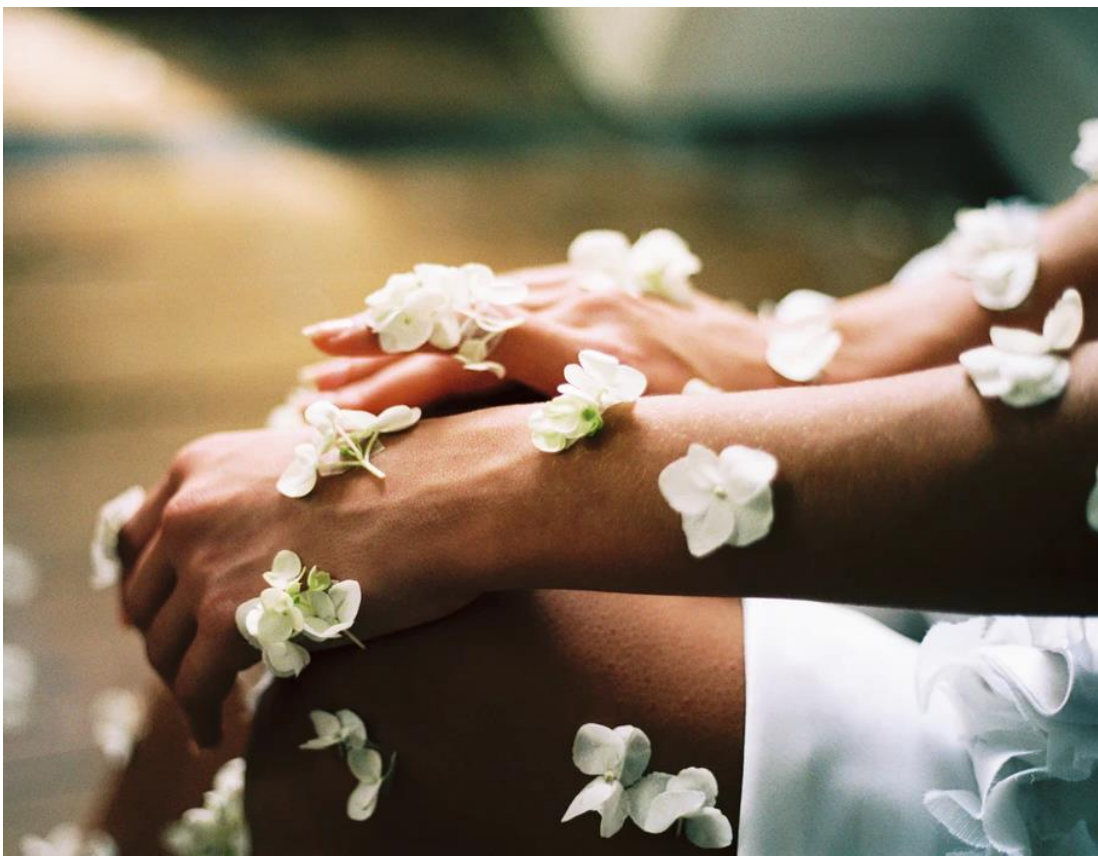
Skin Issues:
Probiotic research update



ATOPIC DERMATITIS

Gut Microbiome and its interplay with dermatological conditions

Changes to the gastrointestinal microbiome—the trillions of microorganisms found in the GI tract—are increasingly being observed in individuals suffering from a number of skin conditions, including atopic dermatitis. Recent analyses have shown differences between the microorganisms present in the GI tract of individuals with atopic dermatitis when compared to individuals without the diagnosis.

Evidence shows that patients with atopic dermatitis have lower gut microbial diversity, reduced levels of Bifidobacteria and fewer short-chain fatty acids, all of which are known to contribute to the maintenance of epithelial barrier function and modulate an anti-inflammatiry effect.

In fact, almost five hundred scientific papers have been published looking at the role of probiotics in atopic dermatitis, making it one of the most researched microbiome topics outside of traditional gastrointestinal diagnoses.

400 million children and 500 million adults live with atopic dermatitis globally

500 scientific papers have been published investigating the role of probiotics in atopic dermatitis

16.5 million U.S. adults say their AD leads to significant emotional and physical distress

ADM

Studying Microbiome Solutions

ADM has a rapidly growing portfolio of clinical trial research investigating the potential role of the microbiome in skin health. In 2017 ADM published in JAMA Dermatology our first randomized, placebo controlled clinical trial examining the role of the unique probiotic blend on the symptoms of atopic dermatitis in children. **We enrolled 50 children aged between 4-17 years with moderate atopic dermatitis, who were given either the probiotic blend**
(BPL1 : *Bifidobacterium lactis* CECT 8145, ES1 : *B. longum* CECT 7347, and BPL4 : *Lactobacillus casei* CECT 9104), or a placebo, for 12 weeks.

