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Review Article

Role of oral probiotics to ameliorate gut microbiota dysbiosis in psoriasis therapy: A literature review

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Abstract Psoriasis is a chronic and recurring inflammatory condition that can occur locally in the skin and systemically. Psoriasis causes significant morbidity and reduces quality of life of its patients. Microbiota and its metabolites are known to play a significant role in both innate and adaptive immune regulation. Disruption of microbial homeostasis known as dysbiosis, can lead to alterations in immunological regulation and disruption of the gastrointestinal barrier. The gut microbiota composes the largest microbiome in the human body. Changes in the diversity of the gut microbiotas and their metabolites are reported in psoriasis patients. Dysbiosis is thought to contribute and intensify the inflammatory process in psoriasis. Probiotics are widely utilized and well-known for its safety profile. Probiotics are currently being widely studied as a therapy for skin disorders, including psoriasis. Probiotics may increase the variety of commensal microbiota, decrease pathobionts, and restore the damaged gastrointestinal epithelium. Probiotic supplementation is expected to ameliorate the dysbiosis that occurs in psoriasis and become a promising adjuvant therapy in psoriasis.

Key words
Psoriasis; Microbiome; Dybiosis; Probiotic; Human and health.

Introduction

Psoriasis is a chronic inflammatory skin disease that affects more than 2% of the world's population. The pathogenesis of psoriasis involves the interaction of internal factors in predisposed individuals with various external factors such as trauma, infection, drugs and psychogenic stress.[1]

Gut microbiome dysbiosis is found in chronic inflammatory diseases and autoimmune disorders. Studies have reported changes in the microbiota profile in patients with psoriasis.[2] Probiotic therapy through direct activity and its metabolites is known to improve gastrointestinal microbiota homeostasis, suppress pathogens, maintain gastrointestinal integrity and play a role in immune system regulation. Thus, probiotics are expected to suppress chronic inflammation in psoriasis.[3]

The pathogenesis of psoriasis is complex and still not fully understood. Exaggerated immune response is thought to be the etiology. Immune dysregulation in psoriasis patients is demonstrated by an increased Th1/Th17 ratio and a decreased Th2/Treg ratio compared to the healthy population. T regulator (Treg) cells play a role in maintaining immune regulation. In psoriasis patients, the function of Treg cells is incompetent to inhibit the pathogenic T cells.[4] Treg are part of the mesenteric lymphoid tissues.

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Treg activity and differentiation are influenced by metabolites produced by the gut microbiota.[5]

Commensal microbiota plays a role in the maturation and regulation of the immune system. This mechanism is mainly mediated by metabolites produced by the microbiota. Short chain fatty acid (SCFA) is the microbiota metabolite believed to play the most important role in immune system modulation. Microbiotas have different production capacities and preferences in producing SCFA. *Bacteroides* produces acetate (C2) and propionate (C3), *Firmicutes* produces butyrate (C4), and *Akkermansia municiphilla* produces C3. In addition to being a source of energy for colonocytes, SCFA are regulators of the innate and the adaptive immune system, SCFA also stimulate epithelial cell proliferation and mucin production to maintain the gastrointestinal barrier.[6] SCFAs are known to stimulate Treg cells and the activation of B cells into plasma cells to produce specific IgA. Propionate (C3) stimulates differentiation of naïve T cell into Treg through the activation of GPR43. The activated Tregs is the subpopulation which has the anti-inflammatory properties.[5,6]

Psoriasis-related changes in the gut microbiome

Gut dysbiosis is hypothesized to initiate psoriasis in predisposed individuals. Studies consistently report changes in diversity, increase in *Firmicutes* and F/ B ratio in psoriasis, and is a decrease in the number of bacteria that produce SCFA such as *Provetella*, *Akkermansia*, *Feacalibacterium* and *Ruminococcus*. Changes in the diversity resulted in an imbalance in certain SCFA levels, an increase in acetate and a decrease in butyrate. Butyrate is anti-inflammatory, suppresses the formation of Reactive Oxygen Species (ROS), inhibits adhesion, proliferation, translocation, and cytokine production by immune cells. Microbiota such as *Bifidobacterium, Faecalibacterium*, and *Akkermansia* have a positive effect on the proliferation of Treg cells, whereas certain bacteria can actually suppress Tregs activity. Dysbiosis also cause gut barrier disruption. Damage to the gut barrier promotes antigen interaction with immune cells and leakage of toxins and metabolites into the systemic circulation, resulting in chronic inflammation.[7]

