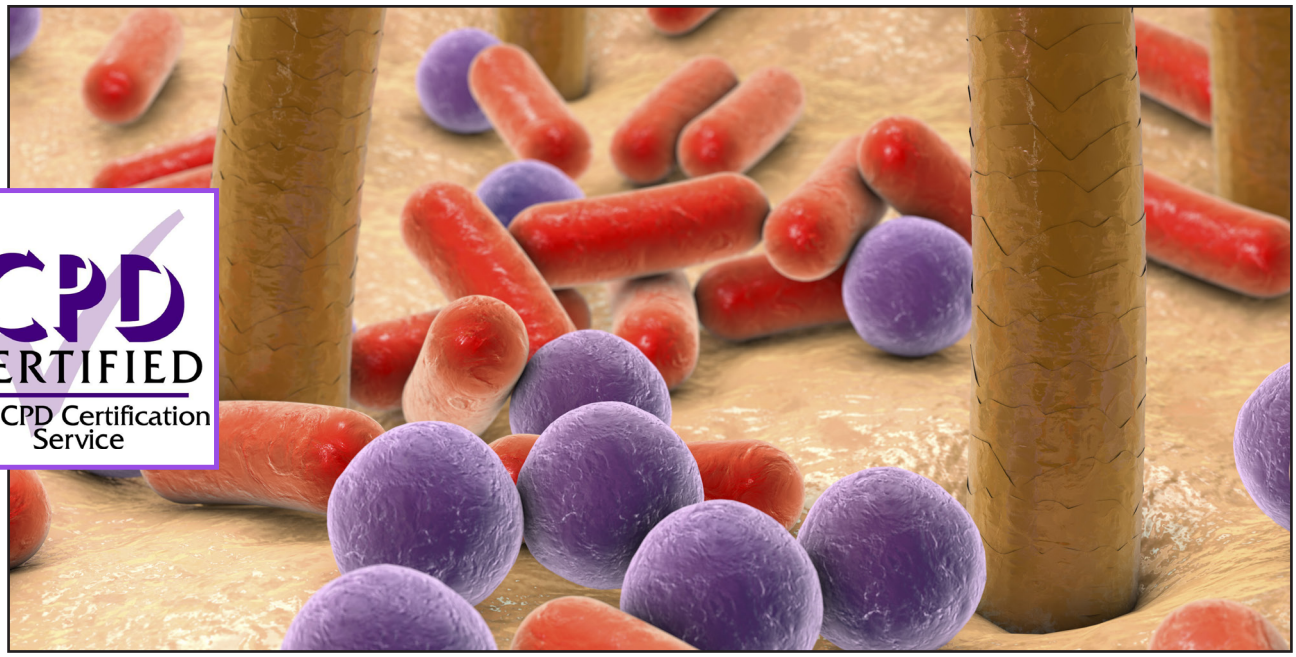


Kateryna Kon/Shutterstock

NEW UNDERSTANDING OF SKIN MICROBIOME

Dr Tiina Orasmae-Meder explores prebiotics, probiotics, biofilms, and a quorum sensing-oriented approach to skin therapy

The human skin microbiome remains a focus for both dermatological and skincare fields.

Recent findings and further developments in our knowledge of the "gut-skin-brain microbiome axis" - host-microbiome interactions, the role of viruses, intrinsic and extrinsic factors etc. - promise a completely new understanding of not just the skin's microbiome, or even its nature, but of the human body in all its complexity. Perhaps we may hope to come to a new understanding of human nature as well.

As we already know, the skin microbiome is a community of vital microorganisms such as bacteria, fungi, viruses, archaea and even protozoa co-existing and maintaining a delicate balance on the skin surface. It is important to understand that the microbiome is not just an isolated collection of microorganisms but also their genomes and microbial metabolites including RNA, proteins etc.

For decades, the primary 'colonist' of the skin was thought to be Staphylococcus epidermidis, along with some other species of coagulase-negative staphylococci (CoNS). Microflora was generally divided into two major categories, resident and transient. Resident microflora is a population of microorganisms maintaining roughly constant numbers. The increased or reduced growth of resident microflora was supposed to result from the skin's own characteristics. The microorganisms of transient flora, on the other hand, reach the skin from exogenous sources and are found primarily on the damaged or infected skin areas.