This blend was shown to:

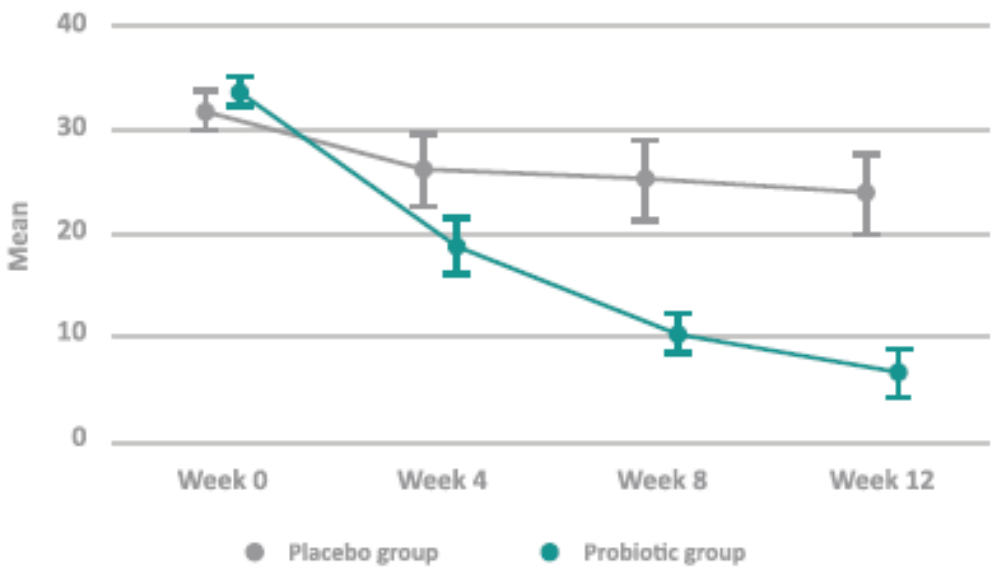
- help reduce severity of atopic dermatitis (SCORAD Index)
- help decrease the spread and intensity of atopic dermatitis
- help reduce the use of topical steroids

ADM

Studying Microbiome Solutions

SCORAX INDEX*

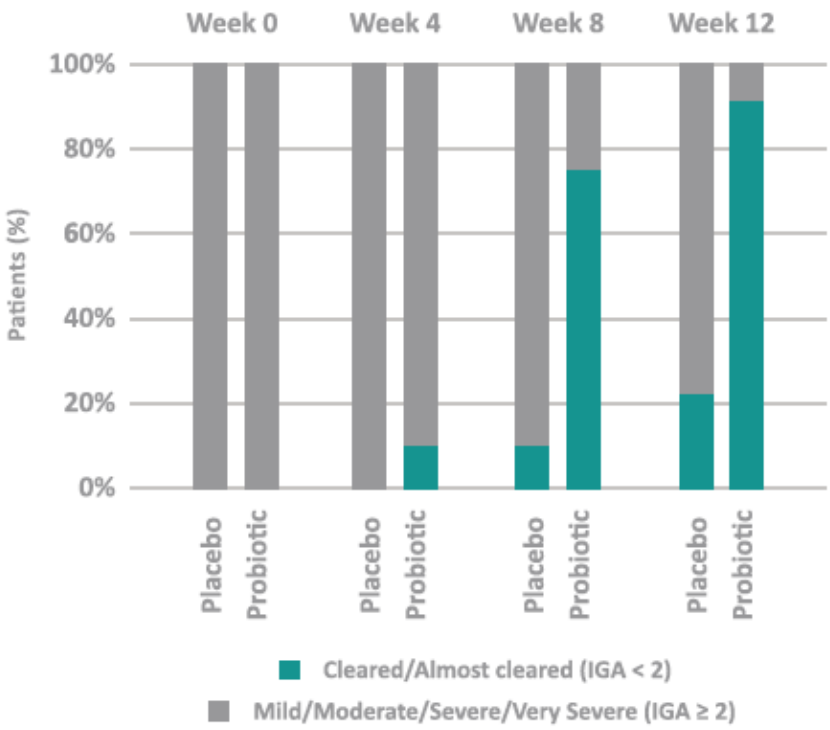
96% of patients in the probiotic group showed an improvement in symptoms (measured by the SCORAD index), compared to 46% in the placebo group.
This decrease represents a highly statistically significant improvement.
After 12 weeks there was a decrease in the SCORAD index of 83% in the probiotic group compared to 24% in the placebo group. This decrease represents a highly statistically significant improvement.
The difference in effectiveness between the two groups was 19.2 SCORAD points, or −59%, in favour of the probiotic, which represents a highly statistically significant improvement ($P < .001$).



**SCORAD: The SCORAD index is a validated clinical tool for assessing the severity of atopic dermatitis. The maximum score is 103. Classification of severity of eczema is divided into mild (<25), moderate (25-50) and severe (≥50).*

Studying Microbiome Solutions

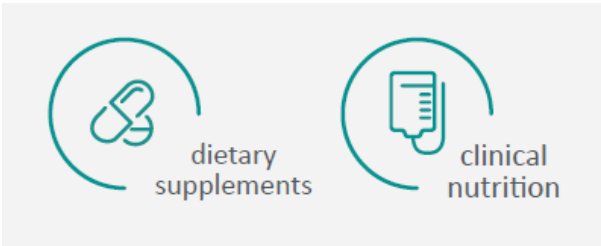
However, 91% of patients in the probiotic group achieved IGA scores of 0 or 1 compared to 21% of patients in the placebo group



More Applications. More Benefits

ADM has a long history of conducting proprietary microbiome research, with an extensive library of pre-clinical and clinical trials to support our growing range of cutting-edge microbiome solutions.

