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1 Review

2 **Functional Role of Probiotics and Prebiotics on Skin**
3 **Health and Disease**4 **Vasiliki Lolou and Mihalis I. Panayiotidis ***5 ¹ Department of Applied Sciences, Northumbria University, Newcastle Upon Tyne, NE1 8ST, UK;
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9 **Abstract:** Scientific and commercial interest on probiotics, prebiotics and their effect on human health
10 and disease has increased in the last decade. The aim of this review article is to evaluate the role of
11 pro- and prebiotics on the normal function of healthy skin as well as their role in the prevention and
12 therapy of skin disease. *Lactobacilli* and *Bifidobacterium* are the most commonly used probiotics and
13 thought to mediate skin inflammation, treat atopic dermatitis (AD) and prevent allergic contact
14 dermatitis (ACD). Probiotics are shown to decolonise skin pathogens (e.g., *P. aeruginosa*, *S. aureus*, *A.*
15 *Vulgaris*, etc.) while kefir is also shown to support the immunity of the skin and treat skin pathogens
16 through the production of antimicrobial substances and prebiotics. Finally, prebiotics (e.g., Fructo-
17 oligosaccharides, galacto-oligosaccharides and konjac glucomannan hydrolysates) can contribute to
18 the treatment of diseases including ACD, acne and photo aging primarily by enhancing the growth
19 of probiotics.

20 **Keywords:** probiotics; prebiotics; skin health; skin disease; dermatitis; skin infections

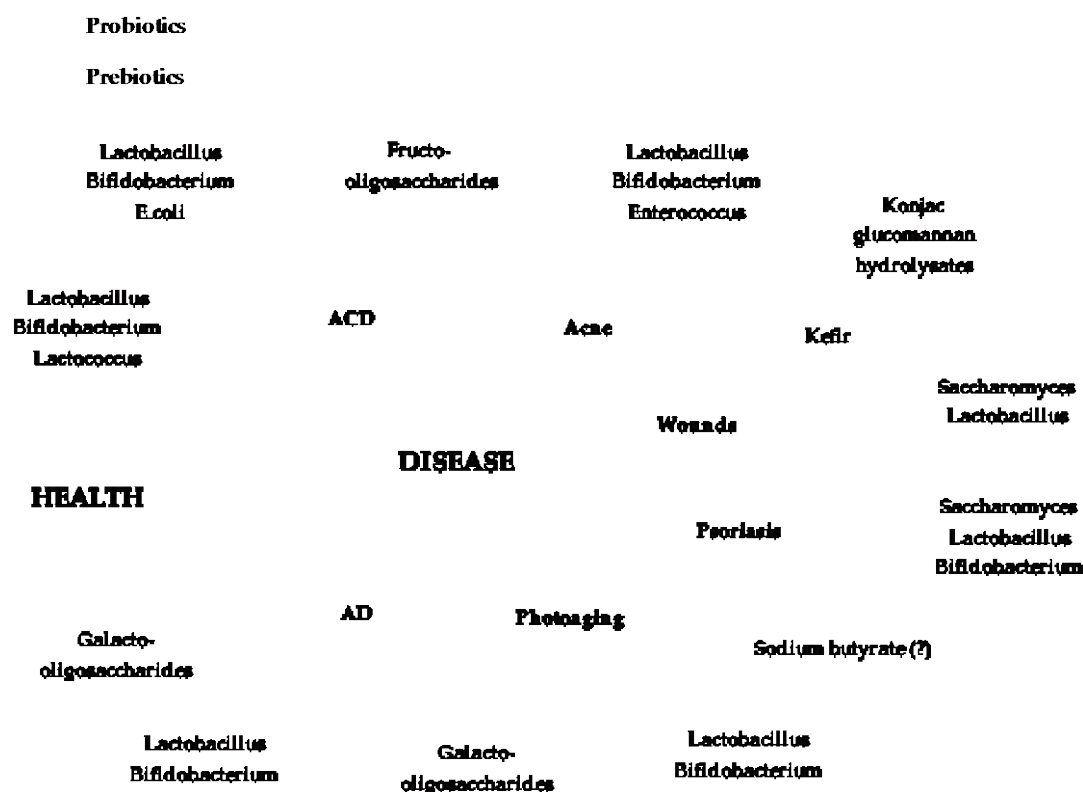
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23 **1. Introduction**

24 Fermented food has been part of our diet, in addition of being used for therapeutic purposes, as
25 early as 7000 BC from Egyptians, Greeks and Italians [1,2,3]. Some of the most ancient fermented
26 foods used in history is wine, bread and milk products such as yoghurt. In fact, it is documented that
27 Georgians were using wine in their diet back at 6000 BC, whilst fermented dairy products were used
28 for the treatment of diarrhea and other gastroenteric infections [4,5]. The relationship between human
29 health and microbiota was first mentioned in 1907, by Elie Metchnikoff, when the enhanced longevity
30 due to the intentionally present bacteria in yogurt was described [6]. In addition, fermented food
31 became famous after Werner Kollath first introduced the term "Probiotic". Food industry started
32 using probiotics in their products as an aiding ingredient and/or as a preservative means since 1989
33 [7]. With the evolution on food processing and preservation and the consumer's interest for a
34 healthier and more balanced diet, probiotics became one of the most marketable ingredients.
35 According to the World Health Organization (WHO), probiotics are live microorganisms that "when
36 administered in adequate amounts, confer a health benefit on the host" [8]. Most common species of
37 probiotics belong in the families of *Lactobacillus*, *Bifidobacterium* and *Streptococcus* [9] with the first two
38 families being mostly used in studies related to human health [10]. As these microorganisms are
39 naturally found in the gut microbiota, most studies are focused on their effects in the context of the
40 natural function in the gut and as preventive or therapeutic agents against disease development [11–
41 18]. To this end, probiotics have been used for the study and treatment of intestinal diseases such as
42 gastroenteritis [19], intestinal hyperpermeability [20], urinary tract infection [21], intestinal dysbiosis
43 [22], irritable bowel syndrome [23], Crohn's disease [24], colon cancer [25,26], ulcerative colitis [27,28]
44 and peptic ulcer [23]. In particular, many studies have shown their involvement in regulating
45 signaling molecules like NFκB, MAPK, PPARγ, HSP, etc. by either activating or inhibiting their

46 expression profile depending on the microorganism studied. Such effect(s), in turn, can trigger other
 47 signaling events including perturbations in the i) phosphorylation content of I κ B α , ii) activation
 48 status of p38, iii) inhibition of nuclear binding by p65 as well as iv) induction of PPAR γ mRNA levels
 49 [29–61]. In addition, probiotics have been extensively utilized in the context of intervention studies
 50 towards prevention and/or treatment of a number of human diseases including those of the skin like
 51 atopic dermatitis [AD] [62–69], allergic rhinitis [66,70,71] and wound healing [72–79] being some of
 52 the major ones (Figure 1).
 53



54
 55 **Figure 1.** The role of probiotics and prebiotics on skin health and disease including Allergic Contact
 56 Dermatitis (ACD), Acne, Wounds, Psoriasis, Photoaging and Atopic Dermatitis (AD).

57 On the other hand, with the term “prebiotics” we refer to specific fermented components that
 58 enhance changes in the composition and the activity of the gut microflora in favor to the host [80].
 59 Prebiotics are characterized by low dosage activity, absence of side effects and persistence through
 60 the gut [81]. The most commonly known prebiotics are oligosaccharides (OS; e.g., glycans), fructans
 61 (inulin-type), sugar alcohols and complex polysaccharides (e.g., β -glucans, cellulose) [82,83]. The
 62 available literature on prebiotics and their effect on human health is limited, compared to the
 63 probiotics, and it is often included in several probiotic studies. These non-digestible compounds are
 64 known for their bifidogenic effect, which varies depending on the type of prebiotic. This is based on
 65 the fact that long-chain OS are fermented in the entire gut whereas the short-chain ones are only
 66 processed in the ascending colon and the caecum. Breast milk mostly consists of prebiotic OS and as
 67 being the first food for infants; it provides the initial intestinal microbiota whose growth is supported
 68 by these OS. Furthermore, recent studies have shown the ability of prebiotics to enhance calcium
 69 absorption and have an effect on bone structure as well [82]. Moreover, these compounds are shown
 70 to affect the immune system by increasing IgA, CD4+ cells, INF- γ and IL-4 in spleen and mesenteric
 71 lymph nodes [84,85,86]. Additionally, other studies on healthy participants have shown a decrease
 72 of toxic fermentation metabolites in the colon (e.g., [H₄] tyrosine and lactose-[N]ureide) after
 73 consumption of pro- (e.g., *L. casei*) and prebiotics (e.g., n9; lactulose) [87].

