Zając Marlena, Borowiecka Monika, Gruca Dariusz, Buksak Dagmara, Wróblewski Wiktor. Gut Microbiome as a Novel Treatment Strategy for Psoriasis. Journal of Education, Health and Sport. 2022;12(9):407-421. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2022.12.09.046
https://apcz.umk.pl/JEHS/article/view/39692
https://zenodo.org/record/7046427

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences). Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
© The Authors 2022;
This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland
Open Access. This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author (s) and source are credited. This is an open access article licensed under the terms of the Creative Commons Attribution Non commercial license Share alike. (http://creativecommons.org/licenses/by-nc-sa/4.0/) which permits unrestricted, non commercial use, distribution and reproduction in any medium, provided the work is properly cited.
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 15.08.2022. Revised: 20.08.2022. Accepted: 01.09.2022.

Gut Microbiome as a Novel Treatment Strategy for Psoriasis

Marlena Zając[1], Monika Borowiecka[1], Dariusz Gruca[1], Dagmara Buksak[1], Wiktor Wróblewski[1]

[1]Medical University of Lublin, Aleje Racławickie Street 1, 20-059 Lublin, Poland

Marlena Zając; marlenzajac11@gmail.com; ORCID: 0000-0002-6251-0175;

Monika Borowiecka; monnikaborowiecka@gmail.com; ORCID: 0000-0003-2612-7838;

Dariusz Gruca; dariusz.gruca1@gmail.com; ORCID: 0000-0002-5583-1229;

Dagmara Buksak; dagmara.buksak@wp.pl; ORCID: 0000-0003-4008-5611;

Wiktor Wróblewski: wiktorwroblewski10@gmail.com; ORCID: 0000-0003-4740-9455

Summary:

Introduction and purpose: Psoriasis is a skin disease that develops following chronic inflammatory signaling and keratinocyte hyperproliferation. The pathogenesis of psoriasis is compound and not yet fully understood. Several studies concerning the gut microbiota composition and its role in disease pathogenesis recently demonstrated significant alterations among psoriatic patients. This study aims to highlight the latest scientific evidence regarding the gut microbiome alterations of psoriatic patients, as well as the state of knowledge in terms of microbiome-targeted therapies as promising preventive and therapeutic tools for psoriasis.

Brief description of the state of knowledge: The current state of knowledge indicates that the main causes of psoriasis may be genetic predisposition, as well as many immunological and environmental factors, including dysbiosis of the intestinal microflora. The article covers clinical and experimental studies which indicate that gut microbiota dysbiosis concerning

diversity as well as composition of microbiome is the potential causal factor of psoriasis and the gut microbiota may serve as promising prevention/therapy target for psoriasis patients.

Conclusions: This review highlighted a strong link between psoriasis and the gut microbiota, with the purpose of adding new knowledge for discovering the relationship between the altered intestinal microbiota in psoriasis patients. Despite all of these interesting findings, there are a lot of limitations and challenges that future studies should face. More precise and greater studies need to be done to fully understand the potential of microbiota-aimed therapies.

Key words: psoriasis; microbiome; gut; dysbiosis; probiotics;

1. Introduction

1.1 Psoriasis

Psoriasis is a skin disease that develops following chronic inflammatory signaling and keratinocyte hyperproliferation [1,2]. It is associated with substantial physical and psychological disability that stems from the pain of the skin lesions, poor body image, and extensive comorbidities [3,4]. Psoriasis affects about 125 million people worldwide [5,6], but the incidence rate varies by race and geographic region [7]. Psoriasis is commonly classified by several factors, including severity, age of onset, and anatomical site (e.g., nail, scalp, genital) [8]. The disease can also be categorized into several clinical variants, including plaque, guttate, erythrodermic, and pustular psoriasis [2]. Plaque psoriasis is characterized by erythematous plaques covered with silvery scales which concentrate mainly on the knees, elbows, and scalp. Guttate type of psoriasis typically features smaller lesions on the trunk and often follows streptococcal infections. Erythrodermic psoriasis is a variant that occurs when psoriatic skin lesions cover the majority of the body, which can be life-threatening if untreated. Finally, pustular psoriasis features painful and purulent skin lesions, which can be general or localized [8]. Chronic plaque psoriasis is the most studied phenotype, as it accounts for 90% of cases [8,9]. The pathogenesis of psoriasis is compound and not yet fully understood. The current state of knowledge indicates that genetic predispositions, as well as many immunological and environmental factors (e.g. drugs, infections, trauma, UV and X-rays, chemical and thermal burns, smoking, drinking alcohol, stress), may be crucial elements, stimulating the keratinocytes to start secreting pro-inflammatory cytokines. This process causes the antigen-independent hyperactivation of T-lymphocytes, which produce TNFα, IL-1, IL-2, IL-6, IL-8, IL-12, IL-17, IL-23 p19/p40, INF-γ, granulocyte-macrophage colony-stimulating factor (GM-CSF) and vascular endothelial growth factor (VEGF), that affect the keratinocytes and blood vessels, leading to abnormal hyperproliferation of keratinocytes, the development of parakeratosis due to shortening the keratinocytes' maturation process in the epidermis, and abnormal angiogenesis with the formation of brittle, twisted vessels with increased permeability in the regions of skin lesions [10].

1.2 Gut microbiome

The term microbiome comprises all of the genetic material within a microbiota (the entire collection of microorganisms in a specific niche, such as the human gut). This can also be

referred to as the metagenome of the microbiota. The gut microbiota is represented by trillions of microorganisms that colonize the gastrointestinal tract and are involved in many systemic and local processes [11,12]. These microorganisms such as bacteria, viruses, and eukaryotic species, and 90% of them belong to Bacteroidetes and Firmicutes phyla, followed by Fusobacteria, Proteobacteria, Tenericutes, Actinobacteria, and Verrucomicrobia [13]. Many factors can influence intestinal microbiota composition and functions, including dietary patterns, antibiotics, as well as the mode of delivery at birth having an essential role in bacterial diversity [14–16]. Commensal bacteria, especially bacteria in the gut, contribute to maintaining a healthy immune system [17]. The intestinal mucosa host's key immune system signaling molecules and cells, such as subpopulations of T cells, neutrophils, natural killer lymphocytes, and macrophages, are sensitive to microbial composition. Dysbiosis, a condition associated with the loss of beneficial microbial composition, as well as an overgrowth of pathogenic microbes, can have a direct impact on gut immune cells [18]. Short-chain fatty acids (SCFAs), such as propionate, acetate, and butyrate, are the end products of dietary fibers digested by gut microbiome components. Many studies suggest that SCFAs have anti-inflammatory properties, can induce regulatory T cells in the colon and maintain their homeostasis, and can modulate the function of intestinal macrophages [19]. In contrast, lipopolysaccharides (LPS), which represent an element of the outer membrane of Gram-negative bacteria, could induce the over-expression of pro-inflammatory cytokines, such as interleukin (IL)-6 and IL-8 tumor necrosis factor (TNF)-α, causing a moderate inflammation status in the human body [20,21]. The link between the gut microbiota and immune system regulation opened a novel angle to understand the pathogenesis of psoriasis and indicated new possibilities for treatment/prevention such as modification of dietary habits, Probiotics, Omega 3 Fatty Acids, Quercetin or even Curcumin supplementation, and fecal microbiota transplant (FMT) [22]

This study aims to highlight the latest scientific evidence regarding the microbiome alterations of psoriatic patients, as well as the state of knowledge in terms of microbiome-targeted therapies as promising preventive and therapeutic tools for psoriasis.