Our blend is the choice ingredient to integrate into dietary supplements or nutritional products targeting the skin. It comes in a bulk powder format and is designed for supplements, excipients, infant and clinical nutrition. It has a shelf life of 18-months:



ADM's strains come from natural sources, are non-GMO and safety evaluated. We will work with you to develop the ideal formulation for your end-product. Our probiotic blend can be easily incorporated into existing formulations and is made from:

3 probiotic strains:
Bifidobacterium lactis CECT 8145
Bifidobacterium longum CECT 7347
Lactobacillus casei CECT 9104

Tapioca Maltodextrin
Sugar

CLAIMS AND CERTIFICATIONS

- FDA Approved
- EU Approved
- GRAS
- Non-GMO
- Organic
- HALAL
- Clean Label
- Gluten Free
- Kosher

ADM

Introduction

Intestinal health plays a key role in the development of atopic dermatitis (AD). Impairment of the intestinal mucosal barrier appears to be involved in the pathogenesis of human AD [1, 2]. Small intestinal biopsy samples taken from children with AD demonstrated enhanced transfer of intact and degraded proteins through the barrier relative to controls, increasing the antigenic load, demonstrating a potential relationship between atopic dermatitis and intestinal permeability [2]. Leaky gut syndrome is a condition in which damage to the small intestine creates spaces between cells, large enough to allow fragments of partially digested food, toxins, and bacteria to migrate from the intestinal tract into the systemic circulation. As they reach the skin, a strong Th2 response is initiated, impairing epidermal differentiation and skin barrier integrity. This Th2 response releases Interleukin 4 (IL-4) that stimulates B cells to secrete IgE causing hypersensitivity reactions by releasing cytokines and other proinflammatory molecules such as histamines by mast cells. This increase in activity via Th2 causes a loss of balance between Th1 / Th2 responses (fig 1)[3]:

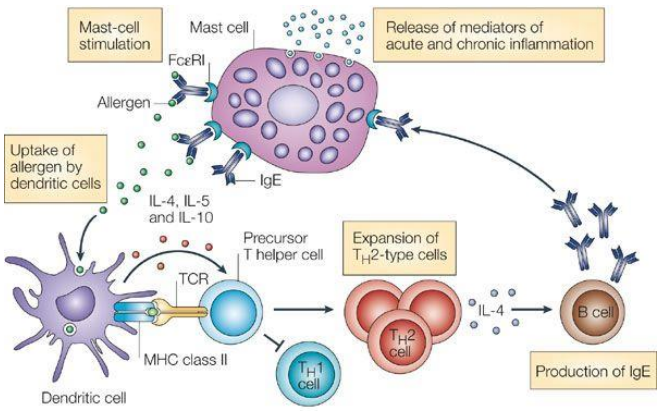


Figure 1. Classic mechanism of atopic dermatitis. Allergens are captured by dendritic cells and presented to T cells. In the absence of microbial exposure at early stages, the balance between T helper 1 (Th1) and Th2 cells is disturbed. Th2 cells stimulate the production of immunoglobulin E (IgE) by B cells. IgE binds to the high affinity receptor in mast cells and proinflammatory molecules are released. Source: Cookson (2004).

Patients with AD often have reduced gut biodiversity, reduced levels of *Bifidobacterium* and fewer short-chain fatty acids (SCFA), with reductions in particular in acetate, propionate, and butyrate levels, which take part in keeping the integrity of the epithelial barrier and pose anti-inflammatory effects
[17–19] (fig 2). Several studies based on murine and in vitro models, have highlighted the potential role of *Bifidobacterium* in reducing inflammation by the production of anti-inflammatory cytokines and suppressing Th2 immune response and IgE production [4-6]. Moreover, significantly higher levels of *Bifidobacterium longum* were isolated in healthy children (30%) vs allergic children (11%), suggestive of a protective effect in healthy children, not presenting with allergic dermatitis. [7]

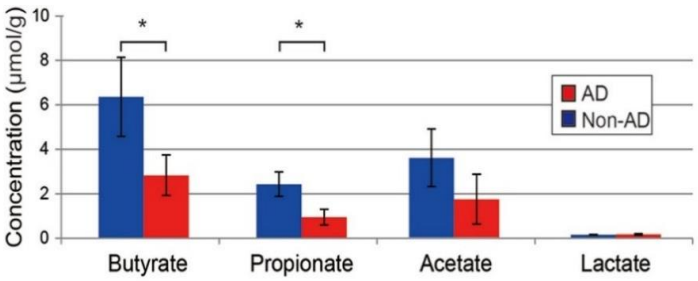


Figure 2. Reduction of the concentration of butyrate and propionate in faecal samples of patients with AD. Samples were obtained from 90 patients with AD and 42 control individuals. Source: Song *et al* (2016).

Butyrate, for example, is a primary energy source for colonocytes and also maintains intestinal homeostasis through anti-inflammatory actions [20], while propionate has an antiallergic effect, since it decreases the ability of dendritic cells to cause allergic inflammation mediated by Th2 cells [21].