74 Finally, the skin represents the largest organ in the human body and as such, its main function
75 is to act as a barrier to extrinsic factors including physical, chemical and microbial threats. In this
76 context, a strong symbiotic relationship between microorganisms exists that constitutes its
77 microbiota. This natural microflora supports the immune system by various ways including the
78 production of natural antimicrobial compounds (e.g., lactic acid) as well as activation of various
79 signaling pathways and modulation of the inflammatory response [88,89]. In this review article, we
80 aim to focus on the beneficial role of pro- and prebiotics on skin health as well as their therapeutic
81 and/or preventive role on specific skin diseases.

82 2. Probiotics and Prebiotics on Skin Health

83 There is a rather small number of studies on healthy subjects to show a beneficial effect of
84 probiotics on skin health (Figure 1) [18,61,90,91,92]. In one such study, when the *L. lactis* strain; H61
85 was supplemented on middle-aged women, daily for 8 weeks, an improvement on skin elasticity and
86 body characteristics were observed (e.g., skin appeared more hydrated and the hair follicles had
87 improved) [92]. Similarly, in another such study, oral intakes of *L. plantarum*; HY7714 from a group
88 of subjects aged 41-59 years old also confirmed the effect of probiotics on increasing skin moisture,
89 decreasing the depth of existing wrinkles and improving the overall skin gloss and elasticity [61].
90 Moreover, other studies have shown that when probiotic and para-probiotic *L. reuteri* were
91 administered orally, for 12 weeks, an increase in melanin and a decrease in Trans-Epidermal Water
92 Loss (TEWL) were observed [91]. Such effects are in agreement with studies utilizing other probiotics
93 (e.g., *L. rhamnosus*, *B. breve* Strain Yakult, *L. lactis*, *S. thermophilus*) and prebiotics (e.g., galacto-
94 oligosaccharides; GOS) (Figure 1) all of which have indicated i) improved levels of skin hydration
95 and cathepsin-L-like activity levels (an indicator of keratinocyte differentiation and a marker of skin
96 barrier function) as well as ii) reduced urine and serum phenol levels (e.g., toxic by-products formed
97 by gut bacteria) [90,93].

98 3. Probiotics and Prebiotics on Skin Disease

99 3.1. Dermatitis

100 3.1.1. Atopic Dermatitis

101 Atopic Dermatitis (AD), also known as atopic eczema, is a skin inflammatory disease that is
102 observed in early stages of life and is linked with allergic rhinitis, food allergies and asthma all of
103 which are more prevalent in children suffering from this disease. One of the most common symptoms
104 of eczema, apart from itchiness, is the reduction of barrier function that leads to allergen exposure
105 and overall reduction of the TEWL, leading to dry skin [94]. In an AD model, allergens can penetrate
106 the stratum corneum, which is altered by the epidermal epithelium deformities. Moreover, symptoms
107 include the presence of pathogenic microorganisms, such as *S. aureus*, that colonize and infect the
108 subjects. Another significant aspect of AD is its relationship with the gut microbiota. More
109 specifically, the balanced microbial profile of the mucosa can promote the production of
110 immunoglobulin A (IgA) which supports the defensive mechanisms of the gut membrane, whilst
111 enhances the expression of the Transforming Growth Factor (TGF) [95]. A relationship between the
112 gut microflora and the development of AD was also observed in infants at high risk for developing
113 AD showing an increased number of clostridia compared to control, disease free infants [96].

114 Specific probiotic microorganisms are shown to have a preventing role on AD and mediate the
115 symptoms of the disease (Figure 1). They appear to do so by influencing a number of biological
116 processes not only in AD but rather in a wide range of skin diseases (e.g., acne, psoriasis, photo aging,
117 wounds, etc.) (Table 1 and Figure 2). More specifically, in a recent study, supplementation with *L.*
118 *rhamnosus* in combination with *L. reuteri* improved the severity of eczema by 56% in children suffering
119 from AD [65]. Moreover, in another study, *L. rhamnosus* was utilized as a supplemented probiotic, to
120 women 4 weeks before delivery and 6 months postnatal, demonstrating to significantly reduce the
121 risk of children developing AD during their first 7 years of age [66]. Finally, when infants at high risk

122 of developing AD were supplemented with a mix of probiotic microorganisms (e.g., *L. acidophilus*, *B.*
 123 *bifidum* and *B. lactis*), during pregnancy and after birth, they showed a reduction of immunoglobulin
 124 E (Ig-E) associated eczema by 40% [62].

125 **Table 1.** Probiotics and their effect on skin diseases.

Probiotics	Disease	Function	Reference
<i>L. rhamnosus</i>	AD ¹	Improvement of severity of eczema, reduction of risk of AD development in infants, reduction of Ig-E ²	[65,66,112]
<i>L. reuteri</i>	AD Infections (<i>S.aureus</i>)	Improvement of eczema. Blocks integrin, Reduces cell death due to <i>S. aureus</i> infection	[65,112]
<i>L. delbrueckii subspecies bulgaricus</i>	Acne	Improvement of Acne symptoms (Acne Vulgaris)	[125]
<i>L. sporogenes</i>	Psoriasis	Improvement of symptoms, reduction of blood sugar levels and fever	[135]
<i>L. plantarum</i>	Photoaging	Inhibition of MMP-1, MMP-2, MMP-9 and MMP-13 ³ , enhancement of procollagen expression, inhibition of phosphorylation of Jun N-terminal kinase, increase of palmitoytransferase mRNA levels, decrease of ceramide mRNA levels, reduction of wrinkles and epidermal thickness	[145,146]
<i>L. fermentum</i>	Infections (wounds)	Production of gNO ⁴ , increases productions of IL-1 and TGF-β ⁵ cytokines	[113,114]
<i>L. acidophilus</i>	AD ACD ⁷ Infections (<i>S.aureus</i>) Acne	Reduction of Ig-E, reduction of eczema, Increase of TGF-β, Foxp3 ⁸ , IFN-γ ⁹ and IL-10 ¹⁰ expression, Inhibition of <i>S. aureus</i> infection, reduction of acne symptoms	[62,103,111,125]
<i>L. casei</i> <i>L. salivarius</i>	ACD Infections (MRSA) ¹¹	Reduction of skin inflammation, inhibition of IFN-γ, CD8 ⁺ T cells, increase in IL-10 production, activation of CD4 ⁺ CD25 ⁺ T cells, inhibition of MRSA	[100,101,111]

<i>B. bifidum</i>	AD Acne	Reduction of Ig-E, reduction of development of AD in infants, reduction of Acne Vulgaris symptoms	[62,125]
<i>B. lactis</i>	AD	Reduction of Ig-E, reduction of development of AD in infants.	[62]
<i>B. pseudolongum</i>	ACD	Reduction of allergic reaction on mice	[104]
<i>B. longum</i>	Photoaging	Prevention of TEWL ¹² , reduction of skin erythema, increase of mRNA expression of CD44, TIMP-1 and Col1.	[147]
<i>B. breve strain Yakult</i>	Photoaging	Prevention of loss of elasticity, suppression of elastase, activation of IL-1 β	[143,144]
<i>B. infantis</i>	Psoriasis	Reduction of plasma TNF- α , increase of IL-6	[136]
<i>S. epidermidis</i>	Acne	Growth inhibition of Propionibacterium acnes and Acne Vulgaris by competitive exclusion	[126]
<i>E. faecalis</i>	Acne	Reduction of inflammation areas, production of bacteriocins	[127]
<i>E. coli Nissle 1917</i>	ACD	Increase of TGF- β , Foxp3, IFN- γ and IL-10 expression	[102]
Kefir grains	Infections	Production of antimicrobial substances (lactic acid, acetic acid, hydrogen peroxide, bacteriocins), Healing of <i>P. aeruginosa</i> infected wounds, Inhibition of <i>S. aureus</i> , <i>S. salivarius</i> , <i>S. pyogenes</i> , <i>P. aeruginosa</i> , <i>C. albicans</i> , <i>S. tympimurium</i> , <i>L. monocytogenes</i> and <i>E. coli</i> growth	[122,124]

126 ¹Atopic Dermatitis; ²Immunoglobulin E; ³Matrix Metalloproteinases (MMPs)-1,-2,-9,-13; ⁴Nitric Oxide;
 127 ⁵Interleukin 1; ⁶Transforming Growth Factor β ; ⁷Allergic Contact Dermatitis; ⁸Forkhead box P3; ⁹Interferon
 128 gamma; ¹⁰Interleukin 10; ¹¹Methicilin Resistant *Staphylococcus aureus*; ¹²Trans Epidermal Water Loss; ¹³Tissue
 129 inhibitor of metalloproteinases 1; ¹⁴Collagen 1; ¹⁵Tumor Necrosis Factor.