It remains unclear whether psoriasis is the result of or the cause of dysbiosis. Dybiosis can cause chronic inflammatory response in psoriasis which upregulate the proinflammatory cytokines in psoriasis. In contrast, chronic inflammation in psoriasis changes the skin and gut microbiome and create dysbiosis. In addition, psoriasis therapy is known to worsen dysbiosis. Immunotherapy such as corticosteroids and tacrolimus can alter the gut microbiota. Cyclophosphamide can increase the colonization of pathogenic bacteria (*Eschericia coli, Enterobacteriaceae, Pseudomona*s and *Enterococci*).[6]

Oral probiotic supplementation in psoriasis

Dysbiosis in the digestive tract is induced by the altered composition of the microbiota and its metabolites. If the dysbiosis condition is corrected, the immune dysregulation can also be resolved. Probiotic administration is hypothesized to restore the gut microbiome homeostasis and is expected to ameliorate the dysbiosis condition in psoriasis patient.[8]

The most commonly used probiotics are *Lactobacilli* and *Bifidobacterium*, which are also the microflora of the human gastrointestinal tract, producing lactic acid and are called Lactic acid producing bacteria (LAB). Administration of probiotics restores the gastrointestinal

microbiota, thereby lowering the pH of the intestinal mucosa, increasing SCFA, improving the gastrointestinal barrier, increasing the production of bacteriocins and suppressing pathogens.[8]

Studies on probiotics for psoriasis treatment are limited **(Table 1)**. Some in vitro and animal model studies demonstrate that probiotics can benefit in psoriasis. Rahter *et al.*, administered the ethanol extract of *Lactobacillus sakei* Probio-65 (SEL001) topically to psoriatic rats. They found that topical *L.sakei* decreased skin lesion thickness and inflammatory cell infiltration compared to controls.[9] Chen *et al.* attempted to create a skin model of psoriasis by inducing epidermal hyperplasia in mouse skin by administering imiquimod (IMQ). Then they gave *Lactobacillus pentosus* GMNL-77 orally for 7 days. Administration of these probiotics was reported to significantly reduce red scale lesions on the skin of rats. In addition, there was a decrease in TNF-α, IL-6, IL-23, IL-17 and IL-2240.[10]

Morevover, fewer clinical trials have been carried out about the benefits of oral probiotics on psoriasis. Groeger *et al.* reported that oral supplementation of *Bifidobacterium infantis* 35624 in 26 psoriasis patients for 8 weeks reduced C-Reactive Protein (CRP) and TNF-α levels significantly.[11] A case report by Vijayashankar and Raghunath provided oral supplementation of probiotic containing Lactobacillus reuteri DSM 19070-2 and Lactobacillus reuteri DSM 12246 in a patient with pustular psoriasis. After 6 months of follow-up, they reported clinical improvement in the patients.[12]

Navarro-Lopez *et al.* provided oral mixture probiotic supplementation (*Bifidobacterium longum* CECT 7347, *B.lactis* CECT 8145 and *Lactobacillus rhamnosus* CECT 8361 (1:1:1) in plaque type psoriasis patients. The results showed a reduction in 75% Psoriasis area and severity index (PASI) score after 12 weeks. However, in this study, there were no changes in the levels of inflammatory markers (TNF-α, IFN-γ, IL-1β, IL-16, IL-12 and IL-23) and gut microbiota composition after intervention. Follow-up after 6 months showed a lower risk of relapse in patients treated with probiotics.[13]

Probiotic dosage for psoriasis

There are no guidelines for probiotic therapy, especially in disorders of dermatology. Existing research uses different types of strains, doses and duration of therapy. Adequate doses are required to achieve the expected benefits. Current research reported the probiotic doses of $5x10^8$ and $5x10^9$ CFU gave the most optimal immune-modulating effect.[14]

The dose of probiotics that is considered adequate for the treatment of dysbiosis is 10^{10} CFU for adults and half ($5x10^9$ CFU) for children. There is no evidence that higher doses are harmful, but higher doses have not been shown to provide better results and are not cost-effective. The duration of administration of psoriasis is different in various studies. The recommendation therapy is 8-12 weeks minimum. The shortest therapy by Vijayashankar *et al.* gave probiotics for 15 days in pustular psoriasis patients.[12]

Side effect and safety profile of probiotic

Probiotics have long been used for treating diarrhea in children and adults. Few studies have investigated the side effects and safety of probiotic supplementation, particularly as a therapy for autoimmune diseases. In general, probiotic supplementation is believed to be relatively safe with minimal side effects and is very rare. Probiotics can be given in early childhood and pregnant women.[15]

Table 1 Studies on probiotic therapy in psoriasis.