Other studies, such as West et al. (2015) demonstrated that a lower relative abundance of potentially immunomodulatory intestinal bacteria, such as Bifidobacteria, is associated with exaggerated responses of inflammatory cytokines to TLR ligands and the subsequent development of eczema associated with IgE [22].

Therefore, and as a summary we can say that intestinal dysbiosis caused by a low colonization by butyrate and propionate producers, together with an increase in pathogenic bacteria causes a weakening of the intestinal barrier, which may result in a leaky gut and a translocation of toxins, allergens and bacteria to the bloodstream. This may then cause an inappropriate chronic stimulation of the Th2-mediated immune system (fig 3).

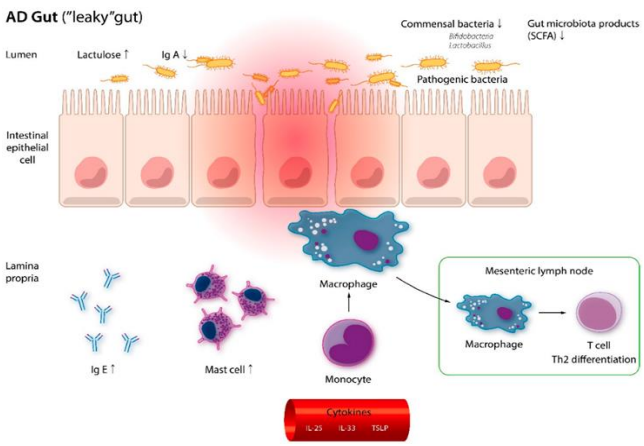


Figure 3. Mucosal barrier disruption in AD. Patients with AD seen to have dysbiosis and less short-chain fatty acids (SCFAs) in the gut. In response to pro-inflammatory cytokines, monocytes migrate and differentiate into macrophages. Greater access to luminal antigen also causes T cells to transform into Th2 cells in the draining lymph nodes. Source: Kim (2018).

What is the importance of Bifidobacterium in Atopic Dermatitis?

Bifidobacterium spp. may be beneficial for human health due to several effects such as vitamin production, immune system stimulation, inhibition of potentially pathogenic bacteria or improved food digestion [23,24]. In the context of allergic diseases, several studies based on murine and in vitro models, have highlighted the potential role of Bifidobacterium in reducing inflammation by the production of anti-inflammatory cytokines and suppressing Th2 immune response and IgE production [25–27]. The absence or lower levels of *Bifidobacterium* in AD children has been observed in several studies [18,28,29] and could lead to a lack of anti-inflammatory effects. For example, significantly higher levels of *Bifidobacterium longum* were isolated in healthy children (30%) vs allergic children (11%), suggestive of a protective effect in healthy children, not presenting with allergic dermatitis [30].

In summary, the importance of Bifidobacteria in relation to atopic dermatitis is due to:

1) Reduce the severity of AD by inhibiting the T-helper cell type-2 (Th2) mediated response and improving the Th1/Th2 ratio [31].

2) Reduce inflammation by reducing proinflammatory cytokines and stimulates the secretion of IL-10 (anti-inflammatory cytokine) [32].

3) Produces short-chain fatty acids (SCFA), which are associated with lower intestinal permeability and maintaining the integrity of the intestinal barrier [32].

4) Bifidobacteria promote the growth of butyrate producers by simultaneously releasing acetate in addition to lactate (normal fermentation end-product).

5) Bifidobacteria produces acids such as lactic acid and acetic acid, which off-set the growth of harmful bacteria, and help to regulate the intestinal environment. It is known that acetic acid is stronger against Gram-negative bacteria than lactic acid, and that acetic acid is produced in greater amounts by bifidobacteria [33].

Rationale for AD consortia

After collecting all the information on the influence of the microbiome on atopic dermatitis and its etiology, the ADM-Biopolis scientific team designed a product that is composed of a mixture of 3 strains (*B. longum* subsp. *longum* CECT 7347, *B. animalis* subsp. *lactis* CECT8145 and *Lactobacillus casei* CECT 9104). All of them have been evaluated for food safety according to WHO guidelines, including the sequencing of their genome and the study of potentially harmful genes.

ADM-Biopolis presents a mixture of probiotics for which there is human clinical trial evidence of benefit in relation to factors in the gut that are linked to AD. The Clinical trial results have been published in JAMA Dermatology (Impact factor: 7.99), the highest-ranking dermatology journal in the world.

This bacterial consortium has been specifically designed to promote:

1) Anti-inflammatory activity in the intestine

2) Supporting protection of the intestinal barrier

3) An antioxidant activity

4) A modulating effect of the microbiota to restore intestinal homeostasis

Rationale for AD consortia

1) Anti-inflammatory capacity

Bifidobacterium longum CECT 7347 strain has been fully characterized in in vitro murine models and its properties tested in clinical trials. The results have been published in several scientific journals. The main results of *B*. *longum* CECT 7347 strain in terms of its anti-inflammatory capacity are:

1) *B*. *longum* CECT 7347 reversed the proinflammatory cytokine profile (TNF-α y IFN-γ) induced by the altered microbiota of the feces of children with celiac disease in peripheral blood mononuclear cells [34].