130

131 *Figure 2.* Linkage of various skin diseases with their respective mode of action through which pro-
 132 and prebiotics exert a beneficial effect. Methicilin Resistant Staphylococcus aureus (MRSA); Trans
 133 Epidermal Water Loss (TEWL).

134 3.1.2. Allergic Contact Dermatitis

135 Allergic contact dermatitis (ACD), also known as eczema, is caused after the skin comes in
 136 contact with an allergenic substance capable of causing an allergic reaction. Symptoms vary but
 137 include skin inflammation, itchiness, dry skin, blisters, etc. The allergic reaction is regulated by CD4⁺
 138 T cells in a manner where peptides derived from allergens activate Th2-type cytokines (produced by
 139 these CD4⁺ T lymphocytes) including interleukins 4, 5 and 13 [99]. Overall, pro- and prebiotics are
 140 shown to have a preventing role on ACD and consequently mediate its symptoms (Figure 1).

141 *L. casei* is found to reduce skin inflammation either by targeting the inhibition of INF-γ
 142 (responsible in producing CD8⁺ effector T cells) [100] or via mechanisms that include the involvement
 143 of regulatory CD4⁺ T cells [101]. In addition, the microorganism has also been shown to increase the
 144 production of IL-10 by promoting the activation of CD⁺4CD25⁺ Tregs thus further supporting its
 145 specific mode of action against skin inflammation [101] (Table 1 and Figure 2). On the other hand, *E.*
 146 *coli* Nissle 1917 (EcN) is another probiotic microorganism shown to prevent ACD by means of
 147 increasing the number of Foxp3⁺ cells (suppress antigen priming of lymphocytes) as well as the
 148 expression of TGF-β, IFN-γ and IL-10 (regulatory cytokine network) thus suggesting an
 149 immunomodulatory function against allergen-induced dermatitis [102] (Table 1 and Figure 2).
 150 Similar observations were made in the case of the para-probiotic *L. acidophilus* strain L-92 which was

151 also shown to induce the activation of CD⁴CD25⁺3⁺ Tregs and consequently suppress ACD [103]
 152 (Table 1 and Figure 2).

153 Finally, in another study, consumption of the prebiotic fructo-oligosaccharide resulted in
 154 suppressed skin inflammation due to a favorable change in the population of the intestinal microbiota
 155 by means of increasing the population of *B. pseudolongum*. This, in turn, has led to reduced contact
 156 hypersensitivity associated with proliferation of *B. pseudolongum* in the intestinal tract of the mice
 157 [104] (Table 2).

158

Table 2. Prebiotics and their effect on skin disease.

Prebiotics	Disease	Function	Reference
Fructo-oligosaccharides	ACD	Reduction of allergic reaction.	[104]
Konjac glucomannan hydrolysates (GMH)	Acne	Inhibition of Acne Vulgaris and P. acnes, growth enhancement of lactic acid bacteria.	[128,129]
Galacto-oligosaccharides	Photoaging	Prevention of ¹ TEWL, reduction of skin erythema, increase of mRNA expression of CD44, ² TIMP-1 and ³ Col1.	[147]
Sodium Butyrate (?)	Psoriasis	Increases Fas, ⁴ TGF-β and p52	[138,139,140,141]
Oligo-saccharides	Photoaging	Modulation of the expression of elastase-type proteases through elastin receptors	[148,149]

159 ¹Trans Epidermal Water Loss; ²Tissue inhibitor of metalloproteinases 1; ³Collagen 1; ⁴Transforming Growth
 160 Factor β.

161 3.2. Skin Infections

162 3.2.1. Wounds

163 Most skin infections are initiated when an opening of the skin is infected with a pathogen.
 164 Briefly, when the cohesion of the skin is disrupted (either accidentally or as an effect of a disease) it
 165 forms a wound which is characterized by torn skin or by a hematoma of the tissue. In the case of a
 166 torn tissue, there are four stages descriptive of the healing process: i) stopping the blood flow to the
 167 damaged blood vessels (hemostasis); ii) initiating an inflammatory response which prevents potential
 168 pathogenic microorganisms to infect the wound and maintains the microbial balance of the skin; iii)
 169 stimulating production of growth factors causing iv) proliferation of fibroblasts and production of
 170 extracellular matrix proteins (e.g., hyaluronan and collagen) [105]. Furthermore, these stages are
 171 characterized by the involvement of other events including generation of oxidative stress [106].

172 There is a great scientific interest regarding the role of skin microflora in the process of wound
 173 healing as it has been shown that the absence of microbiota can decrease the healing time [107]. On

174 another note, wound infections result when bacteria exogenous to the wound become dominant over
175 the systemic and local factors of host resistance. Therefore, it is only when a balance is achieved
176 between bacteria and host that allows for the normal processes of wound healing to proceed [108].
177 Over the years, scientists have turned their interest to topical application of specific probiotic
178 microorganisms in order to evaluate their effectiveness in preventing wound inflammation as well
179 as improving on the speed of the healing process itself. In one such study, when burn wounds were
180 treated with *Saccharomyces cerevisiae* an overall improvement on the healing process was observed
181 [109]. More specifically, an increase in the expression levels of collagen type 1 and transcription
182 growth factor beta 1 (TGF- β 1) were observed accompanied by improved morphological and
183 biomechanical characteristics of the healing wounds [109].

184 Meticillin-resistant *Staphylococcus aureus* (MRSA) is one of the most widely known pathogens
185 with the ability to infect wounds [110]. A number of studies have shown the capacity of specific
186 probiotics (e.g., *L. acidophilus* and *L. casei*) to act as antibacterial agents against MRSA [111] (Table 1
187 and Figure 2). More specifically, the growth of the pathogen was found to be inhibited and eliminated
188 by 99% after 24h at 37°C incubation [111]. Moreover, in another study, three different probiotics (e.g.,
189 *L. reuteri*, *L. rhamnosus* and *L. salivarius*) were tested against *S. aureus* infection on epidermal
190 keratinocytes [112]. Overall, it was found that *L. reuteri* and *L. rhamnosus* (but not *L. salivarius*) reduced
191 the ability of the pathogen to induce keratinocyte cell death. This observation was directly associated
192 with the ability of *L. reuteri* to inhibit the adherence and invasion of the pathogen to keratinocytes
193 while *L. salivarius* did not. Furthermore, the degree of protection was greater in *L. reuteri* than *L.*
194 *rhamnosus* [112] (Table 1). To conclude, given that *S. aureus* adheres with the epidermal keratinocyte
195 cells via the $\alpha 5\beta 1$ integrin, it was suggested that both of the protective probiotics reduce keratinocyte
196 cell death by competitively excluding the pathogen from the integrin's binding sites on these skin
197 cells [112]. Finally, antibiotic properties of probiotics have been also documented in experimental
198 settings where wounds, infected with *S. aureus*, were treated with patches of *L. fermentum*. In these
199 experiments, it was shown an increased wound closure concomitant with production of nitric oxide
200 (gNO) induced by the probiotic [113] (Table 1 and Figure 2). In general, gNO is known to mediate
201 the process of wound healing through promoting the production of IL-1, TGF- β and cytokines all of
202 which play a major role in immune response and inflammation [114].