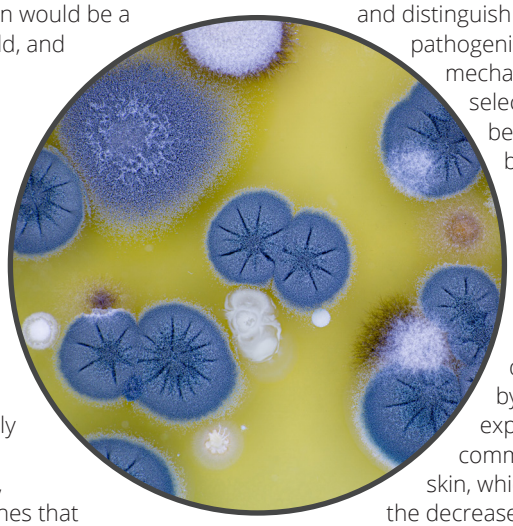
As the studies progressed, coryneform bacteria belonging to the phylum Actinobacteria (Corynebacterium, very familiar to dermatologists Cutibacterium and Brevibacterium) and micrococci have entered the bacterial landscape.

Apart from these, at various times studies have isolated non-bacterial microorganisms, such as fungi, primarily of the Malassezia genus, which are found most often in the areas of active sebum secretion, and make up to 80% of the fungal population. Under certain conditions, however, the Malassezia population decreases and Candidae fungi come out on top. Normally Candidae fungi rarely colonise human skin, but immune deficiency, diabetes complications and antibiotic therapy of infectious diseases can lead to cutaneous candidiasis, including the severe kind.

Parasitic mites, microscopic arthropods - primarily Demodex folliculorum and Demodex brevis - are also regarded as part of normal skin microflora today; even though until very recently finding even a single mite on the skin lead to the diagnosis of demodicosis. For a long time, Demodex infestation has been associated with the pathogenesis of rosacea, and other dermatoses, such as generalised pruritus of unknown origin or chronic blepharitis. We must note that microscopic mites are found in numbers on young people's skin, especially during puberty, and quite clearly prefer to colonise the areas with the prevalence of sebaceous glands. However, it turns out that Demodex can feed on epithelial cells lining pilosebaceous units and on Propionibacterium acnes preventing the excessive growth of their colonies, even in a favourable environment.

Viruses must play an important role among microorganisms populating human skin, but their impact hasn't been studied enough due to insufficient technical means.

Traditionally, skin microflora characteristics were analysed by microbial inoculation, but today, it is clear that only a few bacteria can be identified with the use of this method as most microorganisms are very hard or even impossible to cultivate in isolation. The key role in the formation of the microbial landscape was attributed to the organisms able to develop in a typical environment, which for the skin would be a relatively dry, cold, and acidic medium.



However, hair follicles and sebaceous glands present a practically anoxic environment where active development is possible almost exclusively for anaerobic microorganisms, the very same ones that have been overlooked for so long because they require special methods of microbial inoculation and time for a colony to grow.

Curiously, the vast majority of microorganisms in the skin microbiome are commensals and facultative flora, while no more than 200 species are true pathogens. Recent research ascertains that the changes in the microbiome can create favourable conditions for, and be a key factor in, the development of infections. As a collective microbial genome, the microbiome is an example of very complex and diverse interactions between various microorganisms, including interspecies relations between viruses, fungi, bacteria and parasites.

New evidence shows that antigens from skin commensal bacteria are detected by the skin's immune system and play a role in the setting of the skin barrier. Resident bacteria produce acidic metabolites contributing to the skin's acidic mantle that creates a hostile environment for many pathological microorganisms. A symbiotic relationship between the human host and resident microorganisms are mutually beneficial.

Somehow the skin can recognise conditionally safe commensal microbes and distinguish them from the pathogenic ones. The mechanics of this selection is yet to be discovered, but it is likely to be founded on the induction of immune tolerance. Toll-like-receptors (TLRs) can be desensitised by prolonged exposure of commensals on the skin, which results in the decreased expression of TLR cells of the epidermis or the inhibition of interleukin-1 receptor-associated kinase 3 (IRAK-3 or IRAK-M) occurs. It is also possible that the signalling of cytokines is suppressed, whereas the specificity is achieved by combined recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRPs).

The role of commensal microbes in the formation of the innate immune response has been confirmed, for instance, by the study of Staphylococcus epidermidis that suppresses, selectively, the growth of pathogens, such as S. aureus and Group A Streptococcus. It would appear that Staphylococcus epidermidis, in the course of the response, also inhibits the inflammatory process and activates the synthesis of antimicrobial peptides. Imbalance in the microbiome is associated with different skin conditions, such as eczema, acne, psoriasis, rosacea and many others.