2. State of Knowledge

2.1 Gut-Skin Axis in Psoriasis

Until July 2022, 14 studies concerning gut microbiome composition in psoriasis were conducted in general including 443 psoriatic patients and 630 healthy controls. In 13 out of 14 studies the material was a stool sample, in one study the fecal specimen was collected by inserting a sterile rectal swab 1–2 cm beyond the anus [23]; In one of the studies, blood samples were additionally collected [24]. Bacterial composition was determined mostly using the 16S rRNA sequencing technique (12 studies), fecal real-time polymerase chain reaction (PCR) (1 study), and quantitative PCR (1 study). Blood samples were analyzed using broad-range PCR and nucleotide sequencing analysis. All of these studies focused on the bacterial composition of the gut microbiome.

Studies were based on Caucasian (8/14) and Asian (6/11) populations. All of the studies included adult patients, however, the analyzed population showed heterogeneity concerning other enrolment criteria: some of the authors analyzed not only the gut microbiota composition in skin psoriasis patients but also in patients suffering from psoriatic arthritis [25,26,23,27,29], and 1 study also included patients with inflammatory bowel disease and/or hidradenitis suppurativa [28]. Additionally, methods of matching healthy controls differ among the studies, ranging from household relatives with no history of autoimmune diseases

[19], through gender, age, Body Mass Index (BMI) -compatible controls [26,31], to data of healthy subjects collected from the HMP database [10].

The findings concerning gut microbiota in the analyzed patients were dubious. 13 out of 14 studies showed statistically significant differences between psoriatic patients and the healthy control groups.

One of the studies did not report any difference at baseline and showed relative changes in the abundance of bacterial phyla during treatment in patients receiving secukinumab (once a week at weeks 0, 1, 2, 3, 4, and every 4 weeks thereafter–The study was conducted for 6 months) and no such phenomenon in the compared patients receiving ustekinumab (45 mg at weeks 0 and 4 and thereafter every 3 months). Also, the baseline microbiota composition in patients who responded well to secukinumab and non-responders varied significantly, suggesting a role in the treatment response [23].

At the phylum level, 6/14 studies showed an increase [26,29,32,33,31,34], while 3/14 reported a decrease [25,35,36] in Firmicutes phylum in psoriatic patients compared to the healthy control group. The number of bacteria belonging to the Bacteroidetes phylum was increased in psoriatic patients only in two studies, while 5/11 studies indicated a decrease [37,26,32,33,31]. Five papers compared the relationship between the number of Firmicutes and Bacteroidetes phyla, creating Firmicutes/Bacteroidetes ratio (F/B ratio) and comparing it between psoriatic patients and the healthy control group. The F/B ratio was elevated in all psoriatic cases in comparison to the control group [26,32,33,31,38]. Moreover, it showed a positive correlation with PASI score [38].

Concerning other phyla, the number of Actinobacteria was increased [32,33] as well as decreased [37,38] in 2/14 studies of psoriatic patients versus the control group. The reduction of Actinobacteria showed a negative correlation with PASI in 1 study [38]. Two other studies showed a deterioration in the number of Proteobacteria phylum [32,33] while two studies showed a decrease in Tenericutes phylum and Verrucomicrobia phylum in psoriatic patients [30,36].

Regarding the family, most data come from a study conducted by Hidalgo Cantabrana et al. which showed an increase in the plethora of Ruminococcaceae, Lachnospiraceae, Clostridiales, Peptostreptococcae, Erysipelotrichaceae, Bifidobacteriacae, Coriobacteriaceae, Eggerthellaceae families and a decrease in Bacteroidaceae, Prevotellaceae, Barnesiellaceae, Tannerellaceae, Rikenellaceae, Marinifilaceae, Lactobacillaceae, Streptococcaceae, Veillonellaceae, Pasteurellaceae, Burkholderiaceae, Desulvibrionaceae and Victivallaceae families [32]. Although other researchers from China confirmed the findings concerning Bacteroidaceae, Prevotellaceae, Ruminococcaceae, and Lachnospiraceae [26], a study conducted by Scher showed contrary results concerning Erysipelotrichaceae and Bifidobacteriaceae. Scher et al. also reported a decrease in the abundance of the Porphyromonadaceae family in psoriatic patients [27].

According to a study based on microbiota and inflammation-related variables, microbiota dysbiosis may produce an abnormal immune response in psoriasis. The microbiome changes were correlated with the degree of inflammation-related markers that were irregular in psoriasis patients, specifically the IL-2 receptor, which exhibited a positive relationship with Phascolarctobacterium and a negative relationship with Dialister. This finding indicates that Phascolarctobacterium and Dialister relative abundances could be used as predictors of

psoriasis activity [34]. Furthermore, complement 3 has a negative correlation with Escherichia level [34], which tends to be higher in psoriasis patients [28].

According to a study conducted by Brazilian scientists who studied the composition and diversity of the gut microbiota in 21 subjects with psoriasis, when compared to 24 subjects in the control group, the psoriasis group showed a decrease in the Lachnospira and Akkermansia muciniphila species [36]. This decrease in Akkermansia muciniphila was also highlighted by another study of microbiota composition in 14 psoriasis patients [30]. Such changes were linked to butanoate metabolism and butyrate production in the human colonic microbiota [39,40]. Butyrate has been implicated in the regulation of various inflammatory factors, including lipopolysaccharides, TNF-α, IL-10, and IL-1β [41]. Faecalibacterium spp. showed a lower abundance in psoriasis patients with lower diversity and a difference in β diversity community composition [28,42], while Ruminococcus torques and Ruminococcus gnavus exhibited a greater abundance [42].

2.2 Gut Microbiome-Targeted Therapies for Psoriasis

Current findings suggest that modulation of the composition of gut microbiota, both through dietary approaches, supplementation with probiotics, prebiotics, and other substances, and fecal microbiota transplantation could represent a new therapeutic/prevention target in psoriasis.

2.2.1 Mediterranean diet

Diet is a modifiable factor implicated in chronic systemic inflammation, and the Mediterranean dietary pattern is considered to be a healthy model in terms of morbidity and mortality. It encourages a high consumption of plant-based foods, such as fruits, vegetables, nuts, legumes, grains, and olive oil, while reducing the intake of red meat, dairy products, and processed products [43]. Recent evidence suggests that adherence to the Mediterranean diet could also impact the inflammatory markers in autoimmune diseases [44] and may reduce the severity status of certain dermatological pathologies [45,46]. The anti-inflammatory effects of the Mediterranean diet in psoriasis patients were discussed in a study by Céline Phan et al. [48]. The authors revealed that low adherence to the Mediterranean diet was correlated with a more severe status in psoriasis patients; however, this study did not approach the gut microbiota's role in the anti-inflammatory effects observed in psoriasis patients but more on the biologically active components present in the Mediterranean diet. The same perspective with the same results were also supported by a cross-sectional study conducted in 2015, with a smaller sample of mild-to-severe 62 psoriasis patients, which can represent a limitation of the study [47]. The results showed that the PASI (Psoriasis Area and Severity Index) score, measured for the severity status of psoriasis, presented a significant association with the percentage of the C-reactive protein levels, which was negatively correlated with adherence to the Mediterranean diet. The extra virgin olive oil and fish consumption were both independent predictors of PASI score and C-reactive protein levels [47]. Similarly, an energy-restricted diet intended to enhance the intake of omega-3 and decrease omega-6 PUFAs improved the metabolic profile and increased the responsiveness to immunomodulating treatment in obese psoriatic patients [49].