2) *B. longum* CECT 7347 shown to induce the expression of the anti-inflammatory cytokine IL-10, that inhibits the production of Th1 proinflammatory cytokines and particularly IFN-γ and TNF-α
[34].

3) *B. longum* CECT 7347 also increased the level of IL-10 and reduced the levels of the inflammation promoter TNF-α and CD4 + T lymphocytes in newborn rats with enteropathy generated by gliadin [35].

2) Supporting protection of the intestinal barrier

B. longum CECT 7347 potential for protective effects in newborn rats with enteropathy generated by gliadin, increased significantly the width of the villi of the intestine and the height of the enterocytes compared to the group without probiotic [35].

3) Antioxidant capacity

Oxidative stress is involved in atopic dermatitis (fig 4) as it increases during AD exacerbation and AD patients have a decreased antioxidant capacity [36]. Moreover, cytokines, lipopolysaccharide (LPS) and Reactive Oxygen Species (ROS) can disrupt the tight junctions and compromise the barrier function of the intestinal epithelium, increasing the gut permeability. Thus, if the probiotic contributes to a decrease in oxidative stress and inflammation this may improve tight junction protein expression, as occludins and caderins and thus to restoration of barrier function [37].

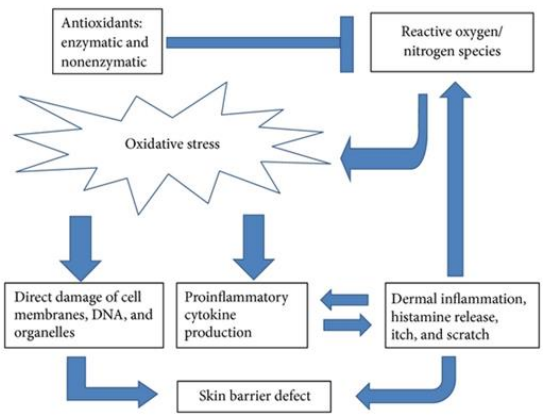


Figure 4. Interaction between oxidative stress, skin barrier defect and inflammation in atopic dermatitis. Source: Ji and Li (2016)

Rationale for AD consortia

1) *Bifidobacterium lactis* CECT 8145 shown to significantly increase the survival of the *Caenhorabditis elegans* model organism by more than 30% under oxidative stress and decrease oxidative stress markers levels, such as oxidized glutathione (GSSG) compared to control without the strain [38].

2) *Bifidobacterium lactis* CECT 8145 reduced levels of malondialdehyde (MDA) in blood, a marker of oxidative stress, in a murine model of genetic obesity and high levels of oxidative stress [39].

4) Modulating effect of the microbiota to restore intestinal homeostasis

1) *B. longum* CECT 7347 decreased significantly *Bacteroides fragilis* levels in feces compared to placebo after 3 months of treatment in newly diagnosed children with celiac disease, demonstrating modulation of the intestinal ecosystem by decreasing the load of harmful bacteria [40].

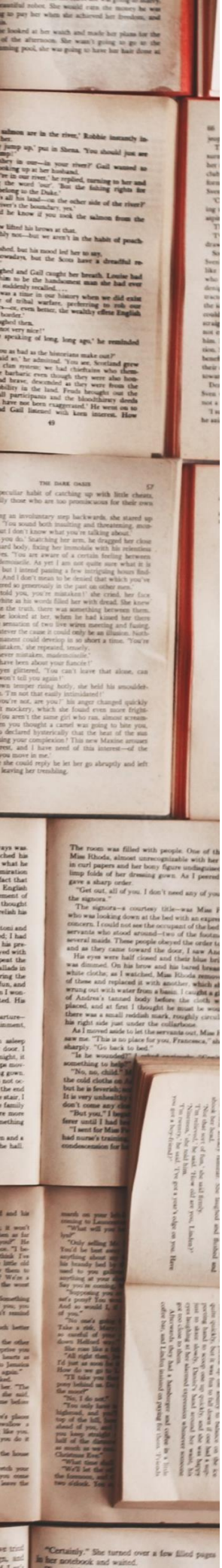
2) After treatment with a mixture of the 3 strains (*B. longum* subsp. *longum* CECT 7347, *B. animalis* subsp. *lactis* CECT8145 and *Lactobacillus casei* CECT 9104) in children with AD, dysbiosis was reverted, with an increase in *Bacteroides*, *Ruminococcus* and *Bifidobacterium*, and lower *Faecalibacterium* levels, compared to placebo (manuscript in preparation).

Summary

1) Certain imbalances in the gut, such as intestinal permeability or dysbiosis can trigger an exacerbated Th2 immune response, key factor in AD.

2) A reduced biodiversity and low levels of *Bifidobacterium* in the gut has been observed in AD patients. Conversely, significantly higher levels of *Bifidobacterium longum* are isolated from healthy children compared to children with allergic dermatitis.

4) ADM Biopolis has designed a probiotic blend focused on AD targets, selected strains were chosen based on their anti-inflammatory and antioxidant properties and their effects on intestinal homeostasis. All these capacities have been tested, demonstrated and published in scientific journals.