Recent research demonstrates a link between the state of the microbiome and some non-pathological/aesthetic skin concerns such as sensitivity, irritation, redness, dryness, oiliness and even age-related changes such as wrinkles or lack of skin elasticity.

Disruptions to the normal balance, at any stage of the interaction between the skin cells and its microbiome, can lead to several skin conditions of varying severity. The causes of imbalance can be endogenous as well as exogenous.

An example of endogenous factors is the genetic variability of the microbe community, related to the particulars of a person's genome, which at some point defined the way their skin was colonised by microflora.

An exogenous factor is, for instance, the use of certain hygiene solutions, like antibacterial hand soap. Recently, the use of triclosan, as an active component of cleansers, was banned in the aftermath of studies revealing that using triclosan-containing soap for years on end leads to the pathological imbalance of the microbiome that causes various skin pathologies, including some dermatoses.

Another unnerving discovery is the development of antibiotic resistance characteristic in patients who had been regularly using triclosan-containing solutions to cleanse their skin.

To achieve a better understanding of skin diseases and infections, microbiologists, dermatologists, immunologists, and geneticists have isolated the following factors defining the microbiome development and its interaction with the host. (See table below).

Excessive use of antibiotics, both systemic and topical, always affects skin and gut microflora and can also lead to the development and spreading of antibiotic-resistant bacterial strains

IuchschenF/Shutterstock

Class of factors	Factors
Host's physiology	Age, sex, skin area
Environment	Climate, geographic location, UV exposure, environmental pollution
Host's genotype	Susceptibility and other characteristics of skin cells' genome
Lifestyle	Occupation, personal hygiene, diet, the use of cleansers, laundry detergents, hobbies, pets, etc.
Immune system	Previous contact with pathogenic/conditionally pathogenic/symbiotic microorganisms, inflammatory changes
Pathobiological changes	Somatic diseases (diabetes and other endocrine diseases, vascular pathology)

presenting a global challenge to infectious disease therapy in general. Radiation and chemotherapy used in cancer treatment also affect the skin's microbiome.

Scientific knowledge acquired up to date allows us to attribute some skin diseases to the changes in the microbiome.

For example, **seborrheic dermatitis** is successfully treated with antifungal solutions — the improvement results from the suppressed growth of Malassezia fungi found in disproportionate quantities in the affected areas of the patients. It has been established that antibacterial therapy brings no relief to seborrheic dermatitis. In the etiopathogenesis of seborrheic dermatitis, the key role is played by the specific metabolism of Malassezia fungi which release the fatty acids, particularly oleic acid, from the sebum. Oleic acid easily penetrates into deep skin layers, activating inflammation and hyperproliferation process, leading to the typical clinical presentation of dermatitis. In the healthy skin microbiome, the amount of Malassezia is insufficient to cause such changes, which suggests that microbiome alterations in the pathologically changed skin are inducive to this disease.

Psoriasis has not, until recently, been associated with an infectious affection or significant microbiome change, but recent studies have, at the very least, brought this assumption into question, if not disproved it entirely. In particular, it has been discovered that in psoriasis patients, Proteobacteria are found in larger numbers and Actinobacteria in smaller numbers; than in people with healthy skin. Psoriasis patients also carry fewer staphylococci and Cutibacteria. It is hard to say yet whether these changes in the microbiome are a cause or an effect of the pathological skin changes. Further research, however, should be able to determine that.

Teenage **acne** is traditionally associated with C. acnes, collected from the affected skin. The genome of C. acnes codifies numerous immunogenic factors, including adherent cell surface proteins and porphyrins. The damage to the pilosebaceous unit caused by C. acnes is well documented - the synthesis of proinflammatory cytokines and neutrophil chemotactic factors. Curiously, molecular methods have been rather sparingly used to determine the role of bacteria in acne, and the results are questionable.

Atopic dermatitis, one of the most common skin pathologies, is also associated with bacterial colonisation and infection. The skin of over 90% atopic dermatitis patients is colonised by S. aureus in both affected and unaffected areas. In people with healthy skin, similar microbiome characteristics are only observed in fewer than 5% of the cases. Traditional therapy of atopic dermatitis involves antibiotics and steroid hormones, allowing at least to reduce the clinical symptoms.