Author, Year	*Sample*	*Intervention*	*Control*	*Research*	*Study design*	*Results*
Deng Yadan *et al*; [22]	Sample: in vitro Hyperproliferation of HaCat cell stimulated by TNF- α	Incubated with supernatant metabolite of *Bifidobacterium* animalis CCFM1148 and *Lactobacillus paracasei* CCFM1147	No control	Proliferation of HaCat cell	In vitro test	Inhibition of HaCat cell proliferation
Chen YH, *et al;* 2016 [22]	Rat skin stimulated with imiquimod cream 62.5 mg for 6 days	Route: Oral Given *Lactobacillus pentosus* GMNL-77 orally for 7 day	- the untreated group - Imiquiomod group + water,	- Clinical assessment - Histopatological examination - Cytokine measurement - Mice's spleen weight	in vivo animal testing, *Case control*	- Clinical improvement (decrease of the erythema and scales) - Histopathological changes (improvement of hyperkeratosis) - Decrease level of IL-6, IL-23, IL-17 dan IL-22 - Decrease of spleen weight
Rather *et al*;, 2017 [21]	30 mices, divided into 5 groups with different intervention	Route: Topical IMQ+ SEL001	- Control without intervention - IMQ group - IMQ+vaselin group - IMQ+clobetasol group - IMQ+SEL001 group	- Clincal evaluation (PASI 0-4: 1-none, 2-moderate, 3-severe and 4-very severe) - Histopatological examination - mRNA analysis of proinflammatory cytokines	In vivo animal testing, *case control*	- PASI score lower in IMQ+clobetasol and IMQ+SEL001 than IMQ+vaselin - The epidermal is thicker in group of IMQ and IMQ+SEL001 - mRNA IL-19, IL- 17, IL-23 lower in group IMQ and IMQ + SEL001 than IMQ + vaselin
avarro- Lopez, Vicente *et al;* 2019 [26]	90 plaques type psoriasis patient 18-70 years old	Route: Oral May 2015- October 2016 Probiotic contain of 3 strain (1:1:1) *Bifidobacterium longum CECT 7347, B. lactis CECT 8145* and *Lactobacillus rhamnosus CECT 8361*	Control with placebo (1:1)	PASI and PGA on day 1, week 2, 6 and 12	*Double blind randomized Controlled clinical trial*	- PASI and PGA index on week 2,6 and 12 - Decrease of PASI score 30/45(66.7%) in probiotic group (p=0,0317) - Decrease of PGA index in the week 12, 22/45(48,9%) on probiotic group (p=0.0853)
Groeger, David *et al*; 2013 [24]	26 plaques type psoriasis patient , 18-60 year old, mild to moderate with PASI <16	Route: Oral *B. infantis* 35624 $1x10^{10}$ for 6-8 weeks	Control with placebo	- Inflammation biomarker - Plasma cytokines level	*Double-blind Randomize placebo-controlled clinical trial*	- Decreased of CRP (p=0,0425), TNF-α (p=0,0405), compare to control
Vijayashankar M dan Raghunath N, 2012 [25]	Woman, 47 year old with pustular psoriasis	Route: oral 1 Sachet of *Lactobacillus sporogenes* and 10mg biotin per day for 15 days	No control	Clinical assessment	Case report	Lesion improvement Systemic improvement (fever)

Conclusion

Psoriasis is a chronic inflammatory disease with high comorbidities that decrease the quality of life. Several studies have found a link between the microbiome and the development and progression of psoriasis. The chronic inflammation and the effect of psoriasis therapy itself can lead to dysbiosis. Changes in the diversity and proportion of microbiota in gastrointestinal were discovered in psoriasis. There was increase in Firmicutes, F/B ratio, Clostridium, Salmonella, E.coli and a decrease in Bacterioides, Akkermansia, Lactobacillus, Bifidobacterium.[7]

Gastrointestinal dysbiosis causes a decrease in SCFA, disruption of gastrointestinal barrier, leakage of antigens and metabolites to the circulation, and changes in the interaction between the microbiota and the immune system. As the result, it activates pro-inflammatory signals and inhibits the differentiation of anti-inflammatory Tregs.[2]