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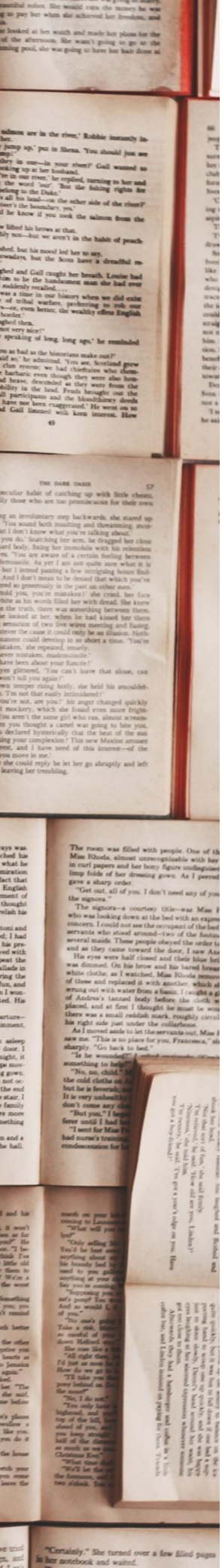

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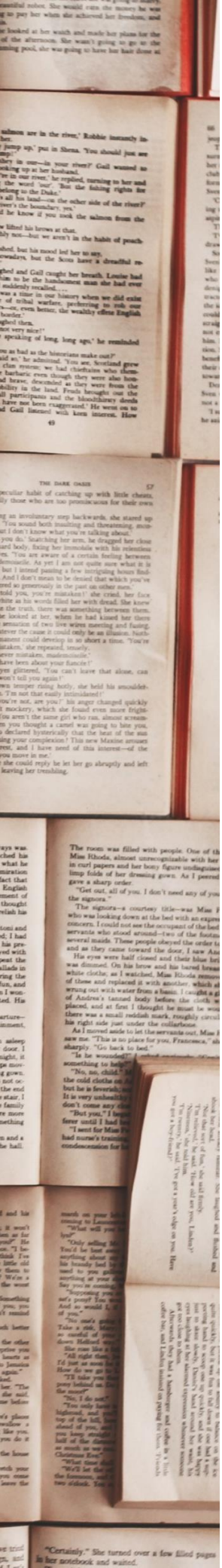

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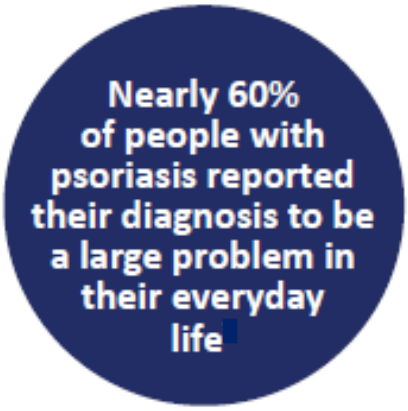
PSORIASIS

Skin Solutions That are More Than Skin Deep

Currently the mainstay of treatment for psoriasis is symptomatic management with topical and systemic pharmacological interventions. Phototherapy also shows benefits for many patients. However the need for treatment is often lifelong.

Consumers are increasingly taking an active interest in their own health and wellbeing. No longer is symptom management left solely to health professionals. Patients now actively seek their own solutions to everyday health and wellness conditions.



ADM

Psoriasis:

A Cutting-Edge Probiotic Blend

ADM's researched formulation is composed of 3 probiotic strains:

ES1 : *Bifidobacterium longum* CECT 7347
BPL1 : *Bifidobacterium lactis* CECT 8145
BPL15 : *Lactobacillus rhamnosus* CECT 8361

This blend has been designed to address a number of the common features associated with psoriasis. These bacterial strains demonstrated anti-inflammatory effects, antioxidant activity and an ability to ameliorate factors associated with the intestinal barrier.

The Clinical Evidence Consists of:

A randomized double-blind, placebo-controlled clinical trial

Women and men aged between 18 and 70 with mild or moderate plaque psoriasis were selected

Intervention: The ADM 3-strain formulation with a total of 1×10^9 colony-forming units (CFU) per capsule once daily for 12 weeks

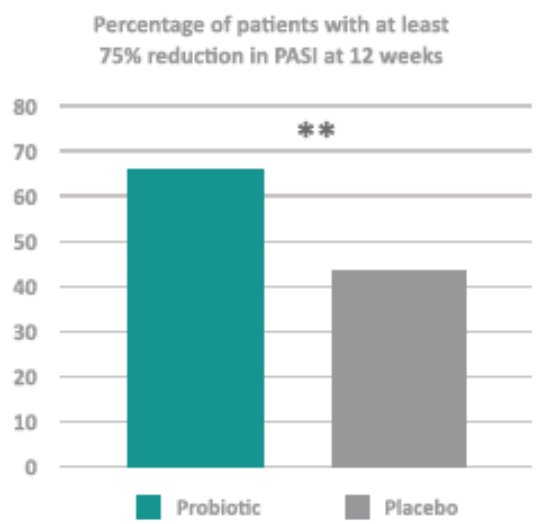
Two outcomes were evaluated to determine clinical response: Psoriasis Area and Severity Index (PASI) and Physician Global Assessment (PGA)

Benefits, Backed by Science

CHANGES IN PSORIASIS AREA AND SEVERITY INDEX (PASI):

A total of 66.7 % of participants taking the psoriasis blend showed significant reduction in PASI index of at least 75% compared to 41.9% in the control group at 12 weeks (p= 0.0317).