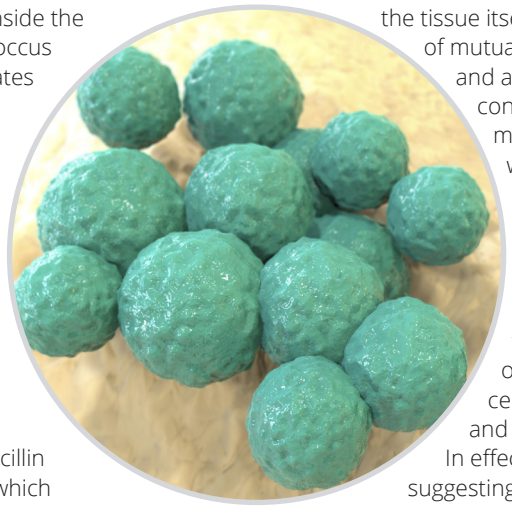
The cases where skin commensals bring about infectious affectation should be noted separately. S. epidermidis, in particular, is the most common culprit in hospital infections developing after cardiac catheterisation or the instalment of a prosthetic cardiac valve.

On the skin surface, Staphylococcus epidermidis does not present any danger and even plays a part in skin protection by participating in an immune response. However, when it enters inside the body, Staphylococcus epidermidis creates biofilms on the surface of catheters, or other prostheses, completely isolating pathogens. Such infections are incredibly resistant to antibiotics, especially to oxacillin and methicillin, which makes therapy very difficult. It would appear that Staphylococcus epidermidis serves as a reservoir for the antibiotic-resistant genes of its close relative, pathogenic microbe S. aureus. It was discovered, however, that P. acnes can counter the development of S. aureus resistance, at least to methicillin, and help to restore control over the growth of S. aureus and pyogenic staphylococcus.

By now, the importance of the skin and body microbiome has been firmly established by numerous studies. The microbiome makes a vital contribution to both immediate immune response and the formation of the immune system in general. Many skin diseases are reliably associated with the changes in the skin microbiome, and molecular analysis confirms significant differences between the microbiome of people, with and without diseases. Moreover, the microbiome of patients with certain diseases shares undeniable similarities, characteristic of their particular pathology. To describe the microbiome imbalance, the term ***skin dysbiosis*** has been suggested, and it is diagnosed more and more, even in oncological skin pathology. However, so far, none of the studies has been able to give a definite answer to what comes first - chicken or egg. Is microbiome disturbance a cause of disease, or does the change in the skin's characteristics lead to dysbiosis?

However, even at this initial stage of researching skin microbiome and dysbiosis, the achieved results open up many possibilities for the treatment of skin diseases and aesthetic correction.

Moreover, there is a shift in our understanding of skin cleansing. Bearing in mind that the skin's functions are enabled by, apart from the tissue itself, a complex of mutually active cells and a live biological conglomerate of microorganisms; we are faced with a necessity to reconsider, on a conceptual level, our treatment of many a cell disease and condition. In effect, we are suggesting a possibility of correcting the skin's condition by changing the microbiome and actively restoring the balance of microorganisms that makes up the skin's healthy (or eco-) flora.



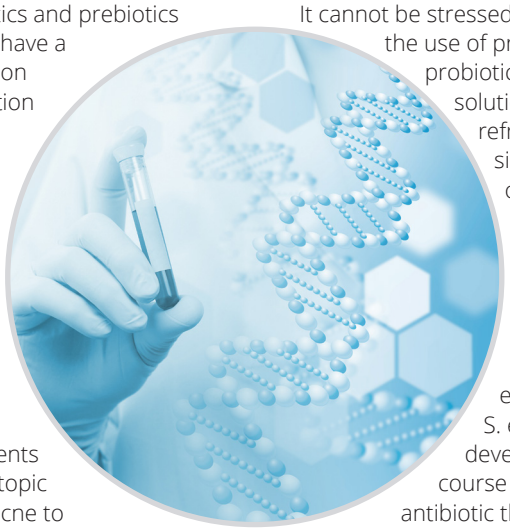
Kateryna Kon/Shutterstock

The key agents affecting the microbiome, both of the skin and digestive tract, are **probiotics and prebiotics**.

Probiotics are cultures of live microorganisms found in a healthy microbiome and, when introduced to the body in adequate quantities, can restore the balance and diversity of

the microbiome. Prebiotics are various agents that can serve as a nutrient medium for commensal and symbiotic microbes, which are a part of a healthy microbiome, increasing their growth and promoting successful colonisation. Both probiotics and prebiotics can be applied topically and taken orally to correct microbiome and skin condition.

