# PROBIOTICS IN PSORIASIS

Review Article

AUTHOR:
Cassará, María L., Pharm. D. Chair, Pablo Cassará Fundation. Argentina
Correspondence: mlcassara@lpc.com.ar

https://doi.org/10.55634/1.3.8

## SUMMARY

Psoriasis is a systemic disease that fundamentally affects the skin, characterized by the appearance of hyperproliferation of epidermal keratinocytes combined with inflammation of the epidermis and dermis. It is estimated that approximately 1 to 5% of the world's population suffers from it at some point in their lives. The term "intestinal microbiota" refers to the microbial ecosystem that colonizes the gastrointestinal tract. The relevance and impact of gut-resident bacteria on host physiology and pathology in patients with psoriasis are well documented. The microbiota and intestinal permeability are the key target for new treatment strategies in psoriasis.

KEY WORDS: psoriasis, microbiome, dysbiosis, probiotics, microbiota.

## INTRODUCTION

Pathophysiologically, psoriasis is characterized by hyperproliferation of epidermal keratinocytes combined with inflammation of the epidermis and dermis [1,2]. Its incidence ranges between 1 and 5% of the world population; light-skinned people are at higher risk of getting the disease than dark-skinned people. Psoriasis onset peaks have a mainly bimodal distribution; most occur between two age ranges: 16-22 years and 57-60 years, although it can appear at any age. According to a North American study by Trusted Source (2021), about 7.5 million American adults over the age of 20 have psoriasis, implying a prevalence rate of 3%. The prevalence rates in that study, by race and ethnicity, are: 3.6% white; 3. 1% non-Hispanic people (including multiracial people); 2.5% Asian; 1.9% Hispanics (including Mexican Americans) and 1.5% of black people.

The cause of psoriasis is unclear, but it is known to involve immunological stimulation of epidermal keratinocytes, with T cells appearing to play a central role. Family history is common and the presence of some genes and extensive human leukocytes (Cw6, B13, B17) has been associated with psoriasis. Genomic linkage analysis has identified numerous psoriasis susceptibility loci; the PSORS1 locus on chromosome 6p21 plays the most important role in determining a patient's susceptibility to developing psoriasis. It is also believed that there may be an environmental trigger that causes an inflammatory response with the consequence of excessive keratinocytes proliferation.

Well-identified triggers include [3,4,5]: Wounds (Koebner phenomenon*), Sunburn, HIV infection, Beta-hemolytic streptococcus infection (guttate psoriasis); Drugs such as beta-blockers, chloroquine, lithium, angiotensin-converting enzyme inhibitors, indomethacin, terbinafine, interferon alpha, and others not yet confirmed; emotional stress; Alcohol; Tobacco and Obesity.

* Koebner's isomorphic phenomenon consists of the reproduction of lesions typical of a dermatosis in areas that have suffered a previous trauma, identical both clinically and histopathologically to the pre-existing dermatosis.

The Keratinocyte overgrowth plaques often develop on joints, such as the elbows and knees. However, they can develop anywhere on your body, including: hands, feet, neck, scalp, face.

Less common types of psoriasis affect the nails, mouth, and perigenital area.

## CUTANEOUS MICROBIOTA

Bacteria, fungi and parasites coexist on the skin surface which, under normal conditions, constitute a complex ecosystem in permanent interaction with the host (Fig. 1). This ecosystem actively participates in the double protective function of the skin, as a physical and immu-

nological barrier. When the balance of the ecosystem is upset, negative consequences are generated that predispose and cause the appearance of diseases, as occurs with psoriasis.

