Journal of Pakistan Association of Dermatologists. 2024;**34(3)**:726-732.

Review Article

The role of microbiome-containing moisturizers in atopic dermatitis

Bonnie Yudistha Anggawirya, Sawitri Sawitri

Department of Dermatology and Venereology, Faculty of Medicine, Airlangga University/Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

Abstract Atopic dermatitis (AD) is a chronic inflammatory and very itchy skin condition. One theory for AD development is microbiota dysbiosis on the skin's surface. Based on this hypothesis, microbiome-containing moisturizers have been investigated as an alternative treatment for AD. This study seeks to provide the most recent information on using moisturizers with microbiomes in AD.

Key words
Atopic dermatitis; Dysbiosis; Microbiome; Microbiota, Moisturizer.

Introduction

Atopic dermatitis (AD) is one of the most prevalent skin conditions in children. It is persistent, itchy, and inflammatory.[1] In developed countries, the prevalence of AD has doubled or tripled since the 1970s.[2] The pathophysiology of AD is complex and multidimensional, involving the skin barrier, skin microbiota, genetics, and environmental factors. Recently, there has been increasing focus on the role of the skin microbiome in the onset and management of AD.[3] Alterations in the equilibrium of the microbiome and the host skin's immune response have been observed to exacerbate AD and lead to secondary skin infections.[4]

Manuscript
Received on: September 28, 2023
Revised on: October 18, 2023
Accepted on: January 07, 2024
Address for correspondence
Dr. Sawitri
Department of Dermatology and Venereology, Faculty of Medicine, University Airlangga, Dr. Soetomo General Hospital, Surabaya – Indonesia.
Jalan Prof. Dr. Moestopo No. 6-8, Surabaya, East Java, 60286, Indonesia.
Phone: +62 8123033993
Email: sawitri@fk.unair.ac.id

Researchers have recently explored how various treatments affect the skin's microbiome in treating AD. Studies have shown that topical corticosteroids, systemic immunomodulating biologic therapy, and other treatments increase the diversity of skin bacteria and reduce the prevalence of *S. aureus*. After treatment, the microbiota's structure increasingly resembles that of healthy individuals.[3] Thus, the success of AD therapy in restoring a normal skin microbiome supports the notion that microbes play a role in AD treatment strategies.[5] The topical application of commensal organisms (e.g., *Staphylococcus hominis or Roseomonas mucosa*) as a treatment for AD is a recent approach explored in recent studies, which appears to reduce the severity of AD. This review aims to describe the use of moisturizers containing skin microbiome content as a treatment option for AD.

Atopic Dermatitis

Atopic dermatitis is an inflammatory skin condition that often affects infants and young children. Both inherited and environmental factors influence it. This chronic condition's characteristics include severe pruritus, crusts, scales, papules, vesicles, erythema, and papillary

eruptions. It may also be accompanied by infections or allergies to irritants, chemicals, or psychogenic factors.[6]

Atopic dermatitis is a problematic skin condition that arises from the interaction of various factors. The epidermis' ability to control water loss (preventing dry skin) and the activation of the immune system by high molecular weight allergens such as dust mite antigens, food, and microorganisms impact the skin's innate immune system. This protective layer comprises lipids, tight junction proteins, and stratum corneum structural proteins.[7] Fibragrin in the stratum corneum produces the natural moisturizing factor (NMF). NMF profoundly influences transepidermal water loss (TEWL), skin pH levels, and other elements that impact skin homeostasis.[8]

The skin microbiome is another environmental component that affects skin immunity and defence.[9] Interactions within the skin microbiome govern the microbial community composition by preventing potential infections and preserving immune homeostasis.[9] *Propionibacterium, Staphylococcus,* and *Corynebacterium spp.*, three of the hundreds of bacterial species that make up the skin microbiome, have also been shown to play a role in the pathogenesis of AD.[10] The microbiome of AD skin differs significantly from normal skin due to *Staphylococcus aureus* overgrowth.[2] The complexity of treating AD depends on several factors, including age, illness severity, location, and duration.[11] The main objective of treatment is to lessen itching while reducing the negative consequences of AD on quality of life through effective management. A comprehensive step-by-step strategy for care includes educating patients and their parents, avoiding irritants and allergens, maintaining appropriate humidity, restoring natural dysbiosis, and using anti-inflammatory drugs.[7] Early, effective treatment is the best way to reduce the chances of developing a chronic illness and the risk of allergen sensitization, although prevention is always preferable.[11]