In 2010, PC Arck et al. put forward a theory of gut-brain-skin axis, according to which prebiotics and prebiotics taken orally can have a beneficial effect on the skin. In addition to oral intake, new emollients and daily care solutions were offered containing bacterial lysates. Such skincare solutions were suggested primarily to patients suffering from atopic dermatitis and acne to restore the epidermal barrier, healthy microbiome, and skin immunity.



The development of topical probiotics was made possible by new technology, such as the 3D imaging of mass spectrometry data and the aforementioned 16S-rRNA microbial sequencing.

It must be mentioned that the topical application of probiotics presents a problematic task. The key difficulty being the preservation of live bacterial culture in a skincare product for many months, as the viability of microorganisms defines the prospects of them colonising a particular area of the skin. Other significant factors, further complicating the topical application of probiotics, are the patient's general skin condition, their lifestyle and, most importantly, the use of cosmetic and hygienic solutions that can hinder the recolonisation and restoration of a healthy microbiome during the active therapy period.

Prebiotics present a much easier to use solution, as the agents with proven prebiotic activity are usually stable enough, easy to incorporate into a cosmetic formulation and, on top of that, affordable and easily manufactured. Initially, the term *prebiotics* was applied only to certain carbohydrates promoting the growth of healthy intestine microflora, such as fructooligosaccharides (FOS), galactooligosaccharides, glucomannan oligosaccharides, inulin, isomalto-oligosaccharides, lactosucrose, lactulose, neosugars, palatinose, raffinose, sorbitol, soy oligosaccharides, xylitol and xylooligosaccharides. Many of the above are used in cosmetic formulations as well.

It cannot be stressed enough that the use of prebiotics and probiotics in topical solutions implies refraining from the simultaneous use of antibacterial solutions, with both direct and indirect antibacterial action. For instance, the elimination of S. epidermidis, developing in the course of topical antibiotic therapy, leads to a sharp drop in the number of antimicrobial peptides and the increased colonisation by potentially pathogenic bacteria, S. aureus in particular, which eventually results in dysbiosis and sometimes even in a clinical manifestation of an inflammatory process. Any alcohol or salicylic acid-containing solutions and nonselective bacterial drugs will, most likely, negate the effect of both prebiotic and probiotic therapy. This limitation must be thoroughly observed when prescribing prebiotics and probiotics, and patients informed of the necessity to look into all of their daily skincare to make sure it won't interfere with treatment.

In recent years, cosmetic formulators have been actively incorporating probiotics and prebiotics into new cosmetic formulae. As we have already mentioned, prebiotics are far less challenging for cosmetic manufacturers, so naturally, the trendy "microbiome-friendly skincare" will most likely imply the use of prebiotics.

Historically, microorganisms have been characterised as planktonic - freely suspended cells - and described based on their growth characteristics in culture media. The phenomenon of biofilms forming, described firstly by van Leeuwenhoek observed on the tooth surfaces, was recognised only recently. By definition, biofilm is an accumulation of surface-associated microbial cells enclosed in an extracellular polymeric substance matrix. Biofilms cannot be removed by rinsing or gentle cleansing, and biofilm-associated microorganisms differ from their planktonic forms. Biofilms are associated with the development of antibiotic-resistant infections, possibly including chronic skin infectious processes as well.

Most interestingly, under normal physiological conditions, human skin prevents the formation of biofilms, even by the bacteria capable of forming them. However, any change in the environment (temperature, pH, TEWL and hydration) can lead to the formation of biofilms enabling multicellular functioning as a survival mechanism and translating into antibiotic resistance and higher virulence. Biofilm research led to a new understanding of the non-physical communication of microorganisms - they release, sense, and respond to small signal molecules called **quorum sensing**.

This way of communication explains the perfect synchronisation that allows unicellular microorganisms to behave as one multicellular organism. Molecules responsible for quorum sensing were named **autoinducers**. This discovery helps create a new pathway for microbiome-oriented skin treatment via the inhibition, elimination or degradation of autoinducers. With autoinducers taken out of the equation, microorganisms cannot synchronise anymore and return to being harmless. This way, the skin is "colonised" but not infected, as strange as it sounds from a traditional point of view. Many plant-derived molecules have shown potential to interfere with quorum sensing.

This approach can be called, I believe, *microbiome communication hacking* opening the door to a new non-antibiotic strategy for treating skin conditions associated with microbial activity, such as acne, rosacea and many others. Many autoinducers are already known, e.g., oligopeptides are used by gram-positive bacteria, and N-acyl homoserine lactone by gram-negative bacteria.