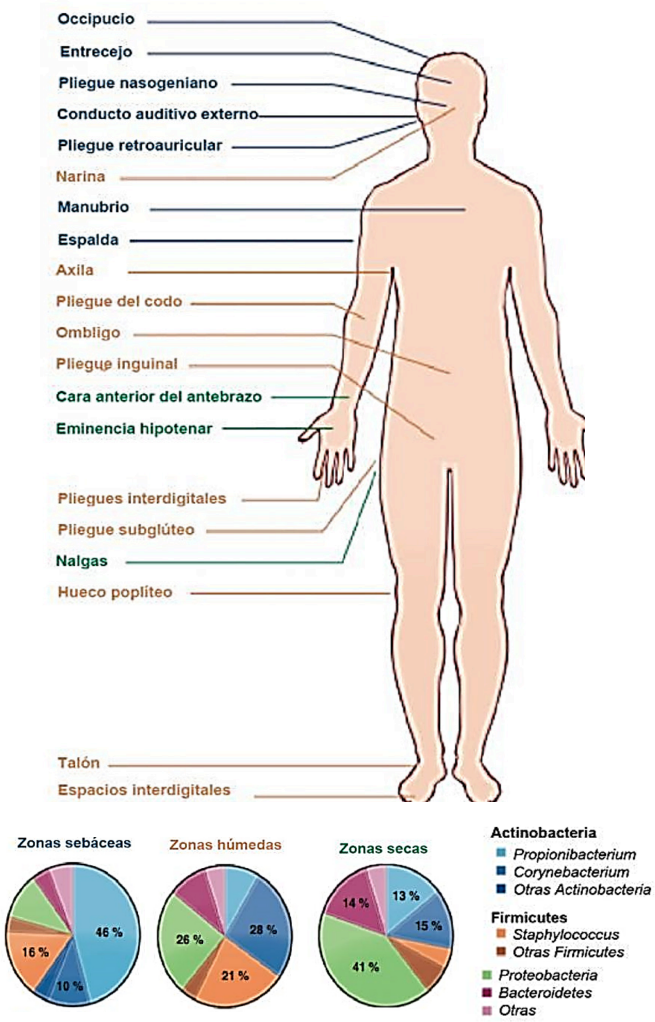


Fig. 1. Different skin microbiota according to areas: sebaceous, wet or dry of the body.

## GUT MICROBIOTA

The term "gut microbiota" refers to the microbial ecosystem that colonizes the gastrointestinal tract. The term "Microbiome" refers to a broader term that encompasses the microbial ecosystem itself, its relationship with the host and the set of genes, enzymes encoded by these genes and the metabolites resulting from the action of the enzymes. Recently developed molecular biology tools suggest that its composition is not yet fully known (Fig. 2). However, the relevance and impact of resident bacteria on host physiology and pathology are well documented. The main functions of the intestinal microflora include: (1) metabolic activities that result in energy and nutrient recovery, and (2) host protection against invasion by pathogenic microorganisms. Gut bacteria play an essential role in the development and homeostasis of the immune system. These bacteria are closely related to the lymphoid follicles of the intestinal mucosa, which are the main areas for the induction and regulation of the immune system. On the other hand, there is evidence implicating the intestinal microbiota in certain pathological processes, including immune dysfunction, colon cancer and inflammatory bowel disease[6,7].

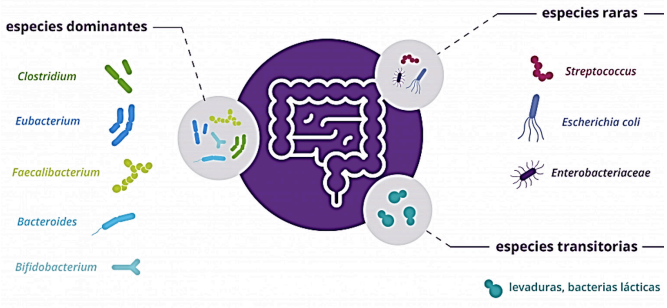


Fig. 2. Composition of the intestinal microbiota

## ROLE OF THE INTESTINAL MICROBIOTA IN PSORIASIS. GUT-SKIN AXIS.

A growing body of scientific evidence emphasizes the role of the skin and gut microbiota in psoriasis. Recent studies show severe intestinal dysbiosis in patients with moderate to severe psoriasis. With this, the concept of the gut-skin axis add one more factor to take into account in the pathophysiology of psoriatic disease.

A study including 55 psoriasis patients and 27 controls found changes in the composition of the gut microbiome according to psoriasis status, with lower diversity and altered relative abundance for certain bacterial taxa compared to the control group. An increase in the Firmicutes/Bacteroidetes ratio was found, as has been described in obesity, type II diabetes and cardiovascular diseases (frequent comorbidities of psoriasis). In particular an increase in Firmicutes and depletion of Bacteroidetes in psoriasis patients is described. Patients with moderate to severe psoriasis had lower biodiversity than patients with mild psoriasis ($p = 0.049$). This study demonstrates the existence of intestinal dysbiosis in patients with psoriasis, which suggests a role in its pathophysiology8. Other studies also show that the gut microbiota of patients with severe psoriasis differs from patients with mild psoriasis and also from healthy controls. Psoriasis patients have significantly altered microbiota profiles[9,10].