A fundamental therapy strategy for children and adults is the regular use of emollients to reduce symptoms and enhance skin moisture. Emollients may also impact the richness of the microbiota and the prevalence of *Staphylococcus species*. Topical corticosteroids are the first-line anti-inflammatory therapy; however, potent anti-inflammatory medications are necessary in the acute stage of the illness. Appropriate use of emollients for hydration is vital to treating AD,[12] as they can improve skin barrier integrity. Emollients have been shown to reduce transepidermal water loss (TEWL), S. aureus colonization rates, and the severity of AD disease.[13]

Microbiome

Joshua Lederberg initially used the word "microbiome" to describe the biological community of commensal, symbiotic, or pathogenic microorganisms that reside directly in a specific area of the body.[14] The human microbiome is most abundant in the gut. Bacteria in the human microbiome play roles in human immunity, nutrition, and growth.[15] The microbiome regulates the body's biological and physiological processes. Immune system dysfunction and inflammatory dysregulation cause non-communicable diseases and conditions (NCDs). Additionally, disruption of the microbiome can increase the risk of infection.[15]

The skin microbiome has been thoroughly investigated for its role in interacting with the immune system. It has been shown that the widely prevalent commensal bacteria *S. epidermidis* alters innate inflammatory reactions

through processes, including toll-like receptor (TLR) cross-talk. By activating TLR2 with lipoteichoic acid (LTA), *S. epidermidis* may reduce TLR3-mediated keratinocyte inflammation resulting from skin damage. Additionally, it may influence T cell maturation and enhance T cell migration to the skin in a germ-free mouse model. Pattern recognition receptors (PRRs) in the epidermis enable keratinocytes to identify the microbial flora on the skin's surface. Beta-defensins 2 and 3 (DEFB-2/DEF-3) are produced due to TLR2's response, protecting the skin against microbial evasion. The skin's microbial flora may strengthen the tight junction barrier and tight junction size by activating TLR2, which may also impact mast cell recruitment. Despite keratinocytes producing AMPs and activating TLRs, commensal microbes exist on the skin's surface. Thus, commensal bacteria may help defend our skin from infections without triggering a constitutively active immune response.[16]

The commensal microbiome is found on the skin surface, for example, *Staphylococcus epidermidis*. Some evidence suggests that *Staphylococcus epidermidis* is a skin commensal that plays an active role in host skin defence, indicating a reciprocal relationship.[17] Cutibacterium composition was reduced in older individuals, *but Corynebacterium, Acinetobacter, Streptococcus*, and *Prevotella* bacteria were found in more significant numbers than in young adults. The decrease in Cutibacterium composition may be related to the decreased sebum secretion in ageing skin, as these bacteria are more lipophilic.[18]

Microbiome Disruption in AD

Disruption of the skin microbiota is an independent risk factor for AD development. Approximately 90% of AD patients have S. aureus on their skin, and 50% of these bacteria release toxins. These toxins may disrupt inflammation and skin barrier by activating host inflammasomes.[19]

One hypothesis for AD is the dysbiosis of the microbiota on the skin surface caused by barrier breakdown due to mutations in the gene encoding filaggrin.[5] In AD, mutations in genes encoding filaggrin and serine peptidase inhibitor Kazal type 5 (SPINK5) play a role in skin barrier breakdown. Mutations in T helper cell 2 (Th2) cytokines IL-4 and IL-13 are also implicated in the pathogenesis of AD.[16] Disruption of the skin barrier leads to microbiota dysbiosis, especially an increased population of *S. aureus* and penetration into deeper layers. The increased S. aureus population on the skin of AD patients is associated with AD exacerbations. Untreated exacerbations will increase the S. aureus population, decrease diversity, and trigger re-exacerbations.[5]

The gut microbiome controls the maturation of the immune system through interactions between the host and the microbiome, which may significantly impact AD development.[20] Changes in the gut microbiome, in particular, may lead to inflammation of the microenvironment and the immune system via metabolites that impact the immune system's balance. Growing evidence shows that gut bacteria produce neuroendocrine substances mediating the gut-skin axis. The evidence points to changes in the composition and ratios of the gut microbiome as being connected to the production of various neurotransmitters and brain modulators relevant to the severity of AD symptoms. They could also impact immune system dysregulation and skin barrier failure, two important pathophysiologies in AD development.[20]