Acne is an interesting example of bacterial interaction - S.epidermidis

CA-SSIS/Shutterstock

prevents and controls the change in virulence of S.aureus and C.acnes whilst virulent S.aureus and C.acnes affect the local population of S.epidermidis changing the microbiome, leading to the formation of biofilm and triggering inflammation as a consequence of acne pathogenesis events.

It is highly likely that many plants used in traditional medicine act as anti-autoinducers. It may explain the previously inexplicable efficacy of the so-called alternative plant-based treatments for some skin conditions or infections. For example, Ruellia patula used in African folk medicine and Siddha traditional medicine used for a variety of infections, including cutaneous, have been recently proven to show anti-biofilm activity. A recently studied plant from the coffee family, Morinda citrifolia, widely used in folk medicine on the Pacific islands, shows anti-autoinducer activity combined with the anti-biofilm effect and the modulation of auto-inducer synthesis by inhibiting the LUX-S gene expression.

This plant extract does not show any disinfecting, antibiotic-like or antiseptic activity but does demonstrate a significant bacteriostatic effect on C. acnes, Corynebacterium striatum, S.aureus, Pseudomonas aeruginosa, Malassezia furfur, and Epidermophyton floccosum, such that it appears promising to apply in the therapy of acne, dandruff, cutaneous and nail infections.

This approach can be described as "*shoot the message, not the messenger*", and it may help us find a way to overcome the rising problem of antibiotic resistance, which is especially obvious in dermatology due to the excessive use of topical and systemic antibiotic treatments in recent years.

A microbiome-oriented approach in dermatology and skincare changes even the sacred paradigm of epidermal anatomy, adding a new layer to the epidermis that can be called a sixth living layer or Stratum microbium© (Givaudan) on top of the Stratum Corneum.

This structure includes an air mantle (gaseous layer creating the skin's microenvironment) and an emulsified layer (a mix of sweat and sebaceous secretion previously referred to as the skin's hydrolipidic mantle but including microbiome as well). The topical treatment of skin conditions or simply a daily skincare regime affect Stratum microbium because they alter the air-emulsified environment, leading to beneficial (or not) changes of the microbiome and of the microbe-host interaction via Toll-like receptors. The use of inappropriate skincare or treatments, physical, chemical, or UV damage can lead to dysbiosis and virulence factors release, the formation of biofilms, and the manifestation of skin pathology. A new awareness of a microbiome-friendly approach can help understand the skin's needs better, where daily care and the efficacy of treatments are concerned.

The study of the human microbiome, *The Human Microbiome Project*, changes not only the way we care about skin and treat the diseases of the skin and gut but our general view of the human body.

In essence, a human's body is not an individual organism but rather a complex of human cells and various microorganisms which cannot be separated and should not be regarded and studied on their own. The number of microorganisms colonising a human body exceeds the number of human cells by about ten times. Microorganisms make up from 1% to 3% of body mass, i.e., on average, a human weighing 100 kg carries about 2 kg of microorganisms. We have 360 times more protein-coding genes of microbial origin than our own human genes.

It would appear that humans and microorganisms are inseparable.

This new knowledge should make us reconsider the use of biocides in cosmetic care that has become widespread in the last decades. Cosmetic skincare with antiseptic and antibacterial properties is, in a way, an anti-prebiotic, and perhaps it is time to treat it with more caution. We cannot stress enough that the use of microbiome-friendly solutions implies that the application of all biocides, including such favourites as alcohol and alpha hydroxy acids (AHAs), must be suspended or terminated altogether.

The development of microbiome-friendly skincare has just begun, and many questions remain unanswered.

Any development in this area will require changes in legislation, amendments and elaborations in marketing and claim regulations. As of today, not all solutions claiming the use of probiotics and prebiotics are using them as ingredients; it is not uncommon to see a probiotic claim on a solution of entirely plant origin. Besides, the research base in this field is still insufficient. We are only just beginning to accumulate relevant knowledge. However, even the practical experience we have gained so far demonstrates that microbiome-friendly skincare is extremely effective and can be applied almost without limitations, unlike many solutions where visible results are achieved by a rather aggressive impact on the skin.

With microbiome, we are never on our own.

The human being as a host can be compared to our planet inhabited by the animal world, humans and organic life in general. We need to find a way to co-exist in mutual harmony with our microbiome, just like we need to find a way to co-exist with other life forms on Earth.

CPD CERTIFIED
The CPD Certification Service

The content of the following has been certified by the CPD Certification Service as conforming to continuing professional development principles.