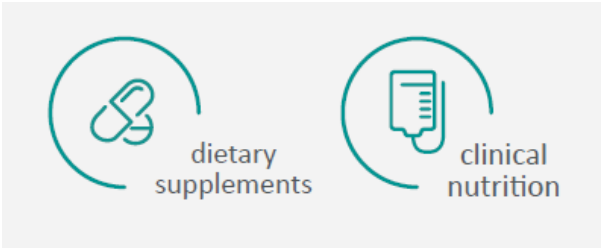
- The decrease seen in the probiotic group was statistically significant when compared to placebo at 6 and 12 weeks.
- At 12 weeks 91% of subjects in the intervention group had a PASI <6 (and therefore no prescription of steroids was necessary, as per the trial protocol) vs 77% in the control group (p= 0.083).



More Applications. More Benefits

ADM has a long history of conducting proprietary microbiome research, with an extensive library of pre-clinical and clinical trials to support our growing range of cutting-edge microbiome solutions.

Our blend is the choice ingredient to integrate into dietary supplements or nutritional products targeting the skin. It comes in a bulk powder format and is designed for supplements, excipients, infant and clinical nutrition. It has a shelf life of 18-months:



CLAIMS AND CERTIFICATIONS

- FDA Approved
- EU Approved
- GRAS
- Non-GMO
- Organic
- HALAL
- Clean Label
- Gluten Free
- Kosher

Introduction

Dysbiosis of both the gut and skin microbiome has been associated with psoriasis. Additionally, dysbiosis of the gut microbiota may contribute to the development of a leaky gut, facilitating bacterial translocation, which may act as a driving force of the inflammatory response. Furthermore, evidence is accumulating that suggests a link between the gut and skin, namely the gut-skin axis (1). It may be possible that dysbiosis of the gut microbiome may alter systemic immunity, resulting in dyshomeostasis and impaired functioning of the skin (Fig 1):

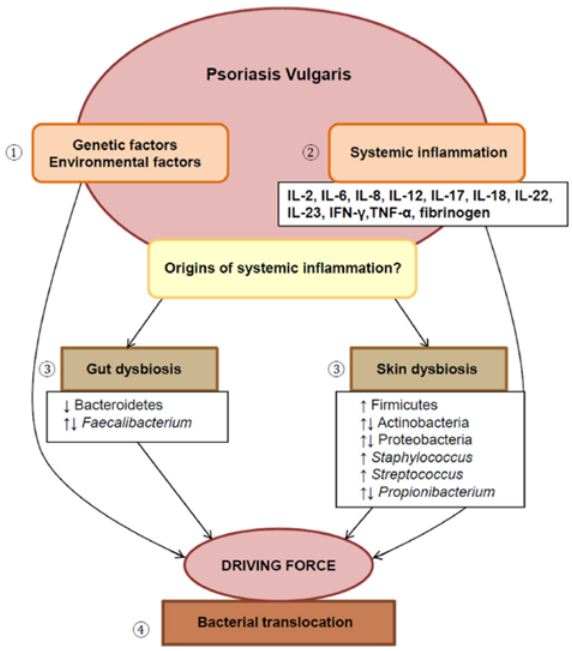


FIGURE 1 | An overview of this paper. (1) The etiology of PV involves complex interplay between genetic and environmental factors. (2) This disease displays localized as well as systemic inflammation, reflected by the presence of various dysregulated inflammatory markers. (3) Dysbiosis of both the gut and skin microbiome are suggested as possible drivers of chronic systemic inflammation, (4) by facilitating the translocation of bacteria from these sites into systemic circulation. IL, interleukin; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor-alpha.

ADM-Biopolis scientific team designed a probiotic blend that is composed of a mixture of 3 strains (*B. longum* CECT 7347, *B. lactis* CECT 8145 and *Lactobacillus rhamnosus* CECT 8145). All of them have been evaluated for food safety according to WHO guidelines, including the sequencing of their genome and the study of potentially harmful genes.

This bacterial consortium has been specifically designed to promote

1) Anti-inflammatory activity in the intestine

2) Supporting protection of the intestinal barrier

3) An antioxidant activity

Targets of therapeutic value for psoriasis

1) Anti-inflammatory capacity

Bifidobacterium longum CECT 7347 strain has been fully characterized in in vitro murine models and its properties tested in clinical trials. The results have been published in several scientific journals. The main results of *B. longum* CECT 7347 strain in terms of its anti-inflammatory capacity are:

- *B. longum* CECT 7347 reversed the proinflammatory cytokine profile (TNF-α y IFN-γ) induced by the altered microbiota of the feces of children with celiac disease in peripheral blood mononuclear cells [2].
- *B. longum* CECT 7347 induced the expression of the anti-inflammatory cytokine IL-10, that inhibits the production of Th1 proinflammatory cytokines and particularly IFN-γ and TNF-α [2].
- *B. longum* CECT 7347 also increased the level of IL-10 and reduces the levels of the inflammation promoter TNF-α and CD4 + T lymphocytes in newborn rats with enteropathy generated by gliadin [3].