2.2.2 Omega-3 Fatty Acids

There is a relationship between the influence of PUFAs on immunity via modulating the gut microbiota proven. For example, one of the studies conducted in 2020 showed that the administration of flaxseed oil in rats resulted in a higher level of SCFA production and a better microbial diversity, with Lactobacillus, Firmicutes, Butyrovibrio, and Bifidobacterium being negatively linked with pro-inflammatory markers (IL-1β, IL-6, IL-10, IL-17A, and TNF-α) [50]. Kåre Steinar Tveit et al. highlighted that supplementation with herring roe oil (containing 292 mg of polyunsaturated fatty acids omega-3) leads to a significant improvement in the PASI score in psoriasis subjects. However, no significant changes were observed at the levels of inflammatory markers [51]. Another randomized clinical trial, which included healthy subjects, highlighted that a daily dose of 500 mg omega-3 increased the Coprococcus spp. and Bacteroides spp. and significantly decreased Collinsella spp. At the same time, serum levels of iso-butyrate and isovalerate seemed to increase by the end of the study [52]. Interestingly, high levels of Collinsella spp. characterize the fecal microbiota of psoriasis subjects [33], while SCFAs and branched SCFAs, such as iso-butyrate and isovalerate, are known for their anti-inflammatory effects [53]. Furthermore, omega-3 PUFAs, which interfere with the synthesis of pro-inflammatory eicosanoids [54], are proven to suppress the transcription of inflammatory cytokines via inhibiting NF KB-mediated inflammation [55].

2.2.3 Quercetin

Quercetin is a plant flavonol from the flavonoid group of polyphenols. It can be found in many fruit, vegetables, leaves, seeds, and grains; capers, red onions, and kale are common foods containing appreciable amounts of it. Many previous studies have shown the advantages of quercetin, especially regarding its anti-inflammatory, cytoprotective and immunosuppressive properties[56-58].

Due to an increased interest in this topic, recent studies have begun to describe the influence of quercetin on the composition of gut microbiota [59,60,61]. For example, quercetin seems to ameliorate gut microbiota dysbiosis that drives hypothalamic damage and hepatic lipogenesis in monosodium glutamate-induced abdominal obesity mice. The quercetin therapy specifically reversed Firmicutes spp. and the Firmicutes/Bacteroidetes ratio was found reduced. Moreover, the scientists confirmed a higher level in the Lachnospiraceae and Ruminococcaceae family, as well as an improvement in intestinal barrier function [62]. A recent study addressed the effect of quercetin supplementation (30, 60, and 120 mg/kg) on imiquimod-induced mice, showing drastically reduced PASI scores, lower temperature of psoriasis-like lesions, and improved psoriatic plaques. Furthermore, quercetin successfully reduced serum TNF-α, IL-6, and IL-17 levels strengthened the anti-inflammatory effect, and reduced buildup in skin tissue produced by imiquimod in mice. The authors indicate that this process might be linked to the regulation of the NFKB pathway [145]. Moreover, oral supplementation with quercetin, a dietary flavonoid extracted from Fagopyrum tataricum, reduced imiquimod-induced psoriasis-like dermatitis in mice, dramatically lowering keratinocyte proliferation and aberrant differentiation, as well as inflammatory cell infiltrates. A reduced expression of cytokines on the IL-23/Th17 axis and a reduced Th17 cell response was noticed after the oral administration of quercetin [146]. Nonetheless, there is more research needed to be done to determine the exact relationship of quercetin with the gut microbiota and whether it may play a crucial role in modulating the gut microbiota among psoriasis patients.

2.2.4 Curcumin

Curcumin is a bright yellow chemical produced by plants of the *Curcuma longa* species, known for its anti-inflammatory effects, accumulates in the gastrointestinal tract following oral intake and may influence its regulatory effect by modulating the microbial diversity and composition of the intestinal microflora [63]. Changes in gut microbiota after curcumin supplementation were highlighted by a human randomized placebo-controlled trial that studied the impact of turmeric and curcumin dietary supplementation in 30 healthy participants. The supplementation group received 6000 mg of Curcuma longa extract daily and the microbiota analyses were performed at the beginning of therapy and after 8 weeks. All of the subjects had substantial changes in microbiota composition, as well as a personalized response to therapy. Most Clostridium spp., Bacteroides spp., Citrobacter spp., Cronobacter spp., Enterobacter spp., Enterococcus spp., Klebsiella spp., Parabacteroides spp., and Pseudomonas spp. were increased evenly in the responsive participants. There was lower relative affluence of many Blautia spp. and the majority of Ruminococcus spp. exhibited in both groups [64]. Moreover, Ohno et al. proved curcumin to be efficient for inducing mucosal immune cells with regulatory features in mice by significantly suppressing NFKB activation in the colonic epithelium and controlling the production of inflammatory mediators [65] What is more, the number of butyrate-producing bacteria and fecal butyrate levels increased, as did the proliferation of CD4+ Foxp3+ regulatory T cells and CD103+ CD8- regulatory dendritic cells [65]. The other scientific paper conducted by Italian scientists showed that oral supplementation with curcumin in psoriasis patients for twelve weeks results in a significant reduction in PASI score with a decrease in IL-22 serum levels [66]. All of those findings support the fact that curcumin supplementation could represent a future perspective regarding the treatment of psoriasis.

2.2.5 Probiotics/Prebiotics/Synbiotics

World Health Organization (WHO) defines probiotics as "live microorganisms which when administered in adequate amounts confer a health benefit on the host."[67]. Probiotics enclose a wide range of microorganisms. Bacteria from the Lactobacillaceae and Bifidobacteriaceae families are the most frequent ones, but other bacteria, as well as yeasts, can be administered as probiotics too [68]. Moreover, nondigestible dietary components, such as inulins, fructooligosaccharides (FOS), or galactooligosaccharides, promote the growth of beneficial bacteria in the intestinal microbiota, which is called prebiotics [69]. When consumed together with the same blend of dietary supplements they are called synbiotics [70].

The effects of administering probiotics include the stabilization of the gut bacterial community and the restoration of the “signature” of bacterial microbiota, which is a result of lowering the pH, producing bacteriocins, altering microRNA (miRNAs), competing with pathogens for certain nutrients and improving the gut barrier function [71] A therapeutic approach of probiotic/prebiotic/synbiotic supplementation among psoriasis patients began to attract the attention of many scientists; so right now several papers address this issue in both experimental and clinical studies.