Article: New understanding of skin microbiome
Literature

CONSULTINGROOM.COM
(1376)

Date: March 2021
Certificate No: A026988

The CPD Certification Service, The Coach House, Ealing Green, London W5 5ER. Tel: 020 8840 4363 Fax: 020 8579 3991
E-mail: info@cpduk.co.uk Web: www.cpduk.co.uk

To download a CPD Reflective Learning Form, produced in association with the British Association of Cosmetic Nurses (BACN) & the British College of Aesthetic Medicine (BCAM), please use the QR code or visit bit.ly/CR-CPD in your web browser.

References

1. The human microbiome project. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. Nature. 2007;449(7164):804-810.
2. Microbial ecology of the skin. Roth RR, James WD Annu Rev Microbiol. 1988; 42():441-64
3. Quantitation of major human cutaneous bacterial and fungal populations. Gao Z, Perez-Perez GI, Chen Y, Blaser MJ J Clin Microbiol. 2010 Oct; 48(10):3575-81.7
4. Medically important bacterial-fungal interactions. Peleg AY, Hogan DA, Mylonakis E. Nature Rev. Microbiol. 2010; 8:340–349.
5. Demodex mites: facts and controversies. Elston DM Clin Dermatol. 2010 Sep-Oct; 28(5):502-4.
6. Demodex and skin infection: fact or fiction. Hay R Curr Opin Infect Dis. 2010 Apr; 23(2):103-5.
7. Mite-related bacterial antigens stimulate inflammatory cells in rosacea. Lacey N, Delaney S, Kavanagh K, Powell FC Br J Dermatol. 2007 Sep; 157(3):474-81.
8. Increased density of Demodex folliculorum and evidence of delayed hypersensitivity reaction in subjects with papulopustular rosacea. Georgala S, et al. J. Eur. Acad. Dermatol. Venereol. 2001;15:441–444.
9. The Ecology of the Human Skin. Bannerstone House, Springfield, Illinois: Charles C Thomas; 1965. A seminal and comprehensive work of classical dermatological microbiology Marples M.
10. Wound microbiology and associated approaches to wound management. Bowler PG, Duerden BI, Armstrong DG Clin Microbiol Rev. 2001 Apr; 14(2):244-69.
11. Role of microorganisms in the evolution of animals and plants: the hologenome theory of evolution. Zilber-Rosenberg I, Rosenberg E. FEMS Microbiol Rev 2008; 32: 723–735
12. Epithelial cells pay a Toll for protection. Strober W
13. PI3K and negative regulation of TLR signaling. Fukao T, Koyasu S. Trends Immunol. 2003 Jul; 24(7):358-63.
14. Selective antimicrobial action is provided by phenol-soluble modulins derived from Staphylococcus epidermidis, a normal resident of the skin. Cogen AL, Yamasaki K, Sanchez KM, Dorschner RA, Lai Y, MacLeod DT, Torpey JW, Otto M, Nizet V, Kim JE, Gallo RL J Invest Dermatol. 2010 Jan; 130(1):192-200.
15. Staphylococcus epidermidis antimicrobial delta-toxin (phenol-soluble modulin-gamma) cooperates with host antimicrobial peptides to kill group A Streptococcus. Cogen AL, Yamasaki K, Muto J, Sanchez KM, Crotty Alexander L, Tanios J, Lai Y, Kim JE, Nizet V, Gallo RL PLoS One. 2010 Jan 5; 5(1):e8557.
16. Activation of TLR2 by a small molecule produced by Staphylococcus epidermidis increases antimicrobial defense against bacterial skin infections. Lai Y, Cogen AL, Radek KA, Park HJ, Macleod DT, Leichtle A, Ryan AF, Di Nardo A, Gallo RLJ Invest Dermatol. 2010 Sep; 130(9):2211-21
17. The skin microbiome: impact of modern environments on skin ecology, barrier integrity, and systemic immune programming. Susan L. Prescott, Danica-Lea Larcombe, Alan C. Logan, Christina West, Wesley Burks, Luis Caraballo, Michael Levin, Eddie Van Etten, Pierre Horwitz, Anita Kozyrskyj and Dianne E Campbell. World Allergy Organization Journal 2017
18. Household triclosan and triclocarban effects on the infant and maternal microbiome. Ribado JV, Ley C, Haggerty TD, Tkachenko E, Bhatt AS, Parsonnet J. EMBO Mol Med. 2017 Dec;9(12):1732-1741.