The gut microbiome has been studied for AD, with probiotics are being used to investigate their potential role in the disease's immunologic processes. Macrophages, epithelial dendritic

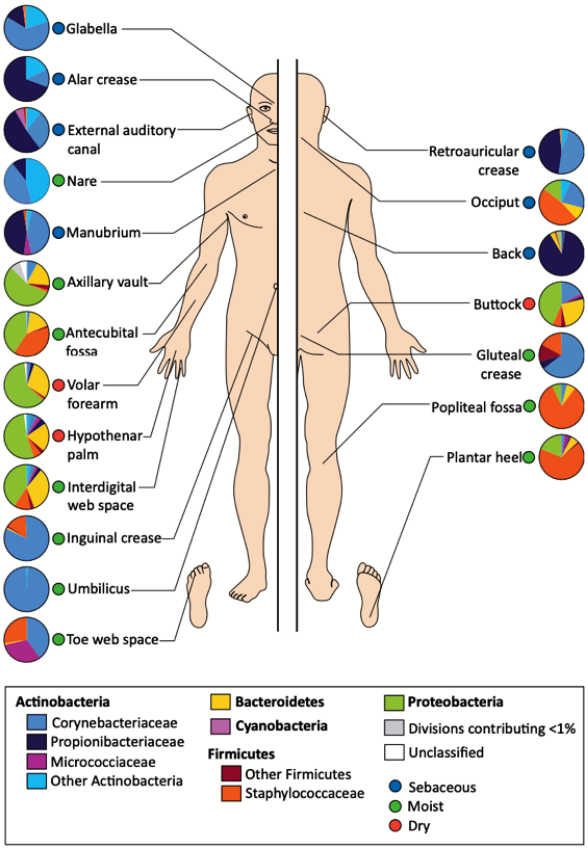

Figure 1 Bacterial topography on the skin. The microenvironment of the sample location significantly influences the skin microbiota. The family-level classification of bacteria occupying a given location is shown, with the species indicated in bold. Sebaceous or oily regions (blue circles), wet areas (typically skin creases) (green circles), and dry, flat surfaces (red circles) were the selected regions.[22]

cells, and mucosa may interact in complex ways with probiotics. Depending on the strain, probiotics may increase inflammatory cytokines like IL-10 and TGF-β or anti-inflammatory cytokines like IL-12, IL-18, and tumour necrosis factor (TNF-α), enhancing tolerance signalling. Dendritic cells and macrophages may promote T cell (Treg) production in an environment rich in cytokines such as IL-10 or TGF-β, which is crucial for sustaining peripheral immunity to tolerance by balancing the ratio of effector and Treg cells. Probiotics are not the only factor that may affect how host immune cells grow; alterations in gut microbiome genes may also impact babies with AD.[21]

The role of the microbiome in AD treatment

Over the last ten years, next-generation biotherapies based on the microbiome have gained popularity and are expected to increase significantly as innovative treatments for AD. The traditional method of treating S. aureus infections in AD involves decontamination with broad-spectrum antibiotics, but doing so risks boosting drug resistance and disrupting microbial commensals.[23]

Normal flora can be normalized using pro-, pre- or synbiotics.[24] In AD, the use of topical probiotics in several studies has shown efficacy **(Table 1)**. Despite the variety of study findings summarized in this review, topical microbiome research in dermatological treatment and skincare is still in its early stages, necessitating more research to demonstrate the efficacy, safety, and mode of action of each medication.

Vitreoscilla filiformis (Vf) is a bacterium that naturally occurs only in some hot springs. Vf is cultivated in a water medium derived from thermal spring water, which has a high concentration of Selenium, beneficial ingredients, especially for atopic skin. This thermal spring water amplifies the biological potential beneficial to Vf, making it a "super bacterium" named Aqua Posae Filiformis (APF). APF then undergoes a fragmentation process to obtain the desired bacterial extract. APF helps balance the microbiome and strengthen the skin barrier function. When incorporated into moisturizing products, APF can reduce itching and alleviate severe dry skin attacks in atopic skin.[25]

Lactiplantibacillus plantarum (formerly *Lactobacillus plantarum*) exhibits antibacterial activity against *S. aureus* clonal type 1, which can alleviate atopic skin symptoms when used topically. The main components of the cell wall of *L. plantarum* bacteria are lipoteichoic acid

Table 1 Studies investigating the role of microbiome-containing moisturizers on AD.