203 In addition, a number of other studies have focused on topical applications of kefir and other
204 fermented products because of their well-known anti-microbial and healing properties. Kefir is the
205 product of milk fermentation that contains grains characterized by specific starter cultures used in
206 the fermentation process [115]. These grains include i) *L. kefir*, ii) species of the genera *Leuconostoc*,
207 *Lactococcus* and *Acetobacter*, iii) lactose fermenting (e.g., *K. marxianus*) as well as iv) non-lactose
208 fermenting (e.g., *S. unisporus*, *S. cerevisiae* and *S. exiguous*) yeasts [115]. However, there are many more
209 microorganisms found in Kefir grains including the species *Lactobacilli*, *Streptococci*, *Lactococci*,
210 *Enterococci*, *Bacillus*, etc. The composition of kefir grains varies depending on their origin and the
211 microorganisms they contain [116]. Another aspect that can change the effect and the composition of
212 kefir is the fermentation time and conditions [117–119]. Collectively, the antimicrobial activity of kefir
213 is the result of the composition of the product that is high in lactic acid, acetic acid, hydrogen peroxide
214 and bacteriocins all of which can have an effect on the growth of pathogens [120] (Table 1 and Figure
215 1). Consequently, the complexity of the kefir grains (and kefir itself) has raised the scientific interest
216 in the context of exploring any potential effect on the growth of existing microorganisms in the
217 human body. To this end, when *B. bifidum* PRL2010 (a dominant microorganism in the human gut)
218 was cultured in the presence of kefir and/or kefiran (the polysaccharide produced by kefir), it was
219 shown that the glycans present in kefir had a beneficial role on the growth of the bacteria (perhaps
220 due to the increased transcriptional activation of genes related to the metabolisms of glycans) [121].
221 Furthermore, a few studies have documented a protective effect of kefir on the wound healing
222 process [79,120,122,123]. To this end, one of the biggest challenges in wound healing is the infection
223 of burn wounds from the antibiotic resistant pathogen *P. aeruginosa*. As a result, this pathogen is
224 responsible for complications on serious illnesses such as hospital acquired infections and sepsis
225 syndromes [73,74,75]. Experiments on burn wounds (after contamination with *P. aeruginosa* and then

226 treatment with kefir) showed a reduction of their size accompanied by reduced healing time when
227 kefir was administered alone than in the co-presence of silver sulfadiazine (a common topical
228 antibiotic used for the treatment of *P. aeruginosa* on burn wounds). Such findings highlight the
229 potential pharmaceutical use of kefir on the treatment of burn wounds [122]. Finally, in another
230 study, burn wounds were contaminated with 8 different pathogens (e.g., *S. aureus*, *S. salivarius*, *S.*
231 *pyogenes*, *P. aeruginosa*, *C. albicans*, *S. tympimurium*, *Listeria monocytogenes* and *E. coli*) and when kefir
232 and /or kefiran were applied to the subject's infected areas the growth of these pathogens was
233 considerably reduced [124].

234 3.2.2. Acne

235 Although not many studies have been conducted on the effect of pro- and prebiotics in acne, a
236 number of them suggest a potential preventive role of pro- and prebiotics on acne thereby mediating
237 its symptoms (Figure 1). More specifically, in a study utilizing a mixture of probiotics (*L. acidophilus*,
238 *B. bifidum* and *L. delbrueckii*), the side effects of minocycline administration (an antibiotic used for the
239 treatment of *A. Vulgaris*) were reduced while still being effective in exerting a synergistic anti-
240 inflammatory effect. These results suggest a potential use of the probiotic mixture as an alternative
241 treatment option against *A. Vulgaris* in addition of being capable in reducing adverse side effects after
242 chronic systemic antibiotic use [125]. Acne is enhanced in the presence of the bacterium *P. acnes*. On
243 the other hand, *S. epidermidis* is naturally found on skin and has been shown to antagonize *P. acnes*
244 thus highlighting its therapeutic potential against acne [126] (Table 1 and Figure 2). In another study,
245 the therapeutic role of *E. faecalis* SL-5 on acne was also evaluated with results demonstrating that
246 bacteriocin (CBT SL-5; an antimicrobial compound produced by *E. faecalis*) was capable of reducing
247 inflammation suggesting the use of *E. faecalis* as an alternative approach to acne therapy thereby
248 avoiding the extensive use of antibiotics [127] (Table 1 and Figure 2).

249 Finally, despite the lack of literature on the effect of prebiotics to skin disease, konjac
250 glucomannan hydrolysates (GMH) have also been shown to inhibit *A. Vulgaris* and *P. acnes* by
251 stimulating the growth of probiotic microorganisms including *lactobacilli*. To this end, it is noteworthy
252 that lactic acid bacteria show selectivity towards a manose:glucose substrate (found in GMH) because
253 of the nature and accessibility of these sugars as carbon sources [128,129] (Table 2 and Figure 2).

254 3.3. Psoriasis

255 Psoriasis is a skin condition that causes a variety of symptoms including flaky skin (patches),
256 itchiness and redness of the area. It is a non-contagious disease and it can affect individuals of any
257 age [130]. There are different types of the disease including pustular psoriasis, psoriatic arthritis and
258 plaque. Even though the literature on the effects of probiotics to skin inflammation and dermatitis
259 is extensive, little is known on their effects to psoriasis. Nevertheless, a number of studies have been
260 conducted on the effect of pro- and prebiotics in psoriasis suggesting a potential preventive role of
261 their action by means of mediating the symptoms of the disease (Figure 1).

262 In general, studies on the role of the human epidermal microbiome in psoriasis and other skin
263 diseases revealed that *S. epidermidis* (although a permanent member of the normal human microbiota)
264 is second most prevalent staphylococcal species only to *S. aureus* [131]. To this end, a recent study
265 was shown that *S. aureus* was at significantly higher levels on diseased skin as opposed to *S.*
266 *epidermidis* and *P. acnes* both of which were shown to be in abundance on healthy skin thereby
267 suggesting that psoriasis is highly associated with the microbial load of the skin [132]. To this end,
268 another study has shown that the abundance of *S. cerevisiae* is decreased in psoriasis patients and that
269 treatment with dimethylfumarate (DMF) successfully restored its levels, a finding of utmost
270 importance given the well-known and beneficial immunomodulatory properties of this yeast species
271 [133]. Moreover, extensive research indicates a strong link between potential mediators of T cell
272 activation and the development of the disease. In particular, CD4⁺ T cells are linked with the
273 development of psoriatic arthritis whilst probiotics regulate T cells and reduce skin inflammation
274 and dryness of the skin [134] (Table 1 and Figure 2). In a recent case report, the probiotic
275 microorganism *L. sporogenes* was successfully used for the treatment of pustular psoriasis as evident

276 by an overall improvement of the appearance of lesions and patient's general condition [135] (Table
277 1). A year later, Groeger et al., 2013 studied the immuno-regulatory effects of *B. infantis* in patients
278 with ulcerative colitis, chronic fatigue syndrome and psoriasis. In the case of psoriasis, reduced
279 plasma levels of C-reactive protein (CRP) and TNF- α were observed thus highlighting the ability of
280 *B. infantis* to reduce systemic pro-inflammatory biomarkers and thus to act as a potential therapeutic
281 approach in treating psoriatic disease [136] (Table 1 and Figure 2).

282 Sodium butyrate is produced by the gut microflora [137] and it is known for its effect on cell
283 cycle [138], tumor growth factors (TGF- β) [139] and protease enzymes [140]. In various studies
284 utilizing human keratinocyte (HaCaT) cells it was shown that exposure to sodium butyrate induced
285 apoptosis by 50% through up-regulation of death receptor Fas with concomitant activation of
286 caspases 8 and 3. In addition, increased expression levels of p52 and TGF- β were also shown
287 suggesting the involvement of cell proliferation and terminal differentiation as well [139]. Finally, a
288 combined treatment protocol with sodium butyrate and PD153035 (an epidermal growth factor
289 receptor inhibitor) was shown capable of enhancing keratinocyte differentiation [141]. Collectively,
290 data suggest that sodium butyrate can act as a potentially additional approach to the management of
291 hyperproliferative skin diseases (including psoriasis) by modulating key cellular processes like
292 apoptosis, proliferation and differentiation (Table 2 and Figure 2). To this end, a recent study
293 examining the gut microbial composition in psoriatic patients revealed that a reduction of butyrate
294 microbiota producers may have an impact on the established anti-inflammatory role of this short
295 chain fatty acid [142] and thus explain, at least partially, its preventive role in psoriasis (among other
296 disorders) [143]. In fact, *F. prausnitzii* (one of the most common microbial inhabitants of the large
297 intestine) serves as an important source of butyrate which, in turn, i) provides energy for colonocytes,
298 ii) reduces oxidative stress and iii) exerts anti-inflammatory action (by triggering regulatory T cells)
299 thereby conferring immune tolerance that goes beyond the GI tract [144,145]. Finally, another study
300 has shown that psoriatic patients possess a substantially reduced number of *F. prausnitzii* when
301 compared to healthy controls [146].