19. Functions of the skin microbiota in health and disease. Sanford JA, Gallo RL. Semin Immunol (2013)
20. The influence of skin microorganisms on cutaneous immunity. Belkaid Y, Tamoutounour S. Nat Rev Immunol. 2016;1 6:353-366
21. Is there a 'gut-brain-skin axis'? Arck P, Handjiski B, Hagen E, Pincus M, Bruenahl C, Bienenstock J, Paus R. Exp Dermatol. 2010 May;19(5):401-5.
22. Skin microbiota and atopic dermatitis: toward new therapeutic options? JP Lacour Ann Dermatol Venereol, 2015
23. Probiotics and primary prevention of atopic dermatitis: a meta-analysis of randomized controlled studies. Panduru M, Panduru NM, Sălăvăstru CM, Tiplica GS. J Eur Acad Dermatol Venereol. 2015 Feb;29(2):232-42.
24. Acne vulgaris, probiotics and the gut-brain-skin axis: from anecdote to translational medicine W.P. Bowe1, N.B. Patel and A.C. Logan Benef Microbes. 2014 Jun 1;5(2):185-99
25. Future of topical therapy. Wohlrab J, Staubach P.Hautarzt. 2014 Mar; 65(3):168.
26. Probiotic topical agents. Volz T, Biedermann T. Hautarzt. 2009 Oct;60(10):795-801.
27. Prebiotic Cosmetics: An Alternative to Antibacterial Products. Bockmühl, D., Jassoy, C., Nieveler, S., Scholtyssek, R., Wadle, A. and Waldmann-Laue, M. (2007), International Journal of Cosmetic Science, 29: 63-64.
28. Biofilms: microbial life on surfaces. Donlan RM. Emerg Infect Dis. 2002;8(9):881-890.
29. Revealing the secret life of skin - with the microbiome you never walk alone. Sfriso R, Egert M, Gempeler M, Voegeli R, Campiche R. Int J Cosmet Sci. 2020;42(2):116-126.
30. The microbiome and dermatological diseases. Mańkowska-Wierzbicka D, Karczewski J, Dobrowolska-Zachwieja A, Adamski Z. Postepy Hig Med Dosw (Online). 2015 Sep 7;69:978-85.
31. The microbiome, a new target for ecobiology in dermatology. Dréno B. Eur J Dermatol. 2019 Apr 1;29(S1):15-18.
32. Microbiome in healthy skin, update for dermatologists. Dréno B, Araviiskaia E, Berardesca E, Gontijo G, Sanchez Viera M, Xiang LF, Martin R, Bieber T. J Eur Acad Dermatol Venereol. 2016 Dec;30(12):2038-2047.
33. Microbiome and skin diseases. Zeeuwen PL, Kleerebezem M, Timmerman HM, Schalkwijk J. Curr Opin Allergy Clin Immunol. 2013 Oct;13(5):514-20.
34. The microbiome: an emerging key player in aging and longevity. Kim M, Benayoun BA. Transl Med Aging. 2020; 4:103-116.
35. Extrinsic Factors Shaping the Skin Microbiome. Moskovicz V, Gross A, Mizrahi B. Microorganisms. 2020; 8(7):1023.
36. Bacterial quorum sensing: its role in virulence and possibilities for its control. Rutherford ST, Bassler BL. Cold Spring Harb Perspect Med. 2012;2(11):a012427. Published 2012 Nov 1.
37. Quorum sensing: how bacteria can coordinate activity and synchronize their response to external signals? Li Z, Nair SK. Protein Sci. 2012;21(10):1403-1417.
38. Multidisciplinary Study to Evaluate the Anti-quorum Sensing Ability of Phyto-compounds in Ruellia patula Jacq. Avicenna Chemmugil P, Lakshmi P, Annamalai A. A J Med Biotechnol. 2019;11(1):48-58.
39. Evaluation of antitumoral and antimicrobial activity of Morinda lcitrifolia L. grown in Southeast Brazil. Candida, Thamyris, França, Jerônimo Pereira de, Chaves, Alba Lucilvânia Fonseca, Lopes, Fernanda Andrade Rodrigues, Gaiba, Silvana, Sacramento, Celio Kersul do, Ferreira, Lydia Masako, & França, Lucimar Pereira de. (2014). Acta Cirúrgica Brasileira, 29(Suppl. 2), 10-14 https://doi.org/10.1590/S0102-86502014001400003
40. Morinda citrifolia (Noni): a literature review and recent advances in Noni research. Wang MY, West BJ, Jensen CJ, Nowicki D, Su C, Palu AK, Anderson G. Acta Pharmacol Sin. 2002 Dec;23(12):1127-41. PMID: 12466051.