Oral probiotic supplementation in psoriasis works by resolving dysbiosis. The microbiota contained in probiotics will integrate with the gastrointestinal microbiotas. Probiotics which are lactate-producing bacteria are expected to restore intestinal pH, suppress the dominance of pathogens, increase the production of SCFA and mucin. Adequate SCFA can restore the integrity of the gastrointestinal tract, stimulate Treg differentiation, suppress the release of proinflammatory cytokines. Probiotics are expected to suppress the inflammatory reaction that plays a role in psoriasis.[13]

References

1. Gudjonsson JE, Elder JT. Psoriasis. In: Kang S *et al.*, editor. Fitzpatrick's Dermatology. 9th ed. New York: McGraw-Hill; 2019. p. 458–532.
2. Myers B, Brownstone N, Reddy V, Chan S, Thibodeaux Q, Truong A, *et al*. The gut microbiome in psoriasis and psoriatic arthritis. *Best Pract Res Clin Rheumatol*. 2019;**33(6)**:101494.
3. Atabati H, Esmaeili SA, Saburi E, Akhlaghi M, Raoofi A, Rezaei N, *et al*. Probiotics with ameliorating effects on the severity of skin inflammation in psoriasis: Evidence from experimental and clinical studies. *J Cell Physiol*. 2020;**235(12)**:8925–37.
4. Nussbaum L, Chen YL, Ogg GS. Role of regulatory T cells in psoriasis pathogenesis and treatment. *Br J Dermatol*. 2021;**184(1)**:14–24.
5. Freedman NJ. From Colon to Aortic Aneurysm: Trek of the Treg. Vol. 7, JACC: Basic to Translational Science. Elsevier Inc.; 2022. p. 948–50.
6. Levy M, Kolodziejczyk AA, Thaiss CA, Elinav E. Dysbiosis and the immune system. *Nat Rev Immunol*. 2017;**17(4)**:219–32. Available from: http://dx.doi.org/10.1038/nri.2017.7
7. Olejniczak-Staruch I, Ciążyńska M, Sobolewska-Sztychny D, Narbutt J, Skibińska M, Lesiak A. Alterations of the skin and gut microbiome in psoriasis and psoriatic arthritis. *Int J Mol Sci*. 2021;**22(8)**:3998.
8. Navarro-lópez V, Núñez-delegido E, Ruzafa-costas B, Sánchez-pellicer P, Agüera-santos J, Navarro-moratalla L. Probiotics in the therapeutic arsenal of dermatologists. *Microorganisms*. 2021;**9(7)**: 1513.
9. Rather IA, Bajpai VK, Huh YS, Han YK, Bhat EA, Lim J, *et al*. Probiotic Lactobacillus sakei proBio-65 extract ameliorates the severity of imiquimod induced psoriasis-like skin inflammation in a mouse model. *Front Microbiol*. 2018;**9**:1-11.
10. Chen YH, Wu CS, Chao YH, Lin CC, Tsai HY, Li YR, *et al*. Lactobacillus pentosus GMNL-77 inhibits skin lesions in imiquimod-induced psoriasis-like mice. *J Food Drug Anal*. 2017;**25(3)**:559–66.
11. Groeger D, Mahony LO, Murphy EF, Bourke JF, Timothy G, Kiely B, *et al*. Bifidobacterium infantis 35624 modulates host inflammatory processes beyond the gut. *Gut Microbes*. 2013;**4(4)**:325–39.
12. Vijayashankar M, Raghunath N. Pustular psoriasis responding to Probiotics – a new

insight. *Our Dermatol Online*. 2012;**3(4)**:326–9.

13. Navarro-López V, Martínez-Andrés A, Ramírez-Boscá A, Ruzafa-Costas B, Núñez-Delegido E, Carrión-Gutiérrez MA *et al*. Efficacy and Safety of Oral Administration of a Mixture of Probiotic Strains in Patients with Psoriasis: A Randomized Controlled Clinical Trial. *Acta Derm Venereol*. 2019;**(99)**:1078-84.
14. Ouwehand AC. A review of dose-responses of probiotics in human studies. *Benef Microbes*. 2017;**8(2)**:143-51.
15. Nole KLB, Yim E, Keri JE. Probiotics and prebiotics in dermatology. *J Am Acad Dermatol*. 2014;**71(4)**:814-21.