302 3.4. Photoaging

303 Skin aging is considered in the context of being either extrinsic or intrinsic. Extrinsic skin aging
304 is caused by a number of environmental factors like UVR exposure (photo aging), smoking and life
305 style habits (diet). In particular, photo aging is characterized by a specific phenotype that includes
306 excessive loss of skin moisture, formation of deep and thick wrinkles, age spots, discoloration, loss
307 of collagen and overall breakdown of the elastin network of the dermis, resulting in loss of skin
308 elasticity [147]. To date, there are few studies investigating into the effects of probiotics/prebiotics to
309 photo aging (Figure 1). In one such study, when hairless mice were administrated probiotic-
310 containing fermented milk together with para-probiotic *B. breve* strain Yakult, and then subjected to
311 UVB irradiation, it was shown an improvement in elasticity and appearance of the skin [148] together
312 with suppression of elastase and IL-1 β activity levels [149] (Table 1). These findings are in agreement
313 with another study where administration of *L. plantarum* HY7714 to hairless mice and human
314 epidermal fibroblasts was followed by UVB exposure and inhibition of MMPs-1,-2,-9 and -13 was
315 recorded indicating rescued procollagen expression accompanied by inhibition of Jun N-terminal
316 kinase phosphorylation and c-Jun expression levels. In addition, wrinkles formation and epidermal
317 thickness were also reduced [150] (Table 1 and Figure 2). Moreover, *L. plantarum* HY7714 was shown
318 to increase the mRNA levels of palmitoyl transferase (SPT) while reducing those of ceramide in
319 human epidermal fibroblasts [151] (Table 1 and Figure 2). Furthermore, Galacto-oligosaccharides
320 (GOS; one of the main prebiotics found in fermented food) were evaluated either alone or in the
321 presence of probiotics (e.g., *B. longum*) in order to assess their effects on skin disease and
322 inflammation. It was shown that the combination of probiotics and prebiotics prevented TEWL and
323 reduced skin erythema whilst increasing the mRNA expression of CD44, TIMP-1 and Col1 [152]
324 (Table 2 and Figure 2). Finally, in other studies, oligo-saccharides were also shown to prevent skin
325 aging by modulating the expression of elastase-type proteases (through elastin receptors) [153]
326 and/or prevent damage to the skin immune system [154].

327 4. Conclusions

328 Scientific and commercial interest on probiotics and prebiotics as well as their effect on human
329 health and disease has increased in the last decade. The aim of this minireview article was to evaluate
330 the role of pro- and prebiotics on the normal function of healthy skin as well as their role in the
331 prevention and therapy of skin disease. Whilst a number of studies have determined the mechanisms
332 by which some of these individual microorganisms can affect specific processes involved in the
333 pathophysiology of skin disease, others have focused on more complex natural products (e.g., kefir)
334 known to contain a mixture of probiotics but nevertheless also capable of exerting a potent beneficial
335 effect. Overall, our manuscript favours the idea of the utilization of probiotics as a means of
336 prevention and/or treatment options in skin disease. Such alternative approach can have a huge
337 impact in the context of therapy as it will aim to reduce the use of antibiotics and thus also reduce the
338 side effects associated with their chronic usage. However, in order to do so, the precise mechanism
339 of their action remains to be fully elucidated whilst, further studies need to explore their benefit in
340 managing the outcome(s) of skin disease(s) at the clinical setting.

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344 References

- 345 1. McGovern, P.E.; Zhang, J.; Tang, J.; Zhang, Z.; Hall, G.R.; Moreau, R.A.; Nunez, A.; Butrym, E.D.;
346 Richards, M.P.; Wang, C-S.; Cheng, G.; Zhao, Z.; Wang, C. Fermented beverages of pre- and proto-
347 historic China. *Proc Natl Acad Sci USA*. **2004**, *101*(51), 17593-17598.
- 348 2. Sicard, D.; Legras, J.L. Bread, beer and wine: Yeast domestication in the *Saccharomyces sensu stricto*
349 complex. *C R Biol*. **2011**, *334*(3), 229-236.
- 350 3. Ozen, M.; Dinleyici, E.C. The history of probiotics: The untold story. *Benef Microbes*. **2015**, *6*(2), 159-165.
- 351 4. Isolauri, E. Probiotics in human disease. *Am J Clin Nutr*. **2001**, *73*(6), 1142S-1146S.
- 352 5. Vandeplass, Y.; Zakharova, I.; Dmitrieva, Y. Oligosaccharides in infant formula: More evidence to
353 validate the role of prebiotics. *Br J Nutr*. **2015**, *113*(9), 1339-1344.
- 354 6. Gordon, S. Ellie Metchnikoff: Father of natural immunity. *Eur J Immunol*. **2008**, *38*(12), 3257-3264.
- 355 7. Collins, M.D.; Phillips, B.A.; Zannoni, P. Deoxyribonucleic acid homology studies of *Lactobacillus casei*,
356 *Lactobacillus paracasei* sp. nov., subsp. *paracasei* and subsp. *tolerans*, and *Lactobacillus rhamnosus* sp.
357 nov., comb. nov. *Int J Syst Bacteriol*. **1989**, *39*(2), 105-118.
- 358 8. Report of a Joint FAO/WHO Working Group on Drafting Guidelines for the Evaluation of Probiotics in
359 Food. Guidelines for the Evaluation of Probiotics in Food. London Ontario, Canada, **2002**, 1-11.
- 360 9. Gasbarrini, G.; Bonvicini, F.; Gramenzi, A. Probiotics History. *J Clin Gastroenterol*. **2016**, *50*, S116-S119.
- 361 10. Ouwehand, A.C.; Salminen, S.; Isolauri, E. Probiotics: an overview of beneficial effect. *Antonie Van*
362 *Leeuwenhoek*. **2002**, *82*(1-4), 279-289.
- 363 11. Britti, M.S.; Roselli, M.; Finamore, A.; Merendino, N.; Mengheri, E. Regulation of immune response at
364 intestinal and peripheral sites by probiotics. *Biologia (Bratislava)*. **2006**, *61*(6), 735-740.
- 365 12. Chen, C.C.; Allan Walker, W. Probiotics and the mechanism of necrotizing enterocolitis. *Semin Pediatr*
366 *Surg*. **2013**, *22*(2), 94-100.
- 367 13. Bansal, S.; Mangal, M.; Sharma, S.K.; Gupta, R.K. Non-dairy Based Probiotics: A Healthy Treat for
368 Intestine. *Crit Rev Food Sci Nutr*. **2016**, *56*(11), 1856-1867.
- 369 14. Wang, X.; Farnell, Y.Z.; Peebles, E.D.; Kiess, A.S.; Wamsley, K.G.; Zhai, W. Effects of prebiotics,
370 probiotics, and their combination on growth performance, small intestine morphology, and resident
371 *Lactobacillus* of male broilers. *Poult Sci*. **2016**, *95*(6), 1332-1340.

