probiotics. However, as we explain in Section 4, there are reasons for why this example was so successful, which led us to a set of criteria to fulfil for the successful implementation of topical probiotics for the skin microbiome.

3. Examples of Unsuccessful Probiotics in Macro-Ecosystems

The example of Yellowstone Park shows the potential for topical probiotics; the re-introduction of one microbe that is known to be a healthy part of the skin microbiome could transform the skin microbiome's health and biodiversity. However, it could just as easily have gone the other way. Introducing species that are not native to a particular ecosystem has a long history of causing widespread damage. These are aptly called 'alien' or 'invasive' species. 'Invasive' is the name given to those species that are alien and cause considerable harm instead of being benign. To explain how this could damage the skin microbiome, we use three prominent examples: the introduction of Japanese knotweed (*Fallopia japonica*) to UK waters, the introduction of the cane toad to Australian farms, and the introduction of the ash dieback (*Hymenoscyphus fraxineus*). Just like the wolves in Section 2, these examples can all be equated to microbes being added to the skin microbiome.

Introduced to Britain as an ornamental garden plant by the Victorians in the 1850s [31], Japanese Knotweed (*Fallopia japonica*) has since become widespread throughout the UK [32]. In Japan, it is kept in check by competition with other large herbs within the ecosystem, natural invertebrate pests, soil fungi, and plant diseases. However, as a non-native plant in the UK, these do not exist, allowing it to outcompete native plants for light and water, alter the habitats of native animals, and reduce biodiversity [32–34]. Its roots can spread

underground by up to seven meters in one season, it can grow through cracks in drainage systems, houses, and concrete, and it can cause significant damage to buildings. In doing so, it can cause significant house devaluation [34]. It could cost the economy over £ 150 million every year in the UK and £ 1.5 billion to control it [34].

Since their introduction in 1935 in a failed attempt to control insects acting as pests, the cane toad has spread rapidly throughout Australia, and the rate of colonisation is increasing [35–37]. Their toxicity means that eating them is potentially fatal for Australian predators; the toads caused a sharp decline in the number of large predator species [30,38]. Australian ecosystems did display some small adaptations to the introduction, but due to the numerous adverse effects, it is still considered an ecological disaster.

Ash dieback is a disease caused by the fungus *Hymenoscyphus fraxineus*, which originated in Asia and has caused devastation to European ash trees [39]. Arriving on the continent on ornamental plants, it was spread to the UK by the wind and further ornamental imports [39]. On its native hosts, the Manchurian ash (*Fraxinus mandshurica*) and the Chinese ash (*Fraxinus chinensis*), it did not cause problems. However, the UK's native ash trees have never been exposed to the fungus. This means that they have no natural defences or resistance to it [40]. Consequently, it is estimated that ash dieback will kill as many as 80% of the UK's ash trees, changing the landscape forever and threatening the habitats of many species [41]. It is estimated to cost the economy 7.6 billion GBP in the next 10 years [42].

4. What Can We Learn from the Examples of Successful and Unsuccessful Probiotics to Apply to the Skin Microbiome?

The examples in Sections 2 and 3 show that the addition of just one type of organism out of many thousands can drastically effect ecosystem health because they are governed by non-linear physical principles. The same delicate balance exists on the skin, and if it is disturbed and the biodiversity is decreased, susceptibility to microbial infections and inflammatory diseases increases [43–45]. Therefore, it is vital to learn the right lessons; understanding what went right and wrong is the key to writing a set of criteria by which to abide in the future use of probiotics. Why was the re-introduction of the wolves to Yellowstone Park so successful for the ecosystem, and why was this same transformative effect not seen in the unsuccessful attempts in Section 3?

Re-introducing the wolves to Yellowstone Park was highly successful for two main reasons.

1. The wolves were known to be an integral part of the ecosystem before their re-introduction; they were not 'alien' to the system.
2. The Park rangers knew the exact number of wolves that were stable in the ecosystem and that contributed a positive effect to it from their experience.

The unsuccessful examples in Section 3 involved the addition of organisms that were 'alien' or non-native, and there was no knowledge of their role as constituents of a healthy ecosystem. In addition, the amount of each organism being introduced was not regulated. This was in stark contrast to the Yellowstone Park example in Section 2, where the park rangers knew that the wolves had been part of the healthy ecosystem for thousands of years. As importantly, they also knew the numbers of wolves that existed in a healthy ecosystem. Without this base knowledge, they would have been acting blindly.

4.1. Criteria for Safe and Effective Topical Probiotic Use

To ensure that a topical probiotic solution has a chance of working, a set of criteria need to be met. The criteria 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 the skin microbiome of the individual and specific body site.

The skin microbiome is an ecosystem, just like Yellowstone Park. Thus, it follows that, to safely utilise probiotics for the skin, one must act as a park ranger for the skin microbiome that one is treating. These criteria are the basis of understanding how the skin microbiome can be improved with topical probiotics. Adherence is even more important now that the skin microbiome is thought to be vital for whole-body health, as well as skin health. Next, we ask whether our current level of skin microbiome knowledge is sufficient to allow these criteria to be met.