References	*Study Design*	*Research Title*	*Population*	*Intervention*	*Comparison*	*Outcome*
DiMarzio, *et al.* (2003)[28]	Double randomized study	Effect of the lactic acid bacterium Streptococcus thermophilus on stratum corneum ceramide levels and signs and symptoms of atopic dermatitis patients.	11 AD patients (4 males and 11 females, aged 18-24 years) and 10 volunteers (5 males and 5 females, aged 17-27 years).	Moisturizer containing *Streptococcus thermophilus* for 2 weeks on one forearm.	Use of base cream alone on contralateral arm.	SCORAD, ceramide levels.
Gueniche, *et al.* (2008)[29]	Double randomized study	Effects of nonpathogenic gram-negative bacterium Vitreoscilla filiformis lysate on atopic dermatitis: a prospective, randomized, double-blind, placebo-controlled clinical study.	75 AD patients (56 females and 19 males, aged 6-70 years).	Moisturizer containing *Vitreoscilla filiformis* for 30 days.	Use of vehiculum cream.	SCORAD, TEWL, VAS, S. *aureus* colonization.
Park, *et al.* (2014)[30]	Double randomized study	Effect of Emollients Containing Vegetable-Derived Lactobacillus in the Treatment of Atopic Dermatitis Symptoms: Split-Body Clinical Trial.	30 AD patients.	Moisturizer containing *Lactobacillus sakei* for 4 weeks.	Placebo	TEWL, VAS, IGA, S. *aureus* colonization.
Blanchet-Réthoré, *et al.* (2017)[31]	Double randomized study	Effect of a lotion containing the heat-treated probiotic strain *Lactobacillus johnsonii* NCC 533 on *Staphylococcus aureus* colonization in atopic dermatitis.	31 AD patients (male and female, aged 18-75 years).	Moisturizer containing *Lactobacillus johnsonii* on one arm for 3 weeks.	The contralateral arm is given the patient's usual moisturizer or nothing is given.	SCORAD, S. *aureus* colonization.
Myles, *et al.* (2018)[32]	Open-label phase I/II	First-in-human topical microbiome transplantation with *Roseomonas mucosa* for atopic dermatitis.	10 adults (age > 18 years) and 5 children (age 7-17 years) with AD.	Moisturizer containing *Roseomonas mucosa* for 6 weeks.	Placebo	SCORAD, S. *aureus* colonization.
Butler, *et al.* (2020)[33]	Double randomized study	*Lactobacillus reuteri* DSM 17938 as a Novel Topical Cosmetic Ingredient: A Proof of Concept Clinical Study in Adults with Atopic Dermatitis.	36 AD patients (aged 18-70 years).	Moisturizer containing *Lactobacillus reuteri* for 8 weeks.	Moisturizing cream without probiotics.	SCORAD, S. *aureus* colonization.
Nakatsuji, *et al.* (2021)[34]	Double randomized study	Development of a human skin commensal microbe for bacteriotherapy of atopic dermatitis and use in a phase 1 randomized clinical trial.	54 adult DA patients.	Moisturizer containing *Staphylococcus hominis* for 1 week.	Placebo	EASI, SCORAD, S. *aureus* colonization.
Seite, *et al.* (2022)[25]	Double randomized study	Clinical efficacy of emollients in atopic dermatitis patients – relationship with the skin microbiota modification.	60 AD patients (27 males and 33 females, age 6 months - 63 years).	Moisturizer containing *Vitreoscilla filiformis* for 28 days.	Creams containing triglycerides, glycerin, shea butter, and ceramides.	SCORAD, recurrence of AD.

and peptidoglycan, both of which promote collagen synthesis. Lipoteichoic acid from *L. plantarum* significantly inhibits the formation of *S. aureus* biofilm. Moisturizers containing shea butter, sunflower oil, vitamin E, and fermented *Lactiplantibacillus plantarum* bacterial lysate help balance the skin microbiome and have a calming effect on atopic skin prone to irritation, itching, and dryness.[26]