- 372 15. Sánchez, B.; Delgado, S.; Blanco-Míguez, A.; Lourenço, A.; Gueimonde, M.; Margolles, A. Probiotics, gut
373 microbiota, and their influence on host health and disease. *Mol Nutr Food Res.* **2017**, *61*(1), 1-15.
- 374 16. Friedrich, A.D.; Paz, M.L.; Leoni, J.; Maglio, D.H. Message in a bottle: Dialog between intestine and skin
375 modulated by probiotics. *Int J Mol Sci.* **2017**, *18*(6), E1067.
- 376 17. Thomas, C.M.; Versalovic, J. Probiotics-host communication. *Gut Microbes.* **2010**, *1*(3), 148-163.
- 377 18. Mori, N.; Kano, M.; Masuoka, N.; Konno, T.; Suzuki, Y.; Miyazaki, K.; Ueki, Y. Effect of probiotic and
378 prebiotic fermented milk on skin and intestinal conditions in healthy young female students. *Biosci*
379 *Microbiota Food Health.* **2016**, *35*(3), 105-112.
- 380 19. Yamada, T.; Nagata, S.; Kondo, S.; Bian, L.; Wang, C.; Asahara, T.; Ohta, T.; Nomoto, K.; Yamashiro, Y.
381 [Effect of Continuous Fermented Milk Intake Containing Lactobacillus casei Strain Shirota on Fever in
382 Mass Infectious Gastroenteritis Rest Home Outbreak]. *Kansenshogaku Zasshi.* **2009**, *83*(1), 31-35.
- 383 20. White, J.S.; Hoper, M.; Parks, R.W.; Clements, W.D.; Diamond, T.; Bengmark, S. The probiotic bacterium
384 Lactobacillus plantarum species 299 reduces intestinal permeability in experimental biliary obstruction.
385 *Lett Appl Microbiol.* **2006**, *42*(1), 19-23.
- 386 21. Anukam, K.C.; Hayes, K.; Summers, K.; Reid, G. Probiotic Lactobacillus rhamnosus GR-1 and
387 Lactobacillus reuteri RC-14 may help downregulate TNF-alpha, IL-6, IL-8, IL-10 and IL-12 (p70) in the
388 neurogenic bladder of spinal cord injured patient with urinary tract infections: a two-case study. *Adv*
389 *Urol.* **2009**, 680363.
- 390 22. Bennett, R.G.; Gorbach, S.L.; Greenough, W.B.; Bartlett, J.G. Treatment of Relapsing Clostridium difficile
391 Diarrhea with Lactobacillus GG. *Nutr Today Suppl.* **1996**, *31*(6), 35-38.
- 392 23. Amara, A.A.; Shibl, A. Role of Probiotics in health improvement, infection control and disease treatment
393 and management. *Saudi Pharm J.* **2015**, *23*(2), 107-114.
- 394 24. Boudeau, J.; Glasser, A.L.; Julien, S.; Colombel, J.F.; Darfeuille-Michaud, A. Inhibitory effect of probiotic
395 Escherichia coli strain Nissle 1917 on adhesion to and invasion of intestinal epithelial cells by adherent-
396 invasive E.coli strains isolated from patients with Crohn's disease. *Aliment Pharmacol Ther.* **2003**, *18*(9),
397 45-56.
- 398 25. Mego, M.; Májek, J.; Končėková, R.; Ebringer, L.; Čierníková, S.; Rauko, P.; Kovac, M.; Trupl, J.; Slezak,
399 P.; Zajac, V. Intramucosal bacteria in colon cancer and their elimination by probiotic strain Enterococcus
400 faecium M-74 with organic selenium. *Folia Microbiol (Praha).* **2005**, *50*(5), 443-447.
- 401 26. Thirabunyanon, M.; Boonprasom, P.; Niamsup, P. Probiotic potential of lactic acid bacteria isolated from
402 fermented dairy milks on antiproliferation of colon cancer cells. *Biotechnol Lett.* **2009**, *31*(4), 571-576.
- 403 27. Abdin, A.A.; Saeid, E.M. An experimental study on ulcerative colitis as a potential target for probiotic
404 therapy by Lactobacillus acidophilus with or without "olsalazine." *J Crohn's Colitis.* **2008**, *2*(4), 296-303.
- 405 28. Imaoka, A.; Shima, T.; Kato, K.; Mizuno, S.; Uehara, T.; Matsumoto, S.; Setoyama, H.; Hara, T.; Umesaki,
406 Y. Anti-inflammatory activity of probiotic Bifidobacterium: Enhancement of IL-10 production in
407 peripheral blood mononuclear cells from ulcerative colitis patients and inhibition of IL-8 secretion in
408 HT-29 cells. *World J Gastroenterol.* **2008**, *14*(16), 2511-2516.
- 409 29. Fujiya, M.; Musch, M.W.; Nakagawa, Y.; Hu, S.; Alverdy, J.; Kohgo, Y.; Schneewind, O.; Jabri, B.; Chang,
410 E.B. The Bacillus subtilis Quorum-Sensing Molecule CSF Contributes to Intestinal Homeostasis via
411 OCTN2, a Host Cell Membrane Transporter. *Cell Host Microbe.* **2007**, *1*(4), 299-308.
- 412 30. Kojima, K.; Musch, M.W.; Ren, H.; Boone, D.L.; Hendrickson, B.A.; Ma, A.; Chang, E.B. Enteric flora and
413 lymphocyte-derived cytokines determine expression of heat shock proteins in mouse colonic epithelial
414 cells. *Gastroenterology.* **2003**, *124*(5), 1395-1407.

- 415 31. Tao, Y.; Drabik, K.A.; Waypa, T.S.; Musch, M.W.; Alverdy, J.C.; Schneewind, O.; Chang, E.B.; Petrof, E.O.
416 Soluble factors from *Lactobacillus GG* activate MAPKs and induce cytoprotective heat shock proteins in
417 intestinal epithelial cells. *Am J Physiol Cell Physiol.* **2006**, *290*(4), C1018-1030.
- 418 32. Petrof, E.O.; Kojima, K.; Ropeleski, M.J.; Musch, M.W.; Tao, Y.; De Simone, C.; Cheng, E.B. Probiotics
419 inhibit nuclear factor- κ B and induce heat shock proteins in colonic epithelial cells through proteasome
420 inhibition. *Gastroenterology.* **2004**, *127*(5), 1474-1487.
- 421 33. Neish, A.S.; Gewirtz, A.T.; Zeng, H.; Young, A.N.; Hobert, M.E.; Karmali, V.; Rao, A.S.; Madara, J.L.
422 Prokaryotic Regulation of Epithelial Responses by Inhibition of I κ B- α Ubiquitination. *Science.* **2000**,
423 *289*(5484), 1560-1563.
- 424 34. Ma, D.; Forsythe, P.; Bienenstock, J. Live *Lactobacillus reuteri* Is Essential for the Inhibitory Effect on
425 Tumor Necrosis Factor Alpha-Induced Interleukin-8 Expression. *Infect Immun.* **2004**, *72*(9), 5308-5314.
- 426 35. Tien, M.T.; Girardin, S.E.; Regnault, B.; Le Bourhis, L.; Dillies, M.A.; Coppee, J.Y.; Bourdet-Sicard, R.;
427 Sansonetti, P.J.; Pedron, T. Anti-Inflammatory Effect of *Lactobacillus casei* on Shigella- Infected Human
428 Intestinal Epithelial Cells. *J Immunol.* **2009**, *176*, 1228-1237.
- 429 36. Frick, J.S.; Schenk, K.; Quitadamo, M.; Kahl, F.; Köberle, M.; Bohn, E.; Aepfelbacher, M.; Autenrieth, I.B.
430 *Lactobacillus fermentum* attenuates the proinflammatory effect of *Yersinia enterocolitica* on human
431 epithelial cells. *Inflamm Bowel Dis.* **2007**, *13*(1), 83-90.
- 432 37. Bai, A.P.; Ouyang, Q.; Zhang, W.; Wang, C.H.; Li, S.F. Probiotics inhibit TNF-alpha-induced interleukin-
433 8 secretion of HT29 cells. *World J Gastroenterol.* **2004**, *10*(3), 455-457.
- 434 38. Sokol, H.; Pigneur, B.; Watterlot, L.; Lakhdari, O.; Bermúdez-Humará, L.G.; Gratadoux, J.J.; Blugeon, S.;
435 Bridonneau, C.; Furet, J.P.; Corthier, G.; Grangette, C.; Vasquez, N.; Pochart, P.; Trugnan, G.; Thomas,
436 G.; Blottiere, H.M.; Dore, J.; Marteau, P.; Seksik, P.; Langella, P. *Faecalibacterium prausnitzii* is an anti-
437 inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients.
438 *Proc Natl Acad Sci USA.* **2008**, *105*(43), 16731-16736.
- 439 39. Haller, D.; Russo, M.P.; Balfour-Sartor, R.; Jobin, C. IKK β and phosphatidylinositol 3-kinase/Akt
440 participate in non-pathogenic gram-negative enteric bacteria-induced RelA phosphorylation and NF- κ B
441 activation in both primary and intestinal epithelial cell lines. *J Biol Chem.* **2002**, *277*(41), 38168-38178.
- 442 40. Ruiz, P.A.; Hoffmann, M.; Szcesny, S.; Blaut, M.; Haller, D. Innate mechanisms for *Bifidobacterium lactis*
443 to activate transient pro-inflammatory host responses in intestinal epithelial cells after the colonization
444 of germ-free rats. *Immunology.* **2005**, *115*(4), 441-450.
- 445 41. Jijon, H.; Backer, J.; Diaz, H.; Yeung, H.; Thiel, D.; McKaigney, C.; De Simone, C.; Madsen, K. DNA from
446 probiotic bacteria modulates murine and human epithelial and immune function. *Gastroenterology*, **2004**,
447 *126*(5), 1358-1373.
- 448 42. Resta-Lenert, S.; Barrett, K.E. Probiotics and commensals reverse TNF- α - and IFN- γ -induced
449 dysfunction in human intestinal epithelial cells. *Gastroenterology.* **2006**, *130*(3), 731-746.
- 450 43. Kelly, D.; Campbell, J.I.; King, T.P.; Grant, G.; Jansson, E.A.; Coutts, A.G.; Petterson, S.; Conway, S.
451 Commensal anaerobic gut bacteria attenuate inflammation by regulating nuclear-cytoplasmic shuttling
452 of PPAR- γ and RelA. *Nat Immunol.* **2004**, *5*(1), 104-112.
- 453 44. Are, A.; Aronsson, L.; Wang, S.; Greicius, G.; Lee, Y.K.; Gustafsson, J.A.; Petterson, S.; Arulampalam, V.
454 *Enterococcus faecalis* from newborn babies regulate endogenous PPAR activity and IL-10 levels in
455 colonic epithelial cells. *Proc Natl Acad Sci USA.* **2008**, *105*(6), 1943-1948.
- 456 45. Ewaschuk, J.B.; Walker, J.W.; Diaz, H.; Madsen, K.L. Bioproduction of Conjugated Linoleic Acid by
457 Probiotic Bacteria Occurs. *J Nutr.* **2006**, *136*, 1483-1487.