On the other hand, intestinal dysbiosis affects the integrity of the mucosal layer, compromising the intestinal barrier, enhancing chronic con and systemic inflammation (Fig. 3). Damage of the intestinal barrier with translocation of bacterial metabolites into the blood modulates the immune response and influences the functioning of other organs such as the skin. This is the basis of the "gut-

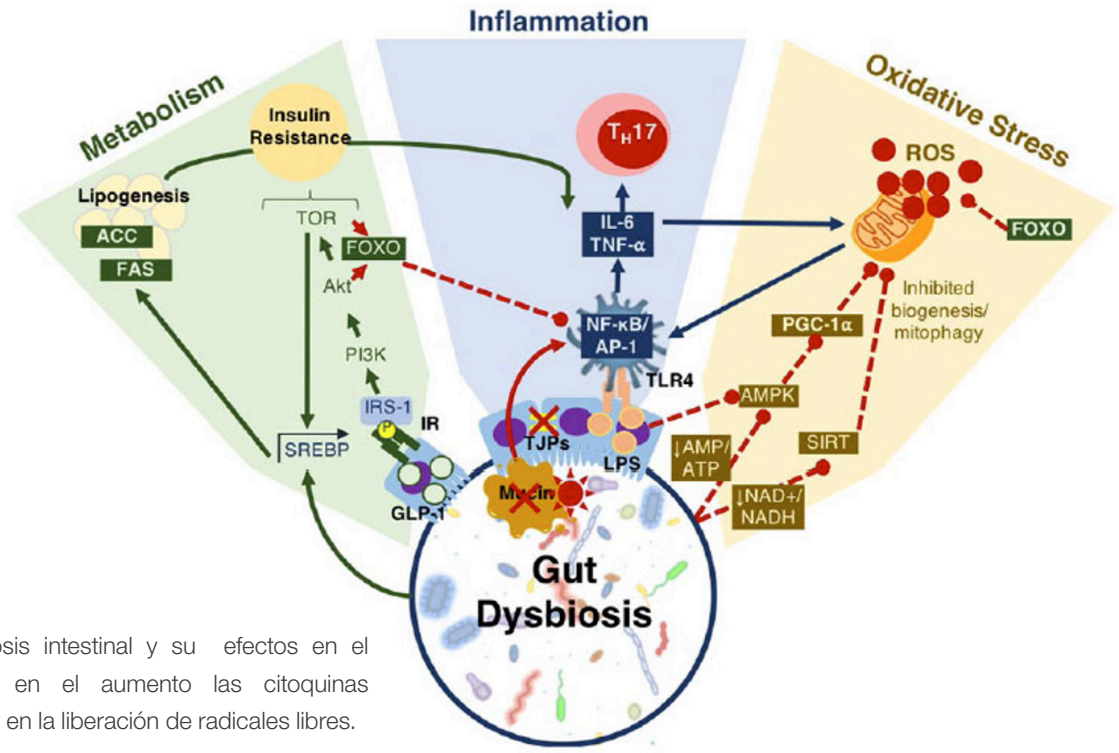


Fig. 3. Disbiosis intestinal y su efectos en el metabolismo, en el aumento las citoquinas inflamatorias y en la liberación de radicales libres.

skin axis" concept. The microbiota and intestinal permeability are the key target for new treatment strategies in psoriasis.

Sikora et al studied the concentrations of claudin-3 (tight junction structure of the intestinal epithelium) and intestinal fatty acid binding protein (I-FABP; marker of enterocyte damage) in the blood of patients with chronic plaque psoriasis ( n = 20) and healthy individuals (n = 20) using enzyme-linked immunoassay test kits. The concentration of claudin-3 was significantly higher in patients with psoriasis compared to controls. Psoriasis patients also showed a significantly elevated concentration of I-FABP in plasma. Thus, an increase in the serological concentration of markers of intestinal integrity is demonstrated in patients with moderate to severe psoriasis [11].