2) Supporting protection of the intestinal barrier

Bacterial DNA translocation (BT) in blood samples has recently been described in patients with psoriasis. These circulating bacterial DNA in blood could originate from intestinal lumen. This indicates the potential role played by healthy intestinal bacterial composition in reducing intestinal permeability and the risk of BT [4]. Psoriasis is a disease characterized by a leaky gut and the comorbidities of this disease are due to systemic endotoxemia. For this reason a key element of our bacterial consortia is to promote factors associated with maintaining the barrier function of the intestine:

- *B. longum* CECT 7347 exerted protective effects in newborn rats with enteropathy: generated by gliadin, increased significantly the width of the villi of the intestine and the height of the enterocytes compared to the group without probiotic [3]

Targets of therapeutic value for psoriasis

3) Antioxidant capacity

Oxidative stress has been demonstrated to be implicated in the pathogenesis of psoriasis. External detrimental agents such as cigarette smoking, air pollution, physical damage as well as biological agents (virus, bacteria etc.) could trigger damage to keratinocytes. Consequently, the breach in skin cell membranes lead to the release of inflammatory mediators and alarmins. These signals sustaining inflammation lead in turn to the growth of ROS generations creating a vicious cycle fundamental in psoriasis pathogenesis [5] (Fig 2).

Moreover, cytokines, lipopolysaccharide (LPS) and Reactive Oxygen Species (ROS) can disrupt the tight junctions and compromise the barrier function of the intestinal epithelium, increasing gut permeability. Thus, if the probiotic contributes to a decrease in oxidative stress and inflammation this may improve tight junction protein expression, as occludins and caderins and thus to restoration of barrier function [6].

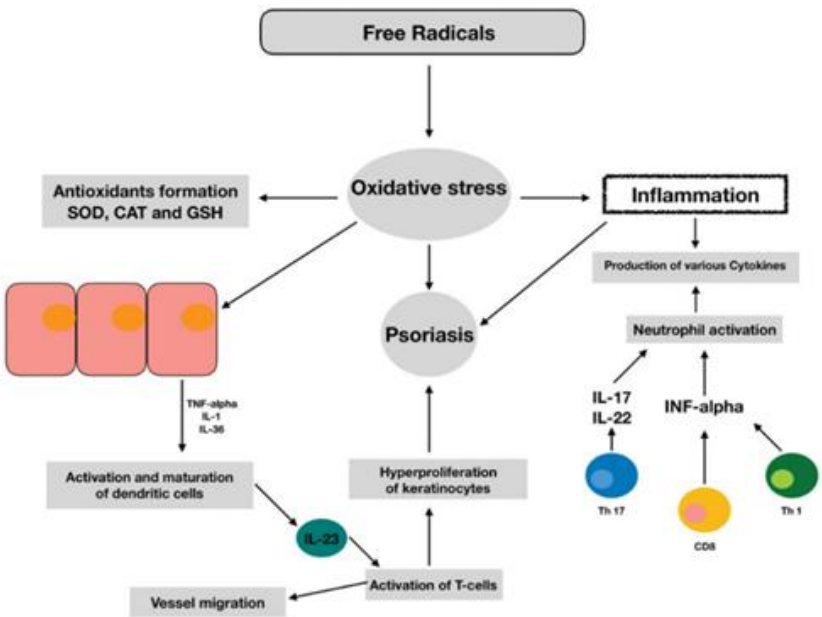
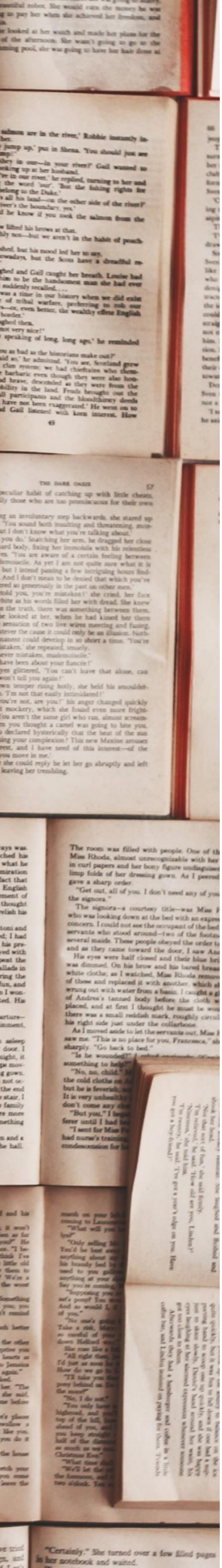


Fig 2: Pathophysiological model of the self-sustaining inflammatory processes typical of Psoriasis with the central role played by oxidative stress (Source: Cannavò et al. 2019).

- *Bifidobacterium lactis* CECT 8145 significantly increased the survival of the *Caenhorabditis elegans* model organism by more than 30% under oxidative stress and decreased oxidative stress markers levels, such as oxidized glutathione (GSSG) compared to control without the strain [7].
- *Bifidobacterium lactis* CECT 8145 reduced levels of malondialdehyde (MDA) in blood, a marker of oxidative stress, in a murine model of genetic obesity and high levels of oxidative stress [8].
- *L. rhamnosus* CECT 8361 and *B. longum* CECT 7347 have a clear antioxidant activity, reduced DNA fragmentation, and decreased intracellular H2O2 in humans [9].



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