A moisturizer containing fermented lysate of *Lactococcus lactis*, ectoin, squalene, panthenol, and shea butter promotes skin regeneration, improves skin barrier function, and reduces dry skin. Ectoin increases the barrier function against water loss, enhancing skin resilience and reducing dehydration by shielding cell membranes from harm caused by surfactants, which are included in many cosmetic products. A topical coenzyme is called panthenol or vitamin B5. This substance preserves skin moisture and elasticity by enhancing corneum layer hydration, reducing TEWL, and preventing damage to the bacterial microbiome. Squalene is a lipid occurring naturally in people, animals, and plants. Shea butter is a lipid derived from plants that moisturizes dry skin and is used in cosmetics and creams.[27]

Conclusion

Successfully treating AD in the future with topical moisturizers containing commensal microbiomes can increase our knowledge of AD aetiology and broaden the range of topical therapeutic options for AD. More research is still required to determine the optimal bacterial species and strains and to combine this information with analyses of gene expression, protein synthesis, and metabolic processes in the skin. The dynamics of many bacterial species populating the skin and their interactions with human immunity will be greatly aided by such investigations, providing vital information. This will fully utilize the potential of microbiome modification to prevent and treat AD.

Financial support and sponsorship None.

Conflict of interest Authors declared no conflict of interest.

Authors' contribution

BYA: Substantial contribution to concept, study design, manuscript writing, final approval of the version to be published.

SS: Substantial contribution to concept, study design, critical review, final approval of the version to be published.

References

1. Kapur S, Watson W, Carr S. Atopic dermatitis. *Allergy Asthma Clin Immunol*. 2018;**14(2)**:43-52.
2. Nakatsuji T, Gallo RL. The role of the skin microbiome in atopic dermatitis. *Ann Allergy Asthma Immunol*. 2019;**122(3)**:263-9.
3. Guo Y, Dou X, Jian XL, Zhang KY, Zheng YJ, Yu B. Effect of treatments on skin microbiota in patients with atopic dermatitis: A protocol for systematic review. *BMJ Open*. 2022;**12(1)**:e053488.
4. Salava A, Lauerma A. Role of the skin microbiome in atopic dermatitis. *Clin Transl Allergy*. 2014;**4**:33.
5. Effendi R, Dwiyana R. Skin Microbiota and its role in atopic dermatitis. *Media Dermato-Venereologica Indonesiana*. 2022; **49(1)**:50–6.
6. Paramita DA, Khairina, Lubis NZ. Bacterial colonization in atopic dermatitis. *Bali Med J*. 2022;**11(3)**:1924–9.
7. Paller AS, Mancini AJ, editors. Eczematous Eruptions in Childhood. In: Hurwitz Clinical Pediatric Dermatology. 6th ed. Missouri: Elsevier; 2022. p. 42–61.
8. Pothmann A, Illing T, Wiegand C, Hartmann AA, Elsner P. The Microbiome and Atopic Dermatitis: A Review. *Am J Clin Dermatol*. 2019;**20**:749-61.
9. Ramadan M, Solyman S, Yones M, Abdallah Y, Halaby H, Hanora A. Skin microbiome differences in atopic dermatitis and healthy controls in Egyptian children and adults, and association with serum immunoglobulin E. *OMICS*. 2019; **23(5)**:247–60.
10. Flohr C, Silverberg JI, Wan J, Langan SM. Epidemiology of Atopic Dermatitis. In: Hoeger P, *et al.*, editors. Harper's Textbook of Pediatric Dermatology. 4th ed. New Jersey: Wiley Blackwell; 2020. p. 167–83.