Another research group studied intestinal bacterial translocation by analyzing bacterial DNA in peripheral blood from patients with mild to moderate psoriasis. They found a higher proportion of bacterial DNA in the blood in patients with plaque psoriasis compared to patients with other psoriasis phenotypes (35.5% vs. 0%; $p < 0.05$). Nucleotide sequencing revealed that E. coli was the predominant source of bacterial DNA. The rest of the bacterial species of the detected genomic fragments also corresponded to the type of flora that is commonly found in the intestinal lumen. Cytokine levels in psoriasis patients with bacterial DNA in the blood were significantly higher than those in psoriasis patients without evidence of bacterial DNA, revealing a significantly greater systemic inflammatory response. Furthermore, the presence of bacterial DNA was evident in patients with longer duration of disease and in those whose disease was diagnosed at a younger age. The results of this work suggest that outbreaks of psoriasis in active plaques may be related to the presence of bacterial DNA circulating in the blood, originating in the intestinal lumen [12].

A double-blind, randomized, placebo-controlled clinical trial of a multistrain probiotic (mixture of Lactobacillus and Bifidobacteria) shows a beneficial effect in reducing the severity of psoriasis as adjunctive treatment together with topical steroids. The study, which was carried out in a group of 90 patients with plaque psoriasis, observed significant differences in the progression of the disease when comparing the group that received the probiotic mixture for 12 weeks with those that took placebo. At 12-week follow-up, patients in the probiotic group achieved PASI75 by 66.7% vs. 41.9% in the placebo group ($p=0.0317$). During the study, patients who received the probiotic mixture had a greater diversity of bacterial population, highlighting the effectiveness of the probiotic in modulating the composition of the intestinal microbiota. During post-study follow-up (at 6 months post probiotic or placebo intake), fewer patients in the probiotic group had a new flare compared with the placebo group (20% vs 41.9%, $p= 0.027$), demonstrating a lower risk of relapse in patients in the probiotic group. The better evolution of the patients, together with the changes observed in

the gut microbiota in patients who previously used the probiotic mixture, suggests a preventive role of probiotics (longer relapse-free time), and not only a therapeutic benefit as adjuvant treatment [13].

Therefore, dysbiosis of the gut microbiota may contribute to the development of leaky gut, facilitating bacterial translocation, which may act as a driving force for the inflammatory response.

## PREBIOTICS AND PROBIOTICS

Prebiotics are generally defined as non-digestible food ingredients (generally high in fiber) that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already established in the colon and therefore, they improve the health of the host[14]. The concept of prebiotic has essentially the same objective as that of probiotic, which is to improve the health of the host through the modulation of the intestinal flora, although by a different mechanism. In very broad terms, it can be said that prebiotics act as nutrients for the human microbiota, while probiotics are supplements or medicines that contain live microorganisms intended to maintain or improve the normal microbiota of the host. Members of the genera Lactobacillus and Bifidobacterium are mainly used as probiotic microorganisms, but not exclusively.

Synbiotics are defined as "mixtures of probiotics and prebiotics that beneficially affect the host by enhancing the survival and implantation of live microorganisms in the host's gastrointestinal tract. Confer a synergistic effect on the intestinal microbiota.

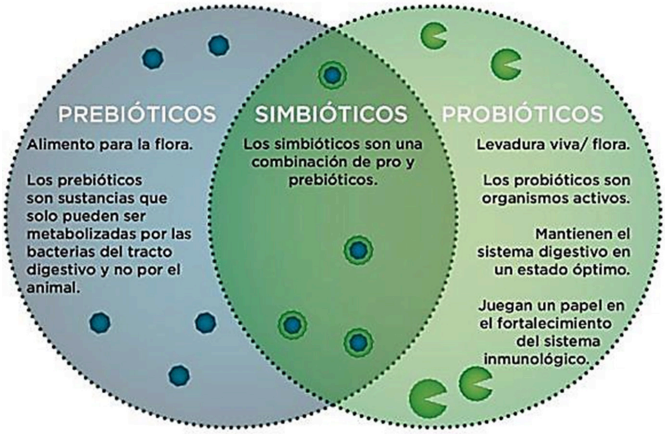


Fig. 4

## REQUIREMENTS FOR A MICROORGANISM TO BE QUALIFIED AS A PROBIOTIC

The definition of probiotic established by the WHO 20 years ago is that of live microorganisms that administered in sufficient quantity, confer benefit to the person who consumes them15. This definition supposes meeting a series of nuances and requirements at present, such as:

– Be correctly identified from the taxonomic point of view, since the beneficial effects demonstrated in a specific strain cannot be extrapolated and attributable to another strain of the same species.

– Lack potential virulence factors for the host. Although it is true that there are many bacteria that naturally colonize the mucous membranes of the human being and that provide a benefit, the vast majority of them are capable of causing -under certain circumstances- infectious processes.