In one of the studies imiquimod-induced psoriasis-like mice were tested, and the supplementation with probiotics for two weeks resulted in great relief from psoriasis-like pathological characteristics [96]. More precisely, Bifidobacterium adolescentis CCFM667, B. breve CCFM1078, Lactobacillus paracasei CCFM1074, and L. reuteri CCFM1132 successfully reduced erythema, scaling, and thickening, but B. animalis CCFM1148, L. paracasei CCFM1147, and L. reuteri CCFM1040 showed modest effects. Moreover, the

immune responses through the IL-23/Th17 axis, B. adolescentis CCFM667, B. breve CCFM1078, L. paracasei CCFM1074, and L. reuteri CCFM1132 were beneficial in alleviating psoriasis by suppressing the cytokine activity. The strains that effectively treated psoriasis symptoms elevated acetate or propionate levels in the gut microbiota. The levels of acetate were considerably conversely connected to IL-17 and IL-23, although the levels of propionate were substantially conversely related to the levels of IL-23. This could prove the practical usefulness of probiotic supplementation in regulating the level of inflammation in patients with psoriasis [72].

Only two original studies concerning probiotics administration in psoriatic patients were identified up until January 2021, both conducted on patients of Caucasian suffering from plaque psoriasis. A randomized, double-blinded, placebo-control study including 22 patients with ulcerative colitis, 48 patients with chronic fatigue syndrome, 22 patients with chronic plaque psoriasis and a control group of 35 healthy people was conducted. Psoriatic patients were identified as having higher levels of serum C-reactive protein (CRP), TNF-α and IL-6 than the control group. Research groups were administered with of one sachet containing 1 × 1010 colony forming units (CFU) viable Bifidobacterium infantis 35,264 per day for 6–8 weeks (the duration depended on the type of disease). A significant decrease in plasma levels of CRP, TNF-α but not IL-6 concentration was observed among psoriatic patients after 8 weeks of daily supplementation [73].

Navarro-Lopez et al. d 90 patients, who were administered with a mixture of three probiotic strains in a 1:1:1 ratio—Bifidobacterium longum CECT 7347, B. lactis CECT 8145 and Lactobacillus rhamnosus CECT 8361 with a total of 1 × 109 CFU per capsule once a day for 12 weeks. They received topical treatment with betamethasone and calcipotriol or mometasone furoate 0.1% during the entire study regardless of the probiotic course [74]. Since adherence to topical treatment in psoriasis patients are usually surprisingly weak (around 38% with once-a-day application) at treatment week 4 [75]), the inclusion of patients in the clinical trial could have had: influence their attitude toward this method and increase their adherence to them. This may be the reason why both 66.7% of the research group and 41.9% of the control group PASI-75 reduction was achieved within 12 weeks; also 48.9% in the probiotic group and 30.2% placebo achieved a PGA score of 0-1 over the 3-month follow-up period. It is hard to determine the exact effect of probiotic supplementation in addition to topical treatment. Nonetheless, patients who received probiotics had a lower risk of relapse over the 6-month follow-up period. That fact indicates that oral administration of probiotics may have a lasting effect on the composition of the intestinal microflora composition and what follows up the course of psoriasis. Furthermore, Chinese researchers investigated the effect of Bacteroides fragilis BF839 in 26 psoriasis patients. They received the probiotic for 12 weeks while maintaining the antipsoriatic treatment. The results showed a statistically significant difference ($p < 0.01$) in the reduction in PASI score, with only one case of constipation as a side effect [76].

2.2.6 Fecal Microbiota Transplantation

Fecal microbiota transplant (FMT), also known as a stool transplant is the process of transferring fecal bacteria and other microbes from a healthy individual into another individual. FMT has proved to be effective in recurrent Clostridioides difficile infection [77]. Encouraging results were performed by Sudarshan Paramsothy et al. in an 8-week clinical trial. FMT caused an increase in gut microbial diversity and altered microbial composition by enhancing the Eubacterium hallii and Roseburia inulivorans species in active UC patients along with the remission of the disease [78]. The effectiveness of FMT in patients with

psoriasis is still a research topic, but the promising results of clinical trials have begun to attract the attention of the medical world. In a five-week Chinese clinical trial, a patient with plaque psoriasis and IBS(irritable bowel syndrome) was administrated FMT twice via endoscopy and colonoscopy. The body surface area, PASI score, dermatology life quality index, intestinal symptoms, and serum level of TNF-α were all enhanced after the treatment and no negative reactions were observed [79]. In another Chinese study conducted on mice using fecal microbial transplantation (FMT), 16S rRNA gene-based taxonomic profiling and *Lactobacillus* supplement assessed the effect of FMT from healthy individuals on psoriasis-like skin inflammation and associated immune disorders in imiquimod-induced psoriasis mice. The results showed that using mice with psoriasis humanized stools from healthy donors and psoriasis patients, it was found that imiquimod-induced psoriasis in mice with stool of psoriasis patients was significantly worsened compared to mice with stools of healthy donors. Further analyzes showed that the fecal microflora of healthy people is protected against Treg / Th17 imbalances in psoriasis. Moreover, they found out that the gut and cutaneous microbiome of mice receiving the gut microbiota of normal (HD) subjects differed from that of mice receiving the gut microbiota of psoriasis patients (PSD). Lactobacillus reuteri was significantly enriched in the stool and skin microbiome of HD mice compared to PSD mice. Interestingly, supplementation with Lactobacillus reuteri was sufficient to increase the expression of the anti-inflammatory gene IL-10, reduce the number of Th17 cells, and confer immunity to imiquimod inflammation in mice with dysbiosis of the intestinal microflora [80]. However, all of these results suggest that gut microbiota dysbiosis is the potential causal factor of psoriasis and the gut microbiota may serve as a promising therapeutic target for psoriasis patients more clinical trials are needed to be done to investigate whether or not modulation of the gut microbiota plays a substantial role in this process.

3. Conclusions and Further Perspectives

This review highlighted a strong link between psoriasis and the gut microbiota, with the purpose of adding new knowledge for discovering the relationship between the altered intestinal microbiota in psoriasis patients. Almost all studies concerning the intestinal microflora showed compelling changes in patients with psoriasis. Certain parameters such as the Firmicutes / Bacteroidetes ratio or Psoriasis Microbiome Index were developed to distinguish healthy subjects from psoriasis patients. Despite all of these interesting findings, there are a lot of limitations and challenges that future studies should face. Firstly, DNA extraction in both animal and human studies has to be collected, transported, stored, and tested in the same way to allow optimal comparisons between studies. Moreover, additional studies on humans that include an accurate nutritional evaluation and therapeutic protocols are required in order to better understand the relationship between diet and microbiota in patients suffering from psoriasis. Furthermore, there is still too little data to confirm the potential therapeutic approach to modulating the gut microbiota for better outcomes in psoriasis patients. Fecal microbiota transplantation from healthy individuals to psoriatic patients seems to be a promising therapeutic approach in microbiota composition restoration. More studies need to be done to fully understand the potential of microbiota-aimed therapies.