- 458 46. Fitzpatrick, L.R.; Small, J.; Hoerr, R.A.; Bostwick, E.F.; Maines, L.; Koltun, W.A. In vitro and in vivo
459 effects of the probiotic Escherichia coli strain M-17: Immunomodulation and attenuation of murine
460 colitis. *Br J Nutr.* **2008**, *100*(3), 530-541.
- 461 47. Yan, F.; Polk, D.B. Probiotic bacterium prevents cytokine-induced apoptosis in intestinal epithelial cells.
462 *J Biol Chem.* **2002**, *277*(52), 50959-50965.
- 463 48. Yan, F.; Cao, H.; Cover, T.; Whitehead, R.; Washington, M.K.; Polk, D.B. Soluble Proteins Produced by
464 Probiotic Bacteria Regulate Intestinal Epithelial Cell Survival and Growth. *Gastroenterology.* **2007**, *132*,
465 562-575.
- 466 49. Watanabe, T.; Nishio, H.; Tanigawa, T.; Yamagami, H.; Okazaki, H.; Watanabe, K.; Tominaga, K.;
467 Fujiwara, Y.; Oshitani, N.; Asahara, T.; Nomoto, K.; Higuchi, K.; Takeuchi, K.; Arakawa, K. Probiotic
468 Lactobacillus casei strain Shirota prevents indomethacin-induced small intestinal injury : involvement
469 of lactic acid Probiotic Lactobacillus casei strain Shirota prevents indomethacin-induced small intestinal
470 injury : involvement of lactic acid. *Am J Physiol Gastrointest Liver Physiol.* **2009**, *297*, 506-513.
- 471 50. Sougioultzis, S.; Simeonidis, S.; Bhaskar, K.R.; Chen, X.; Anton, P.M.; Keates, S.; Pothoulakis, C.; Kelly,
472 C.P. Saccharomyces boulardii produces a soluble anti-inflammatory factor that inhibits NF- κ B-mediated
473 IL-8 gene expression. *Biochem Biophys Res Commun.* **2006**, *343*(1), 69-76.
- 474 51. Ménard, S.; Candalh, C.; Bambou, J.C.; Terpend, K.; Cerf-Bensussan, N.; Heyman, M. Lactic acid bacteria
475 secrete metabolites retaining anti-inflammatory properties after intestinal transport. *Gut.* **2004**, *53*(6),
476 821-828.
- 477 52. Kim, H.G.; Kim, N.R.; Gim, M.G.; Lee, J.M.; Lee, S.Y.; Ko, M.Y.; Kim, J.Y.; Han, S.H.; Chung, D.K.
478 Lipoteichoic Acid Isolated from Lactobacillus plantarum Inhibits Lipopolysaccharide-Induced TNF-
479 Production in THP-1 Cells and Endotoxin Shock in Mice. *J Immunol.* **2008**, *180*(4), 2553-2561.
- 480 53. Matsuguchi, T.; Takagi, A.; Matsuzaki, T.; Nagaoka, M.; Ishikawa, K.; Yokokura, T.; Yoskikai, Y.
481 Lipoteichoic Acids from Lactobacillus Strains Elicit Strong Tumor Necrosis Factor Alpha-Inducing
482 Activities in Macrophages through Toll-Like Receptor 2. *Clin Diagn Lab Immunol.* **2003**, *10*(2), 259-266.
- 483 54. Kim, S.O.; Sheikh, H.I.; Ha, S.D.; Martins, A.; Reid, G. G-CSF-mediated inhibition of JNK is a key
484 mechanism for Lactobacillus rhamnosus-induced suppression of TNF production in macrophages. *Cell*
485 *Microbiol.* **2006**, *8*(12), 1958-1971.
- 486 55. Klebanoff, S.J.; Watts, D.H.; Mehlin, C.; Headley, C.M. Lactobacilli and vaginal host defense: activation
487 of the human immunodeficiency virus type 1 long terminal repeat, cytokine production, and NF-
488 kappaB. *J Infect Dis.* **1999**, *179*(3), 653-660.
- 489 56. Miettinen, M.; Lehtonen, A.; Ilkka, J.; Matikainen, S. Lactobacilli and Streptococci Activate NF- κ B and
490 STAT Signaling Pathways in Human Macrophages. *J Immunol.* **2000**, *164*(7), 3733-3740.
- 491 57. Chiu, Y.H.; Hsieh, Y.J.; Liao, K.W.; Peng, K.C. Preferential promotion of apoptosis of monocytes by
492 Lactobacillus casei rhamnosus soluble factors. *Clin Nutr.* **2010**, *29*(1), 131-140.
- 493 58. Iyer, C.; Kosters, A.; Sethi, G.; Kunnumakkara, A.B.; Aggarwal, B.B.; Versalovic, J. Probiotic Lactobacillus
494 reuteri promotes TNF-induced apoptosis in human myeloid leukemia-derived cells by modulation of
495 NF- κ B and MAPK signalling. *Cell Microbiol.* **2008**, *10*(7), 1442-1452.
- 496 59. Horinaka, M.; Yoshida, T.; Kishi, A.; Akatani, K.; Yasuda, T.; Kouhara, J.; Wakada, M.; Sakai, T.
497 Lactobacillus strains induce TRAIL production and facilitate natural killer activity against cancer cells.
498 *FEBS Lett.* **2010**, *584*(3), 577-582.
- 499 60. Zhang, Y.; Li, J.; Tang, L. Cancer-preventive isothiocyanates: Dichotomous modulators of oxidative
500 stress. *Free Radic Biol Med.* **2005**, *38*(1), 70-77.