– In practice, probiotics come from the elements used in the fermentation of food, mainly lactobacilli and bifidobacteria. These microorganisms have been recognized as GRAS (Generally Recognized As Safe) and QPS (Qualified Presumption of Safety) organisms by the Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA), respectively.

– Scientifically demonstrate the beneficial effects on the health of the host and the safety of the microorganism that produces them.

– Show tolerance to the environment, and remain viable and functionally active in the gastrointestinal tract. To do this, they must be resistant to destruction by gastric and bile secretions, and must have the ability to adhere to the intestinal epithelium, as well as to colonize the gastrointestinal tract.

– Be in a sufficient quantity to be able to exert the desired effect (from one hundred to one billion colony-forming units (CFU) per daily dose).

–microorganisms must be viable in the products into which they are incorporated; and they have to be resistant to processing and storage conditions.

## SITES OF ACTION AND BENEFITS PRODUCED BY PROBIOTICS:

Probiotics shed from the intestinal ecosystem by affecting mucosal immune mechanisms, interacting with commensal or potentially dangerous microorganisms, metabolic products such as short-chain fatty acids, and communicating with host cells using chemical signals. These mechanisms can lead to the antagonism of potential pathogens, an improvement of the intestinal environment, a reinforcement of the intestinal barrier, the negative regulation of inflammation and the positive regulation of the immune response to antigenic provocations[15].

Short chain fatty acids (SCFA: lactate, acetate and butyrate) and substances such as CO2 and H2O2, are the main metabolites produced by microbial fermentation of prebiotics in the intestine. SCFAs lower luminal pH, creating an environment unfavorable for pathogen growth, improving the solubility and absorption of minerals such as calcium, and upregulating hormones. Probiotics restore barrier integrity,

modulate transepithelial fluid transport, improve intestinal transit, and relieve symptoms associated with leaky gut.

**The effects produced by the consumption of probiotics are described below:**

***1. Gut lumen***

– Probiotics modulate the composition of the intestinal microbiota, either by inhibiting pathogenic microorganisms, or by favoring the presence and diversity of commensal bacteria. The intestinal microbiota has a great influence on digestive health and the immune system. The intake of probiotics is capable, by reducing the pH of the medium and the production of antibacterial compounds (bacteriocins, hydrogen peroxide), of reducing the adherence, replication and action of potentially pathogenic flora for the host.

- The modification of the flora modifies some of the metabolic functions of it, among which we can mention: absorption of certain nutrients, degradation of non-digestible food in the diet, regulation of energy storage, synthesis of essential vitamins (vitamin K and some of complex B) and increased absorption of minerals, among others.

***2. Intestinal mucosa and epithelium***

– They improve the intestinal defense barrier function. The manifestation of disorders such as chronic inflammatory bowel disease, psoriasis, celiac disease, enteric infections, some autoimmune diseases, may be the result of the compromise of the integrity of the epithelial barrier. In stress conditions, the mechanisms for the formation of intestinal biofilms are also favored, which further deteriorates intestinal permeability and the imbalance of the intestinal microbiota. The intake of probiotics contributes to the maintenance of the integrity of the barrier, as well as prevents the damage done to the intestinal mucosa by the action of food allergens, pathogenic microorganisms, proinflammatory cytokines, and facilitates its repair; normalizes the increased permeability and improves the intestinal inflammatory response. Probiotics stimulate mucin production by the epithelium, increasing transepithelial resistance, decreasing bacterial translocation and improving barrier function.

– They intervene in the metabolism of lactose (β-galactosidase activity), of proteins and lipids, in the synthesis of amino acids and vitamins, fermentation of carbohydrates with the obtaining of short-chain fatty acids and increase the absorption of minerals such as calcium, magnesium and iron through a decrease in intestinal pH.

– Optimizes the immune system. The intestine is the organ with the most important immune function in the body and where immune responses are controlled