References

1. Greb, J.E.; Goldminz, A.M.; Elder, J.T.; Lebwohl, M.G.; Gladman, D.D.; Wu, J.J.; Mehta, N.N.; Finlay, A.Y.; Gottlieb, A.B. Psoriasis. Nat. Rev. Dis. Primers 2016, 2, 16082. https://doi.org/10.1038/nrdp.2016.82
2. Armstrong, A.W.; Read, C. Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review. JAMA 2020, 323, 1945–1960. https://doi.org/10.1001/jama.2020.4006
3. Obradors, M.; Blanch, C.; Comellas, M.; Figueras, M.; Lizan, L. Health-Related Quality of Life in Patients with Psoriasis: A Systematic Review of the European Literature. Qual. Life Res. 2016, 25, 2739–2754. https://doi.org/10.1007/s11136-016-1321-7
4. Takeshita, J.; Grewal, S.; Langan, S.M.; Mehta, N.N.; Ogdie, A.; Van Voorhees, A.S.; Gelfand, J.M. Psoriasis and Comorbid Diseases: Implications for Management. J. Am. Acad. Dermatol. 2017, 76, 393–403. https://doi.org/10.1016/j.jaad.2016.07.065
5. AlQassimi, S.; AlBrashdi, S.; Galadari, H.; Hashim, M.J. Global Burden of Psoriasis-Comparison of Regional and Global Epidemiology, 1990 to 2017. Int. J. Dermatol. 2020, 59, 566–571. **https://doi.org/10.1111/ijd.14864**
6. Parisi, R.; Iskandar, I.Y.K.; Kontopantelis, E.; Augustin, M.; Griffiths, C.E.M.; Ashcroft, D.M. National, Regional, and Worldwide Epidemiology of Psoriasis: Systematic Analysis and Modelling Study. BMJ 2020, 369, m1590. https://doi.org/10.1136/bmj.m1590
7. Michalek, I.M.; Loring, B.; John, S.M. A Systematic Review of Worldwide Epidemiology of Psoriasis. J. Eur. Acad. Dermatol. Venereol. 2017, 31, 205–212. https://doi.org/10.1111/jdv.13854
8. Raychaudhuri, S.K.; Maverakis, E.; Raychaudhuri, S.P. Diagnosis, and Classification of Psoriasis. Autoimmun. Rev. 2014, 13, 490–495. https://doi.org/10.1016/j.autrev.2014.01.008
9. Ogawa, E.; Okuyama, R.; Seki, T.; Kobayashi, A.; Oiso, N.; Muto, M.; Nakagawa, H.; Kawada, A. Epidemiological Survey of Patients with Psoriasis in Matsumoto City, Nagano Prefecture, Japan. J. Dermatol. 2018, 45, 314–317. https://doi.org/10.1111/1346-8138.14101
10. Rendon, A.; Schäkel, K. Psoriasis Pathogenesis and Treatment. Int. J. Mol. Sci. 2019, 20, 1475. https://doi.org/10.3390/ijms20061475
11. Wang, J.; Li, W.; Wang, C.; Wang, L.; He, T.; Hu, H.; Song, J.; Cui, C.; Qiao, J.; Qing, L.; et al. Enterotype Bacteroides Is Associated with a High Risk in Patients with Diabetes: A Pilot Study. J. Diabetes Res. 2020, 2020, 1–11. https://doi.org/10.1155/2020/6047145
12. De Moraes, A.; Fernandes, G.D.R.; da Silva, I.T.; Petitto, B.D.A.; Gomes, E.P.; Pereira, A.D.C.; Ferreira, S.R.G. Enterotype May Drive the Dietary-Associated Cardiometabolic Risk Factors. Front. Cell. Infect. Microbiol. 2017, 7, 47. https://doi.org/10.3389/fcimb.2017.00047
13. Mobeen, F.; Sharma, V.; Prakash, T. Enterotype Variations of the Healthy Human Gut Microbiome in Different Geographical Regions. Bioinformation 2018, 14, 560–573. https://doi.org/10.6026/97320630014560
14. Kahleova, H.; Rembert, E.; Alwarith, J.; Yonas, W.N.; Tura, A.; Holubkov, R.; Agnello, M.; Chutkan, R.; Barnard, N.D. Effects of a Low-Fat Vegan Diet on Gut Microbiota in Overweight Individuals and Relationships with Body Weight, Body Composition, and Insulin Sensitivity. A Randomized Clinical Trial. Nutrients 2020, 12, 2917. https://doi.org/10.3390/nu12102917
15. Tonon, K.M.; Morais, T.B.; Taddei, C.R.; Araújo-Filho, H.B.; Abrão, A.C.F.V.; Miranda, A.; de Morais, M.B. Gut Microbiota Comparison of Vaginally and Cesarean Born Infants Exclusively Breastfed by Mothers Secreting α1–2 Fucosylated Oligosaccharides in Breast Milk. PLoS ONE 2021, 16, e0246839. https://doi.org/10.1371/journal.pone.0246839
16. Liou, J.-M.; Chen, C.-C.; Chang, C.-M.; Fang, Y.-J.; Bair, M.-J.; Chen, P.-Y.; Chang, C.-Y.; Hsu, Y.-C.; Chen, M.-J.; Chen, C.-C.; et al. Long-Term Changes of Gut Microbiota, Antibiotic Resistance, and Metabolic Parameters after Helicobacter Pylori Eradication: A Multicentre, Open-Label, Randomised Trial. Lancet Infect. Dis. 2019, 19, 1109–1120. https://doi.org/10.1016/S1473-3099(19)30272-5