11. Solman L, Glover M. Management of Atopic Dermatitis. In: Hoeger P, Kinsler V, Yan A, editors. Harper's Textbook of Pediatric Dermatology. 4th ed. New Jersey: WIley Blackwell; 2020. p. 253–64.
12. Popadić S, Gajić-Veljić M, Prćić S, Mijušković Ž, Jovanović D, Kandolf-Sekulović L, *et al*. National Guidelines for the Treatment of Atopic Dermatitis. *Serbian J Dermatol Venereol*. 2016;**8(3)**:129–53.
13. Dou J, Zeng J, Wu K, Tan W, Gao L, Lu J. Microbiosis in pathogenesis and intervention of atopic dermatitis. *Int Immunopharmacol*. 2019;**69**:263-9.
14. Dietert RR, Dietert JM. The microbiome and sustainable healthcare. *Healthcare*. 2015; **3(1)**:100–29.
15. Sudarmono PP. The Microbiome: New understanding of the role of microorganisms in human life. *eJournal Kedokteran Indonesia*. 2016;**4(2)**:71–5.
16. Williams MR, Gallo RL. The Role of the Skin Microbiome in Atopic Dermatitis. *Curr Allergy Asthma Rep*. 2015;**15(65)**:1–10.
17. Schommer NN, Gallo RL. Structure and function of the human skin microbiome. *Trends Microbiol*. 2013;**21(12)**:660–8.
18. Luna PC. Skin Microbiome as years go by. *Am J Clin Dermatol*. 2020;**21(1)**:12–7.
19. Wollina U. Microbiome in atopic dermatitis. *Clin Cosmet Investig Dermatol*. 2017;**10**:51-6.
20. Lee SY, Lee E, Park YM, Hong SJ. Microbiome in the Gut-Skin Axis in atopic Dermatitis. *Allergy Asthma Immunol Res*. 2018;**10(4)**:354-62.
21. Umborowati MA, Salsabila Nurdini Wilda, Damayanti, Anggraeni S, Prakoeswa CRS. The role of skin and gut microbiome in atopic dermatitis. *J Pak Assoc Dermatol*. 2022;**32(1)**:48–55.
22. Powers CE, McShane DB, Gilligan PH, Burkhart CN, Morrell DS. Microbiome and pediatric atopic dermatitis. *J Dermatol*. 2015;**42(12)**:1137-42.
23. Koh LF, Ong RY, Common JE. Skin microbiome of atopic dermatitis. *Allergol Int*. 2022;**71(1)**:31-9.
24. Ananda S, John E, Tamami MF, Hidajat D. Skin Microbiome and the role of probiotics in atopic dermatitis. *Jurnal Kedokteran Unram*. 2022;**11(1)**:739–46.
25. Seité S, Zelenkova H, Martin R. Clinical efficacy of emollients in atopic dermatitis patients - relationship with the skin microbiota modification. *Clin Cosmet Investig Dermatol*. 2017;**10**:25–33.
26. Christensen IB, Vedel C, Clausen ML, Kjærulff S, Agner T, Nielsen DS. Targeted screening of lactic acid bacteria with antibacterial activity toward staphylococcus aureus clonal complex type 1 associated with atopic dermatitis. *Front Microbiol*. 2021;**12**:733847.
27. Crespo C. Bacterial derivatives of lactococcus lactis and ectoin for atopic dermatitis: Dermal compatibility and cosmetic acceptability. *Pharm Pharmacol Int J*. 2017;**5(6)**:226-31.
28. Di Marzio L, 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*. 2003;**12**:615-20.
29. Gueniche A, Knaudt B, Schuck E, Volz T, Bastien P, Martin R, *et al*. Effects of nonpathogenic gram-negative bacterium Vitreoscilla filiformis lysate on atopic dermatitis: A prospective, randomized, double-blind, placebo-controlled clinical study. *Br J Dermatol*. 2008;**159(6)**:1357–63.
30. Park SB, Im M, Lee Y, Lee JH, Lim J, Park YH, *et al*. Effect of emollients containing vegetable-derived lactobacillus in the treatment of atopic dermatitis symptoms: Split-body clinical trial. *Ann Dermatol*. 2014;**26(2)**:150–5.
31. 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*. 2017;**10**:249-57.
32. Myles IA, Earland NJ, Anderson ED, Moore IN, Kieh MD, Williams KW, *et al*. First-in-human topical microbiome transplantation with Roseomonas mucosa for atopic dermatitis. *JCI Insight*. 2018;**3(9)**:e120608.
33. Butler É, Lundqvist C, Axelsson J. Lactobacillus reuteri DSM 17938 as a novel topical cosmetic ingredient: A proof of concept clinical study in adults with atopic dermatitis. *Microorganisms*. 2020;**8(7)**:1-15.
34. Nakatsuji T, Hata TR, Tong Y, Cheng JY, Shafiq F, Butcher AM, *et al*. Development of a human skin commensal microbe for bacteriotherapy of atopic dermatitis and use in a phase I randomized clinical trial. *Nat Med*. 2021;**27(4)**:700–9.