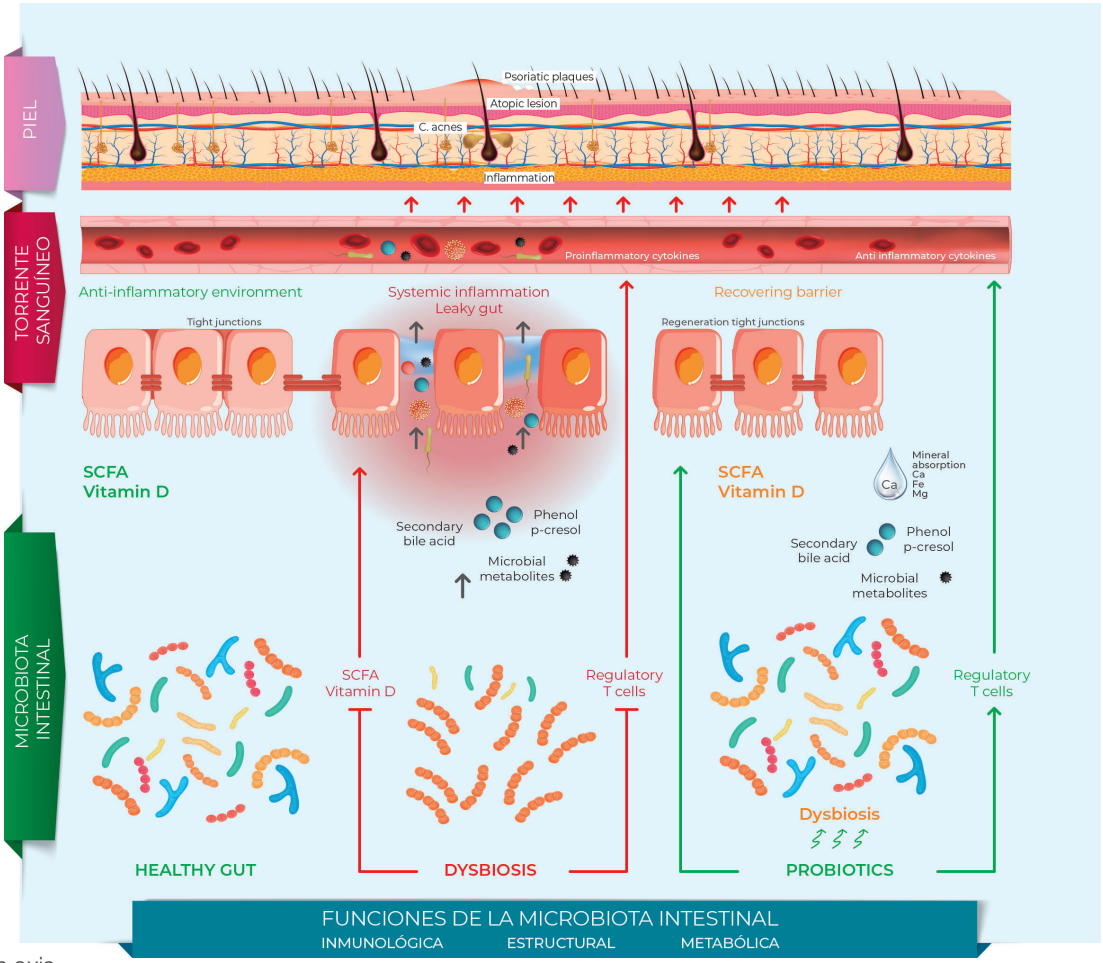


FIG 5. Gut-skin axis

against dietary proteins (prevention of food allergies) and against pathogenic microorganisms: viruses (rotavirus, poliovirus), bacteria (Salmonella, Listeria, Clostridium , etc.), parasites (Toxoplasma). The immunological benefits could be summarized in the activation of local macrophages so that they increase the presentation of antigens to B lymphocytes and the production of local and systemic secretory immunoglobulin A; cytokine profiles are modulated and hyporesponse to food antigens is induced.

***3. Other organs, such as the skin***

Numerous clinical studies have shown the existence of an interrelationship between the intestinal microbiota and the skin microbiota, called the gut-skin axis.

The gastrointestinal mucosa is made up of epithelial cells that establish an effective barrier, through intercellular junctions, allowing the selective passage of certain substances, and preventing access to others. In healthy intestine conditions, toxic substances do not permeate. Intestinal dysbioses caused by infectious, metabolic or inflammatory diseases lead to inflammatory processes and loss of the intestinal barrier function. The altered intestinal barrier function (leaky gut) allows the translocation of bacteria and the passage of antigens, toxins, and microbial products that enter the systemic circulation and impact other organs. This favors the development of exaggerated immune responses, both at the intestinal level as well as in other structures of the body, including the skin, resulting in the deterioration of homeostasis and the functioning of the skin barrier[16].

With the intentional modulation of the microbiome, probiotics, prebiotics and synbiotics have been shown to be beneficial in the prevention or treatment of inflammatory skin diseases such as atopic dermatitis[17], acne vulgaris[18] and psoriasis[13].