17. Wastyk, H.C.; Fragiadakis, G.K.; Perelman, D.; Dahan, D.; Merrill, B.D.; Yu, F.B.; Topf, M.; Gonzalez, C.G.; van Treuren, W.; Han, S.; et al. Gut-Microbiota-Targeted Diets Modulate Human Immune Status. Cell 2021, 184, 4137–4153.e14. https://doi.org/10.1016/j.cell.2021.06.019
18. Bojovi´c, K.; Ignjatovi´c, Đ.I.; Baji´c, S.S.; Milutinovi´c, D.V.; Tomi´c, M.; Goli´c, N.; Tolinaˇcki, M. Gut Microbiota Dysbiosis Associated with Altered Production of Short Chain Fatty Acids in Children With Neurodevelopmental Disorders. Front. Cell. Infect. Microbiol. 2020, 10, 223.
19. Eslick, S.; Williams, E.J.; Berthon, B.S.; Wright, T.; Karihaloo, C.; Gately, M.; Wood, L.G. Weight Loss and Short-Chain Fatty Acids Reduce Systemic Inflammation in Monocytes and Adipose Tissue Macrophages from Obese Subjects. Nutrients 2022, 14, 765. https://doi.org/10.3390/nu14040765
20. Rorato, R.; de Borges, B.C.; Uchoa, E.T.; Antunes-Rodrigues, J.; Elias, C.F.; Kagohara Elias, L.L. LPS-Induced Low-Grade Inflammation Increases Hypothalamic JNK Expression and Causes Central Insulin Resistance Irrespective of Body Weight Changes. Int. J. Mol. Sci. 2017, 18, 1431. https://doi.org/10.3390/ijms18071431
21. López-Moreno, J.; García-Carpintero, S.; Jimenez-Lucena, R.; Haro, C.; Rangel-Zúñiga, O.A.; Blanco-Rojo, R.; Yubero-Serrano, E.M.; Tinahones, F.J.; Delgado-Lista, J.; Pérez-Martínez, P.; et al. Effect of Dietary Lipids on Endotoxemia Influences Postprandial Inflammatory Response. J. Agric. Food Chem. 2017, 65, 7756–7763.
22. Buhaș, Mihaela Cristina et al. "Gut Microbiota in Psoriasis." *Nutrients* vol. 14,14 2970. 20 Jul. 2022, doi:10.3390/nu14142970
23. Yeh, N.; Hsu, C.; Tsai, T.; Chiu, H. Gut Microbiome in Psoriasis is Perturbed Differently During Secukinumab and Ustekinumab Therapy and Associated with Response to Treatment. Clin. Drug Investig. 2019, 39, 1195–1203. https://doi.org/10.1007/s40261-019-00849-7
24.Codoñer, F.; Ramirez-Bosca, A.; Climent, E.; Carrion-Gutierrez, M.; Guerrero, M.; Perez-Orquin, J.; de la Parte, J.; Genoves, S.; Ramon, D.; Navarro-Lopez, V.; et al. Gut microbial composition in patients with psoriasis. Sci. Rep. 2018, 8, 3812.] https://doi.org/10.1038/s41598-018-22125-y
25. . Scher, J.; Ubeda, C.; Artacho, A.; Attur, M.; Isaac, S.; Reddy, S.; Marmon, S.; Neimann, A.; Brusca, S.; Patel, T.; et al. Decreased bacterial diversity characterizes the altered gut microbiota in patients with psoriatic arthritis, resembling dysbiosis in inflammatory bowel disease. Arthritis Rheumatol. 2015, 67, 128–139. https://doi.org/10.1002/art.38892
26. Chen, Y.; Ho, H.; Tseng, C.; Lai, Z.; Shieh, J.; Wu, C. Intestinal microbiota profiling and predicted metabolic dysregulation in psoriasis patients. Exp. Dermatol. 2018, 27, 1336–1343. https://doi.org/10.1111/exd.13786
27. Huang, L.; Gao, R.; Yu, N.; Zhu, Y.; Ding, Y.; Qin, H. Dysbiosis of gut microbiota was closely associated with psoriasis. Sci. China Life Sci. 2019, 62, 807–815. https://doi.org/10.1007/s11427-018-9376-6
28. Eppinga, H.; Sperna Weiland, C.; Thio, H.; van der Woude, C.; Nijsten, T.; Peppelenbosch, M.; Konstantinov, S. Similar Depletion of Protective Faecalibacterium prausnitzii in Psoriasis and Inflammatory Bowel Disease, but not in Hidradenitis Suppurativa. J. Crohns Colitis 2016, 10, 1067–1075. https://doi.org/10.1093/ecco-jcc/jjw070
29. Lin CY, Hsu CY, He HR, et al. Gut microbiota differences between psoriatic arthritis and other undifferentiated arthritis: A pilot study. Medicine (Baltimore). 2022;101(28):e29870. Published 2022 Jul 15. https://doi.org/10.1097/MD.0000000000029870
30. Tan, L.; Zhao, S.; Zhu, W.; Wu, L.; Li, J.; Shen, M.; Lei, L.; Chen, X.; Pen, C. The Akkermansia muciniphila is a gut microbiota signature in psoriasis. Exp. Dermatol. 2018, 27, 144–149. https://doi.org/10.1111/exd.13463
31. Dei-Cas, I.; Giliberto, F.; Luce, L.; Dopazo, H.; Penas-Steinhardt, A. 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, 10, 12754. https://doi.org/10.1038/s41598-020-69537-3
32. Hidalgo-Cantabrana, C.; Gomez, J.; Delgado, S.; Requena-Lopez, S.; Queiro-Silva, R.; Margolles, A.; Coto, E.; Sanchez, B.; Coto-Segura, P. Gut microbiota dysbiosis in a cohort of patients with psoriasis. Br. J. Dermatol. 2019, 181, 1287–1295. https://doi.org/10.1111/bjd.17931
33. Shapiro, J.; Cohen, N.; Shalev, V.; Uzan, A.; Koren, O.; Maharshak, N. Psoriatic patients have a distinct structural and functional fecal microbiota compared with controls. J. Dermatol. 2019, 46, 595–603. https://doi.org/10.1111/1346-8138.14933
34. Zhang, Xinyue et al. "Dysbiosis of gut microbiota and its correlation with dysregulation of cytokines in psoriasis patients." *BMC microbiology* vol. 21,1 78. 8 Mar. 2021
35. Singh, R.K.; Chang, H.-W.; Yan, D.; Lee, K.M.; Ucmak, D.; Wong, K.; Abrouk, M.; Farahnik, B.; Nakamura, M.; Zhu, T.H.; et al. Influence of Diet on the Gut Microbiome and Implications for Human Health. J. Transl. Med. 2017, 15, 73. https://doi.org/10.1186/s12967-017-1175-y
36. Schade, L et al. "The gut microbiota profile in psoriasis: a Brazilian case-control study." *Letters in applied microbiology* vol. 74,4 (2022): 498-504. https://doi.org/10.1111/lam.13630
37. Wu, C.-Y.; Chang, Y.-T.; Juan, C.-K.; Shieh, J.-J.; Lin, Y.-P.; Liu, H.-N.; Lin, J.-T.; Chen, Y.-J. Risk of Inflammatory Bowel Disease in Patients with Rosacea: Results from a Nationwide Cohort Study in Taiwan. J. Am. Acad. Dermatol. 2017, 76, 911–917. https://doi.org/10.1016/j.jaad.2016.11.065
- 38. Masallat, D.; Moemen, D.; State, A. Gut bacterial microbiota in psoriasis: A case control study. Afr. J. Microbiol. Res. 2016, 10, 1337–1343. https://doi.org/10.5897/AJMR2016.8046
39. Esquivel-Elizondo, S.; Ilhan, Z.E.; Garcia-Peña, E.I.; Krajmalnik-Brown, R. Insights into Butyrate Production in a Controlled Fermentation System via Gene Predictions. mSystems 2017, 2, e00051-17. https://doi.org/10.1128/mSystems.00051-17
40. Louis, P.; Flint, H.J. Formation of Propionate and Butyrate by the Human Colonic Microbiota. Environ. Microbiol. 2017, 19, 29–41. https://doi.org/10.1111/1462-2920.13589
41. Gao, J.; Guo, X.; Wei, W.; Li, R.; Hu, K.; Liu, X.; Jiang, W.; Liu, S.; Wang, W.; Sun, H.; et al. The Association of Fried Meat Consumption With the Gut Microbiota and Fecal Metabolites and Its Impact on Glucose Homoeostasis, Intestinal Endotoxin Levels, and Systemic Inflammation: A Randomized Controlled-Feeding Trial. Diabetes Care 2021, 44, 1970–1979. https://doi.org/10.2337/dc21-0099
42. Todberg, T.; Egeberg, A.; Zachariae, C.; Sørensen, N.; Pedersen, O.; Skov, L. Patients with Psoriasis Have a Dysbiotic Taxonomic and Functional Gut Microbiota*. Br. J. Dermatol. 2022, 187, 89–98. https://doi.org/10.1111/bjd.21245
43. . Fostering Healthier and More Sustainable Diets—Learning from the Mediterranean and New Nordic Experience. Available online: https://www.euro.who.int/en/health-topics/noncommunicable-diseases/obesity/news/news/2018/5/fosteringhealthier-and-more-sustainable-diets-learning-from-the-mediterranean-and-new-nordic-experience (accessed on 10 May 2022).
44. Chicco, F.; Magrì, S.; Cingolani, A.; Paduano, D.; Pesenti, M.; Zara, F.; Tumbarello, F.; Urru, E.; Melis, A.; Casula, L.; et al. Multidimensional Impact of Mediterranean Diet on IBD Patients. Inflamm. Bowel Dis. 2020, 27, 1–9. https://doi.org/10.1093/ibd/izaa097
45. Barrea, L.; Fabbrocini, G.; Annunziata, G.; Muscogiuri, G.; Donnarumma, M.; Marasca, C.; Colao, A.; Savastano, S. Role of Nutrition and Adherence to the Mediterranean Diet in the Multidisciplinary Approach of Hidradenitis Suppurativa: Evaluation of Nutritional Status and Its Association with Severity of Disease. Nutrients 2018, 11, 57. https://doi.org/10.3390/nu11010057