4.2. Is Our Understanding of the Skin Microbiome Sufficient for the Criteria to Be Met?

At our current level of knowledge, we are very far from being able to definitively say what amounts of microbes exist on healthy skin [10]. There have been shifts in the skin microbiome associated with health and disease. For example, a correlation between eczema severity and *S. aureus* colonisation has been demonstrated [46], and high levels of the same bacteria are seen in many skin and tissue infections [47]. However, there is little conclusive evidence linking exact amounts of different microbes to health and disease [10,48]. For example, even after years of researching the contribution of *Propionibacterium acnes* to the pathogenesis of acne vulgaris, its role is unclear, especially as it is an important part of a healthy skin microbiome [49,50].

This is made more complicated by the fact that every human has a virtually unique microbiome, which does not just differ significantly between people, but also between body sites on the skin [51–53]. Therefore, knowledge of the makeup of a healthy microbiome for each person and their body sites should be intimately understood to be able to propose probiotic solutions. It is not possible to use a ‘one size fits all’ approach for the skin microbiome. Reverting to the analogy in Section 2, introducing wolves to every failing ecosystem across the world could produce disastrous results. Wolves are not a constituent of a healthy ecosystem in the Serengeti, so it is highly likely that they would not benefit the ecosystem, in the same way in which the unsuccessful examples in Section 3 did not.

Furthermore, even if a microbe is an integral part of a healthy skin microbiome, if it is added in the wrong amounts, it has the potential to upset the balance. Imagine adding thousands of wolves to Yellowstone Park every week instead of the initial 31. This could decimate elk numbers and create undesired negative effects that could cause a ripple effect down the food chain.

The ash dieback problem in Section 3 reveals another interesting conclusion related to the immense inter- and intra-personal variation of the microbiome of the human skin. Just like the fungus was part of a healthy tree ecosystem in Asia and was destructive to European ash trees, on one person, a certain type of microbe may perform a different role from that on another person depending on the variation in the two skin microbiomes. Previous work has shown, contrary to previous ideas, that bacteria can be harmless or pathogenic depending on the health and biodiversity of the microbiome, not the inherent properties [43,54]. Therefore, it is even more vital not to rush into probiotic solutions that are not personalised. This echoes previous work on the gut [5].

The one conclusion that can be said with a high degree of certainty is that biodiversity of the microbiome is the most reliable indicator of its health [10,17]. This is echoed unanimously in ecosystems across nature. With regards to the exact constituents and proportions of a healthy skin microbiome, it is likely to take many more years of research. Any future topical probiotic solution should aim to increase the biodiversity of the skin microbiome. The example of Yellowstone Park in Section 2 saw a drastic increase in biodiversity following the re-introduction of wolves, but in the unsuccessful examples in Section 3, the biodiversity decreased. The same will apply to the skin. Get probiotics right, and they could increase biodiversity, but fail to follow the criteria that we set out here, and the microbiome could be significantly damaged, especially for the immunocompromised [6].

5. Future Research

In follow-up work, we will analyse current topical probiotic research and commercial products by using the criteria described here. We also aim to update the criteria by setting out how the success or failure of probiotics should be measured. We aim to answer some important questions that were not addressed in this paper.

Firstly, do current topical probiotic solutions adhere to the criteria in this work? That is, do they involve the addition of alien microbes to the skin or an inappropriate number of microbes? For example, the common use of *Lactobacilli* microbes in topical probiotics needs scrutiny because it is unclear whether they are a constituent of a healthy skin microbiome. They are a well-known constituent of a healthy gut microbiome, but the skin and gut harbour very different microbial communities [55]. Furthermore, it appears that a ‘one size fits all’ approach is used, which is unlikely to cater to the needs of individual people and body sites. This is especially relevant for commercial probiotic products. Even if a microbe is an integral part of a healthy skin microbiome, if it is added in the wrong amounts, it has the potential to upset the ecosystem’s delicate balance. This can be likened to adding thousands of wolves to Yellowstone Park every week instead of the initial 31. This could decimate elk numbers and have undesired negative effects that could cascade down the food chain.

Secondly, how do we measure the effectiveness of a solution? Has it helped the skin microbiome, and how can we tell? It is common for research to use one parameter, such as the inhibition of a certain microbe, to judge. However, this is fraught with difficulties because it can cause the effect on the overall ecosystem health to be misinterpreted.

Lastly, we aim to summarise the alternatives to topical probiotics as a solution for restoring the lost microbial biodiversity in the skin microbiome. Similarly to this paper, we will use examples from other ecosystems in nature to explain. For example, what would a gardener do if no plants were growing in their garden? A common solution is to replace the old soil with new, fertile soil, thus creating the right conditions.

6. Conclusions

In conclusion, we argue that the safe and effective administration of topical probiotics is currently not possible because they do not fulfil the criteria laid out in this paper. Due to the large intra- and inter-personal variation of the skin microbiome, our current knowledge of the community structure of a healthy skin microbiome is not complete enough. A ‘one size fits all’ approach will not be successful because of this variation. For topical probiotics to fulfil these criteria, they must only introduce microbes that are known to be an important part of a healthy skin microbiome for a specific person and body site, and only in amounts that are known to be healthy.

To build the criteria, we looked at examples of the successful and unsuccessful introduction of species to an ecosystem. The successful re-introduction of wolves to Yellowstone Park highlighted the incredible potential power of topical probiotics in treating skin ailments, while the unsuccessful examples showed the dangers of introducing alien species to an ecosystem. The foundation of this paper was formed by looking to re-create the success of Yellowstone and to avoid the failures of the other examples.

In a follow-up study, we will investigate whether current topical probiotic research and products meet the criteria in this study, the challenges, including the measurement of success, and commercial topical probiotics.

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