Benefits of the administration of probiotics as a therapeutic complement in other dermatological inflammatory pathologies in addition to Psoriasis.

In recent decades, knowledge of probiotic strains that improve atopic dermatitis has deepened. Passeron et al. compared the use of probiotics and prebiotics in children with atopic dermatitis and found that both significantly improved atopic dermatitis[19]. Different strains of Lactobacillus have been shown to have beneficial effects on moderate-severe atopic dermatitis, suggesting that the use of probiotics could have a potential effect on reducing the SCORAD index (Severity Scoring of Atopic Dermatitis) in children with atopic dermatitis[20].

It was study In a randomized, double-blind, placebo-controlled trial, the effect of a synbiotic of seven strains of probiotic bacteria (Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermo philus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium infantis, Lactobacillus bulgaricus) and fructooligosaccharides in the treatment of atopic dermatitis in children 3 months to 6 years of age. Children in the synbiotic group achieved substantial and statistically significant reductions in SCORAD after 4 and 8 weeks. This study provides evidence that a mixture of seven strains of probiotics and fructooligosaccharides can clinically improve the severity of AD in young children[21].

Navarro-López et al. conducted a clinical trial in 50 children aged between 4 and 17 years to evaluate oral treatment with a mixture of Bifidobacterium lactis, Bifidobacterium longum (infantis) and Lactobacillus casei strains for 12 weeks in children with moderate atopic dermatitis. The probiotic mixture used proved to be effective in reducing the intensity and duration of outbreaks, the extent and intensity of eczema, and the use of topical corticosteroids[22].

In the treatment of mild to moderate acne vulgaris, oral administration of probiotics as adjunctive therapy plays an effective role in acne management by directly preventing the growth of opportunistic bacteria or controlling inflammation. A randomized, double-blind, placebo-controlled study of 20 adult acne subjects treated with Lactobacillus rhamnosus over a 12-week period normalized skin expression of genes involved in insulin signaling and improved the appearance of adult acne[18].

In this emerging field of the gut microbiome, future research should improve our understanding of the complex mechanisms underlying the gut-skin axis and investigate the therapeutic potential of long-term modulation of the gut microbiome for clinical improvement of dermatological chronic inflammatory pathologies such as psoriasis, atopic dermatitis, acne, alopecia, rosacea and skin aging.

## CONCLUSIONS

The correction of intestinal dysbiosis can play an important role in the moderation, and even in the disappearance, of conditions whose relationship with it has been demonstrated. Among them, psoriasis is a highly prevalent entity, in which affected individuals could benefit markedly from the use of these compounds, so effective and well tolerated.

REFERENCES:

1- Update on psoriasis: A review Jagadish P Rajguru 1, Deepthi Maya 2, Dinesh Kumar 3, Prerna Suri 4, Shweta Bhardwaj 5, Nishitkumar D Patel PMID: 32110559 PMCID: PMC7014874 DOI:

10.4103/jfmpc.jfmpc_689_19 J Family Med Prim Care. 2020 Jan 28;9(1):20-24. doi: 10.4103/jfmpc.jfmpc_689_19.
2- A review on updates in management and Treatment of Psoriasis January 2021 DOI: 10.51847/g6sNNo5abAlbtihal M. AlhammadAmal M. AseriSultan A. M. AlqahtaniShow all 11 authorsAlaa E. Nuqali Researchgate.
3- van de Kerkhof PCM and Schlkwijk J. (2008) "Psoriasis." In: Bolognia JL, Jorizzo JL, et al. editors. Dermatology, 2nd ed. Spain, Mosby Elsevier: p. 115.
4- Alexis AF, Blackcloud P. "Psoriasis in skin of color: epidemiology, genetics, clinical presentation, and treatment nuances." J Clin Aesthet Dermatol. 2014;7(11):16-24.
5- Susan Bard: Everything You Need to Know About Psoriasis. Healthline. Skin. Updated on November 18, 2021
6- Moore W.E., Moore L.H. Intestinal floras of populations that have a high risk of colon cancer. Appl. Environ. Microbiol. 1995;61:3202–3207. doi: 10.1128/aem.61.9.3202-3207.1995.
7- Yun Kit Yeoh et al. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19.Gut. 2021 Apr; 70(4): 698–706Published online 2021 Jan 11. doi: 10.1136/gutjnl-2020-323020
8- Ignacio Dei-Cas, et al. Metagenomic analysis of gut microbiota in non-treated plaque psoriasis patients stratified by disease severity: development of a new Psoriasis-Microbiome Index. Sci Rep. 2020 Jul 29;10(1):12754. doi: 10.1038/s41598-020-69537-3.
9- C Hidalgo-Cantabrana , J Gómez , S Delgado , S Requena-López , R Queiro-Silva , A Margolles , E Coto , B Sánchez , P Coto-Segura . Gut microbiota dysbiosis in a cohort of patients with psoriasis. Br J Dermatol. 2019 Dec;181(6):1287-1295. doi: 10.1111/bjd.17931. Epub 2019 Jul 18.
10- Linsheng Huang , Renyuan Gao, Ning Yu, Yefei Zhu, Yangfeng Ding , Huanlong Qin .Dysbiosis of gut microbiota was closely associated with psoriasis. Sci China Life Sci. 2019 Jun;62(6):807-815. doi: 10.1007/s11427-018-9376-6. Epub 2018 Sep 26.
11- Mariusz Sikora, Magdalena Chrabąszcz , Cezary Maciejewski , Michał Zaremba , Anna Waąkiel , Małgorzata Olszewska, Lidia Rudnicka . Intestinal barrier integrity in patients with plaque psoriasis. J Dermatol. 2018 Dec;45(12):1468-1470. doi: 10.1111/1346-8138.14647. Epub 2018 Sep 17.
12- Ana Ramírez-Boscá , Vicente Navarro-López, Asunción Martínez-Andrés , José Such , Rubén Francés , José Horga de la Parte , Manuel Asín-Llorca. Identification of Bacterial DNA in the Peripheral Blood of Patients With Active Psoriasis. JAMA Dermatol. 2015 Jun;151(6):670-1. doi: 10.1001/jamadermatol.2014.5585.
13- Vicente Navarro-López , 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 Nov 1;99(12):1078-1084. doi: 10.2340/00015555-3305.
14- G R Gibson, M B Roberfroid. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics J Nutr.1995 Jun;125(6):1401-12. doi: 10.1093/jn/125.6.1401.
15- Probiotics in food: Health and nutritional properties and guidelines for evaluation - FAO Food and Nutrition Paper 85. 2006.
16- Iman Salem, Amy Ramser, Nancy Isham, Mahmoud A Ghannoum. The Gut Microbiome as a Major Regulator of the Gut-Skin Axis. Front Microbiol. 2018 Jul 10;9:1459. doi: 10.3389/fmicb.2018.01459. eCollection 2018.
17- Chang Y., Trivedi M. K., Jha A., Lin Y., Dimaano L., García-Romero M. T. (2016). Synbiotics for prevention and treatment of atopic dermatitis: a meta-analysis of randomized clinical trials. JAMA Pediatr. 170 236–242. 10.1001/jamapediatrics.2015.3943
18- Fabbrocini G., Bertona M., Picazo Ó., Pareja-Galeano H., Monfrecola G., Emanuele E. (2016). Supplementation with Lactobacillus rhamnosus SP1 normalises skin expression of genes implicated in insulin signalling and improves adult acne. Benef. Microbes 7 625–630. 10.3920/BM2016.0089
19- Passeron T, Lacour JP, Fontas E, Ortonne JP. Prebiotics and synbiotics: two promising approaches for the treatment of atopic dermatitis in children above 2 years. Allergy. 2006 Apr;61(4):431-7.
20- Huang R, Ning H, Shen M, Li J, Zhang J, Chen X. Probiotics for the treatment of atopic dermatitis in children: a systematic review and meta-analysis of randomized controlled trials. Front Cell Infec Microbiol. 2017; 7: 392.
21- Farid R, Ahanchian H, Jabbari F, Moghiman T. Effect of a new symbiotic mixture on atopic dermatitis in children: a randomized-controlled trial. Iran J Pediatr 2011;21:225-30.
22- Navarro-López V, Ramírez-Boscá A, Ramón-Vidal D, Ruzafa-Costas B, Genovés-Martínez S, Chenoll-Cuadros E, Carrión-Gutiérrez M, et al. Effect of Oral Administration of a Mixture of Probiotic Strains on SCORAD Index and Use of Topical Steroids in Young Patients With Moderate Atopic Dermatitis: A Randomized Clinical Trial. JAMA dermatol. 2018; 154: 37-43.