46. Barrea, L.; Donnarumma, M.; Cacciapuoti, S.; Muscogiuri, G.; de Gregorio, L.; Blasio, C.; Savastano, S.; Colao, A.; Fabbrocini, G. Phase Angle and Mediterranean Diet in Patients with Acne: Two Easy Tools for Assessing the Clinical Severity of Disease. J. Transl. Med. 2021, 19, 1–15. https://doi.org/10.1186/s12967-021-02826-1
47. Barrea, L.; Balato, N.; di Somma, C.; Macchia, P.E.; Napolitano, M.; Savanelli, M.C.; Esposito, K.; Colao, A.; Savastano, S. Nutrition and Psoriasis: Is There Any Association between the Severity of the Disease and Adherence to the Mediterranean Diet? J. Transl. Med. 2015, 13, 18. https://doi.org/10.1186/s12967-014-0372-1
48. Phan, C.; Touvier, M.; Kesse-Guyot, E.; Adjibade, M.; Hercberg, S.; Wolkenstein, P.; Chosidow, O.; Ezzedine, K.; Sbidian, E. Association Between Mediterranean Anti-Inflammatory Dietary Profile and Severity of Psoriasis. JAMA Dermatol. 2018, 154, 1017–1024. https://doi.org/10.1001/jamadermatol.2018.2127
49. Guida, B.; Napoleone, A.; Trio, R.; Nastasi, A.; Balato, N.; Laccetti, R.; Cataldi, M. Energy-Restricted, n-3 Polyunsaturated Fatty Acids-Rich Diet Improves the Clinical Response to Immuno-Modulating Drugs in Obese Patients with Plaque-Type Psoriasis: A Randomized Control Clinical Trial. Clin. Nutr. 2014, 33, 399–405. https://doi.org/10.1016/j.clnu.2013.09.010
50. Wang, T.; Sha, L.; Li, Y.; Zhu, L.; Wang, Z.; Li, K.; Lu, H.; Bao, T.; Guo, L.; Zhang, X.; et al. Dietary α-Linolenic Acid-Rich Flaxseed Oil Exerts Beneficial Effects on Polycystic Ovary Syndrome Through Sex Steroid Hormones—Microbiota—Inflammation Axis in Rats. Front. Endocrinol. 2020, 11, 284. https://doi.org/10.3389/fendo.2020.00284
51. Tveit, K.; Brokstad, K.; Berge, R.; Sæbø, P.; Hallaråker, H.; Brekke, S.; Meland, N.; Bjørndal, B. A Randomized, Double-Blind, Placebo-Controlled Clinical Study to Investigate the Efficacy of Herring Roe Oil for Treatment of Psoriasis. Acta Derm. Venereol. 2020, 100, adv00154. https://doi.org/10.2340/00015555-3507
52. Vijay, A.; Astbury, S.; Le Roy, C.; Spector, T.D.; Valdes, A.M. The prebiotic effects of omega-3 fatty acid supplementation: A six-week randomised intervention trial. Gut Microbes 2020, 13, 1–11. https://doi.org/10.1080/19490976.2020.1863133
53. Nakkarach, A.; Foo, H.L.; Song, A.A.-L.; Mutalib, N.E.A.; Nitisinprasert, S.; Withayagiat, U. Anti-Cancer and Anti-Inflammatory Effects Elicited by Short Chain Fatty Acids Produced by Escherichia Coli Isolated from Healthy Human Gut Microbiota. Microb. Cell Factories 2021, 20, 1–17. https://doi.org/10.1186/s12934-020-01477-z
54. Fu, Y.; Wang, Y.; Gao, H.; Li, D.; Jiang, R.; Ge, L.; Tong, C.; Xu, K. Associations among Dietary Omega-3 Polyunsaturated Fatty Acids, the Gut Microbiota, and Intestinal Immunity. Mediat. Inflamm. 2021, 2021, 1–11. https://doi.org/10.1155/2021/8879227
55. . Adkins, Y.; Kelley, D.S. Mechanisms Underlying the Cardioprotective Effects of Omega-3 Polyunsaturated Fatty Acids. J. Nutr. Biochem. 2010, 21, 781–792. https://doi.org/10.1016/j.jnutbio.2009.12.004
56. Huang, R.-Y.; Yu, Y.-L.; Cheng, W.-C.; OuYang, C.-N.; Fu, E.; Chu, C.-L. Immunosuppressive Effect of Quercetin on Dendritic Cell Activation and Function. J. Immunol. 2010, 184, 6815–6821. https://doi.org/10.4049/jimmunol.0903991
57. Chirumbolo, S. The Role of Quercetin, Flavonols and Flavones in Modulating Inflammatory Cell Function. Inflamm. Allergy Drug Targets 2010, 9, 263–285. https://doi.org/10.2174/187152810793358741
58. Endale, M.; Park, S.-C.; Kim, S.; Kim, S.-H.; Yang, Y.; Cho, J.Y.; Rhee, M.H. Quercetin Disrupts Tyrosine-Phosphorylated Phosphatidylinositol 3-Kinase and Myeloid Differentiation Factor-88 Association and Inhibits MAPK/AP-1 and IKK/NF-KBInduced Inflammatory Mediators Production in RAW 264.7 Cells. Immunobiology 2013, 218, 1452–1467. https://doi.org/10.1016/j.imbio.2013.04.019

59. Zhao, L.; Zhang, Q.; Ma, W.; Tian, F.; Shen, H.; Zhou, M. A Combination of Quercetin and Resveratrol Reduces Obesity in High-Fat Diet-Fed Rats by Modulation of Gut Microbiota. Food Funct. 2017, 8, 4644–4656. https://doi.org/10.1039/c7fo01383c
60. Wang, P.; Gao, J.; Ke, W.; Wang, J.; Li, D.; Liu, R.; Jia, Y.; Wang, X.; Chen, X.; Chen, F.; et al. Resveratrol Reduces Obesity in High-Fat Diet-Fed Mice via Modulating the Composition and Metabolic Function of the Gut Microbiota. Free Radic. Biol. Med. 2020, 156, 83–98. https://doi.org/10.1016/j.freeradbiomed.2020.04.013
61. Cai, T.-T.; Ye, X.-L.; Li, R.-R.; Chen, H.; Wang, Y.-Y.; Yong, H.-J.; Pan, M.-L.; Lu, W.; Tang, Y.; Miao, H.; et al. Resveratrol Modulates the Gut Microbiota and Inflammation to Protect Against Diabetic Nephropathy in Mice. Front. Pharmacol. 2020, 11, 1249. https://doi.org/10.3389/fphar.2020.01249
62. Zhao, L.; Zhu, X.; Xia, M.; Li, J.; Guo, A.-Y.; Zhu, Y.; Yang, X. Quercetin Ameliorates Gut Microbiota Dysbiosis That Drives Hypothalamic Damage and Hepatic Lipogenesis in Monosodium Glutamate-Induced Abdominal Obesity. Front. Nutr. 2021, 8, 671353. https://doi.org/10.3389/fnut.2021.671353
63. Shen, L.; Liu, L.; Ji, H.-F. Regulative Effects of Curcumin Spice Administration on Gut Microbiota and Its Pharmacological Implications. Food Nutr. Res. 2017, 61, 1361780. https://doi.org/10.1080/16546628.2017.1361780
64. . Peterson, C.T.; Vaughn, A.R.; Sharma, V.; Chopra, D.; Mills, P.J.; Peterson, S.N.; Sivamani, R.K. Effects of Turmeric and Curcumin Dietary Supplementation on Human Gut Microbiota: A Double-Blind, Randomized, Placebo-Controlled Pilot Study. J. Evid. Based Integr. Med. 2018, 23, 2515690X18790725. https://doi.org/10.1177/2515690X18790725
65. Ohno, M.; Nishida, A.; Sugitani, Y.; Nishino, K.; Inatomi, O.; Sugimoto, M.; Kawahara, M.; Andoh, A. Nanoparticle Curcumin Ameliorates Experimental Colitis via Modulation of Gut Microbiota and Induction of Regulatory T Cells. PLoS ONE 2017, 12, e0185999. https://doi.org/10.1371/journal.pone.0185999
66. Antiga, E.; Bonciolini, V.; Volpi, W.; Del Bianco, E.; Caproni, M. Oral Curcumin (Meriva) Is Effective as an Adjuvant Treatment and Is Able to Reduce IL-22 Serum Levels in Patients with Psoriasis Vulgaris. BioMed Res. Int. 2015, 2015, 1–7 https://doi.org/10.1155/2015/283634
67. Schlundt, Jorgen. "Health and Nutritional Properties of Probiotics in Food including Powder Milk with Live Lactic Acid Bacteria" (PDF). *Report of a Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria*. FAO / WHO.
68. Probiotics: What You Need To Know|NCCIH. Available online: https://www.nccih.nih.gov/health/probiotics-what-you-needto-know (accessed on 9 April 2022)
69. Davani-Davari, D.; Negahdaripour, M.; Karimzadeh, I.; Seifan, M.; Mohkam, M.; Masoumi, S.J.; Berenjian, A.; Ghasemi, Y. Prebiotics: Definition, Types, Sources, Mechanisms, and Clinical Applications. Foods 2019, 8, 92. https://doi.org/10.3390/foods8030092
70. Synbiotics — An Overview. ScienceDirect Topics. Available online: https://www.sciencedirect.com/topics/immunology-andmicrobiology/synbiotics (accessed on 9 April 2022). https://doi.org/10.1016/B978-0-323-85170-1.00018-X
71. Zhao, Y.; Zeng, Y.; Zeng, D.; Wang, H.; Zhou, M.; Sun, N.; Xin, J.; Khaique, A.; Rajput, D.; Pan, K. Probiotics and MicroRNA: Their Roles in the Host-Microbe Interactions. Front. Microbiol. 2021, 11, 604462. https://doi.org/10.3389/fmicb.2020.604462
72. Lu, W.; Deng, Y.; Fang, Z.; Zhai, Q.; Cui, S.; Zhao, J.; Chen, W.; Zhang, H. Potential Role of Probiotics in Ameliorating Psoriasis by Modulating Gut Microbiota in Imiquimod-Induced Psoriasis-Like Mice. Nutrients 2021, 13, 2010. https://doi.org/10.3390/nu13062010
73. Groeger, D.; Mahony, L.; Murphy, E.; Bourke, J.; Dinan, T.; Kiely, B.; Shanahan, F.; Quigley, E. Bifidobacterium infantis 35624 modulates host inflammatory processes beyond the gut. Gut Microbes 2013, 4, 325–339.

74. Navarro-López, V.; Martínez-Andrés, A.; Ramírez-Boscá, A.; Ruzafa-Costas, B.; Núñez-Delegido, E.; Carrión-Gutiérrez, M.; Prieto-Merino, D.; Codoner-Cortes, F.; Ramon-Vidal, D.; Genoves-Martinez, S.; 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, 1078–1084. https://doi.org/10.2340/00015555-3305
75. Svendsen, M.; Andersen, F.; Andersen, K.; Pottegård, A.; Johannessen, H.; Möller, S.; August, B.; Feldman, S.; Andersen, K. A smartphone application supporting patients with psoriasis improves adherence to topical treatment: A randomized controlled trial. Br. J. Dermatol. 2018, 179, 1062–1071. https://doi.org/10.1111/bjd.16667
76. Lin, C.; Zeng, T.; Deng, Y.; Yang, W.; Xiong, J. Treatment of Psoriasis Vulgaris Using Bacteroides Fragilis BF839: A Single-Arm, Open Preliminary Clinical Study. Sheng Wu Gong Cheng Xue Bao 2021, 37, 3828–3835. https://doi.org/10.13345/j.cjb.210198
77. Xu, H.; Huang HZhou, Y.; Zhao, H.; Xu, J.; Shou, D.; Liu, Y.; Zhou, Y.; Nie, Y. Fecal Microbiota Transplantation: A New Therapeutic Attempt from the Gut to the Brain. Gastroenterol. Res. Pract. 2021, 20, 6699268. https://doi.org/10.1155/2021/6699268
78. Paramsothy, S.; Nielsen, S.; Kamm, M.A.; Deshpande, N.P.; Faith, J.J.; Clemente, J.C.; Paramsothy, R.; Walsh, A.J.; van den Bogaerde, J.; Samuel, D.; et al. Specific Bacteria and Metabolites Associated with Response to Fecal Microbiota Transplantation in Patients with Ulcerative Colitis. Gastroenterology 2019, 156, 1440–1454.e2. https://doi.org/10.1053/j.gastro.2018.12.001
79. Yin, G.; Li, J.F.; Sun, Y.F.; Ding, X.; Zeng, J.Q.; Zhang, T.; Peng, L.H.; Yang, Y.S.; Zhao, H. Fecal Microbiota Transplantation as a Novel Therapy for Severe Psoriasis. Zhonghua Nei Ke Za Zhi 2019, 58, 782–785. https://doi.org/10.3760/cma.j.issn.0578-1426.2019.10.011
80. Chen, H. L., Zeng, Y. B., Zhang, Z. Y., Kong, C. Y., Zhang, S. L., Li, Z. M., Huang, J. T., Xu, Y. Y., Mao, Y. Q., Cai, P. R., Han, B., Wang, W. Q., & Wang, L. S. (2021). Gut and Cutaneous Microbiome Featuring Abundance of *Lactobacillus reuteri* Protected Against Psoriasis-Like Inflammation in Mice. *Journal of inflammation research*, *14*, 6175–6190.