- 501 61. Lee, D.E.; Huh, C.S.; Ra, J.; Choi, I.D.; Jeong, J.W.; Kim, S.H.; Ryu, J.H.; Seo, Y.K.; Koh, J.S.; Lee, J.H.; Sim,
502 J.H.; Ahn, Y.T. Clinical evidence of effects of *Lactobacillus plantarum* HY7714 on skin aging: A
503 randomized, double blind, placebo-controlled study. *J Microbiol Biotechnol.* **2015**, *25*(12), 2160-2168.
- 504 62. Pite, H. Effect of probiotic mix (*Bifidobacterium bifidum*, *Bifidobacterium Lactis*, *Lactobacillus*
505 *acidophilus*) in the primary prevention of eczema: a double-blind, randomized, placebo -controlled trial.
506 *Rev Port Imunoalergologia.* **2010**, *18*(4), 385-386.
- 507 63. Brouwer, M.L.; Wolt-Plompen, S.A.; Dubios, A.E.; van der Heide, S.; Jansen, D.F.; Hoijer, M.A.;
508 Kauffman, H.F., Duiverman, E.J. No effects of probiotics on atopic dermatitis in infancy: A randomized
509 placebo-controlled trial. *Clin Exp Allergy.* **2006**, *36*(7), 899-906.
- 510 64. Weston, S.; Halbert, A.; Richmond, P.; Prescott, S.L. Effects of probiotics on atopic dermatitis: A
511 randomised controlled trial. *Arch Dis Child.* **2005**, *90*(9), 892-897.
- 512 65. Rosenfeldt, V.; Benfeldt, E.; Valerius, N.H.; Pærregaard, A.; Michaelsen, K.F. Effect of probiotics on
513 gastrointestinal symptoms and small intestinal permeability in children with atopic dermatitis. *J Pediatr.*
514 **2004**, *145*(5), 612-616.
- 515 66. Kalliomäki, M.; Salminen, S.; Poussa, T.; Isolauri, E. Probiotics during the first 7 years of life: A
516 cumulative risk reduction of eczema in a randomized, placebo-controlled trial. *J Allergy Clin Immunol,*
517 **2007**, *119*(4), 1019-1021.
- 518 67. Cho, S.H., Strickland, I., Boguniewicz, M., Leung, D.Y. Fibronectin and fibrinogen contribute to the
519 enhanced binding of *Staphylococcus aureus* to atopic skin. *J Allergy Clin Immunol.* **2001**, *108*(2), 269-274.
- 520 68. Taylor, A.L.; Dunstan, J.A.; Prescott, S.L. Probiotic supplementation for the first 6 months of life fails to
521 reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children:
522 A randomized controlled trial. *J Allergy Clin Immunol.* **2007**, *119*(1), 184-191.
- 523 69. Lee, J.; Seto, D.; Bielory, L. Meta-analysis of clinical trials of probiotics for prevention and treatment of
524 pediatric atopic dermatitis. *J Allergy Clin Immunol.* **2008**, *121*(1), 116-121.
- 525 70. Odamaki, T.; Iwabuchi, N.; Xiao, J. Effects and Mechanisms of Probiotics on the Prevention and
526 Treatment of Allergic Rhinitis. In *Lactic Acid Bacteria and Bifidobacteria: Current Progress in Advanced*
527 *Research*. 1st ed.; Sonomoto, K.; Yokota, A. Eds.; Publisher: Caizer Academic Press, Norfolk, UK, **2011**;
528 239-251.
- 529 71. Nogueira, J.C.; Gonçalves, M.C. Probiotics in allergic rhinitis. *Braz J Otorhinolaryngol.* **2011**, *77*(1), 129-
530 134.
- 531 72. Jebur, M.S. Therapeutic efficacy of *Lactobacillus acidophilus* against bacterial isolates from burn
532 wounds. *N Am J Med Sci.* **2010**, *2*(12), 586-591.
- 533 73. Bassetti, M.; Vena, A.; Croxatto, A.; Righi, E.; Guery, B. How to manage *Pseudomonas aeruginosa*
534 infections. *Drugs Context.* **2018**, *7*, 212527.
- 535 74. Defez, C.; Fabbro-Peray, P.; Bouziges, N.; Gouby, A.; Mahamat, A.; Daurès, J.P.; Sotto, A. Risk factors for
536 multidrug-resistant *Pseudomonas aeruginosa* nosocomial infection. *J Hosp Infect.* **2004**, *57*(3), 209-216.
- 537 75. Livermore, D.M. Multiple Mechanisms of Antimicrobial Resistance in *Pseudomonas aeruginosa*: Our
538 Worst Nightmare? *Clin Infect Dis.* **2002**, *34*(5), 634-640.
- 539 76. Peral, M.C.; Rachid, M.M.; Gobbato, N.M.; Huaman-Martinez, M.A.; Valdez, J.C. Interleukin-8
540 production by polymorphonuclear leukocytes from patients with chronic infected leg ulcers treated with
541 *Lactobacillus plantarum*. *Clin Microbiol Infect.* **2010**, *16*(3), 281-286.
- 542 77. Sonal Sekhar, M.; Unnikrishnan, M.K.; Vijayanarayana, K.; Rodrigues, G.S.; Mukhopadhyay, C. Topical
543 application/formulation of probiotics: Will it be a novel treatment approach for diabetic foot ulcer? *Med*

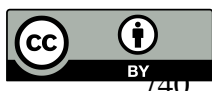
- 544 *Hypotheses*. **2014**, 82(1), 86-88.
- 545 78. Peral, M.C.; Huaman Martinez, M.A.; Valdez, J.C. Bacteriotherapy with *Lactobacillus plantarum* in
546 burns. *Int Wound J*. **2009**, 6(1), 73-81.
- 547 79. Atalan, G.; Demirkan, I.; Yaman, H.; Cihan, M.; Onder F.; Sozmen, M. Effect of topical kefir application
548 on open wound healing on in vivo study. *Kafkas Univ Vet Fak Dderg*. **2003**, 9(1), 43-47.
- 549 80. Frei, R.; Akdis, M.; O'Mahony, L. Prebiotics, probiotics, synbiotics, and the immune system:
550 Experimental data and clinical evidence. *Curr Opin Gastroenterol*. **2015**, 31(2), 153-158.
- 551 81. Pandey, K.R.; Naik, S.R.; Vakil, B.V. Probiotics, prebiotics and synbiotics- a review. *J Food Sci Technol*.
552 **2015**, 52(12), 7577-7587.
- 553 82. Scholz-Ahrens, K.E.; Adolphi, B.; Rochat, F.; Barclay, D.V.; de Vrese, M.; Açil, Y.; Schrezenmeir, J. Effects
554 of probiotics, prebiotics, and synbiotics on mineral metabolism in ovariectomized rats - impact of
555 bacterial mass, intestinal absorptive area and reduction of bone turn-over. *NFS J*. **2016**, 3, 41-50.
- 556 83. Hutkins, R.W.; Krumbeck, J.A.; Bindels, L.B.; Cani, P.D.; Fahey, G.; Goh, Y.J.; Hamaker, B.; Martens, E.C.;
557 Mills, D.A.; Rastal, R.A.; Vaughan, E.; Sanders, M.E. Prebiotics: Why definitions matter. *Curr Opin*
558 *Biotechnol*. **2016**, 37, 1-7.
- 559 84. Schley, P.D.; Field, C.J. The immune-enhancing effects of dietary fibres and prebiotics. *Br J Nutr*, **2002**,
560 87(2), S221-S230.
- 561 85. Yamada, K.; Tokunaga, Y.; Ikeda, A.; Ohkura, K.; Mamiya, S.; Kaku, S.; Sugano, M.; Tachibana, H.
562 Dietary effect of guar gum and its partially hydrolyzed product on the lipid metabolism and immune
563 function of Sprague-Dawley rats. *Biosci Biotechnol Biochem*, **1999**, 2163-2167.
- 564 86. Yun, C.H.; Estrada, A.; Van Kessel, A.; Gajadhar, A.; Redmond, M.; Laarveld, B. Immunomodulatory
565 effects of oat beta-glucan administered intragastrically or parenterally on mice infected with *Eimeria*
566 *vermiformis*. *Microbiol Immunol*. **1998**, 42(6), 457-465.
- 567 87. de Preter, V.; Geboes, K.; Verbrugghe, K.; de Vuyst, L.; Vanhoutte, T.; Huys, G.; Swings J.; Pot, B.;
568 Verbeke, K. The in vivo use of the stable isotope-labelled biomarkers lactose-[N]ureide and [H4]tyrosine
569 to assess the effects of pro- and prebiotics on the intestinal flora of healthy human volunteers. *Br J Nutr*.
570 **2004**, 92(3), 439-446.
- 571 88. Cogen, A.L.; Nizetà, V.; Gallo, R.L. Skin microbiota : a source of disease or defence ? *Br J Dermatol*. **2008**,
572 158(3), 442-455.
- 573 89. Grice, E.A. The skin microbiome: potential for novel diagnostic and therapeutic approaches to cutaneous
574 disease. *Semin Cutan Med Surg*. **2014**, 33(2), 98-103.
- 575 90. Kano, M.; Masuoka, N.; Kaga, C.; Sugimoto, S.; Iizuka, R.; Manabe, K.; Sone, T.; Oeda, K.; Nonaka, C.;
576 Miyazaki, K.; Ishikawa, F. Consecutive Intake of Fermented Milk Containing *Bifidobacterium breve*
577 Strain Yakult and Galacto-oligosaccharides Benefits Skin Condition in Healthy Adult Women. *Biosci*
578 *Microbiota Food Health*. **2013**, 32(1), 33-39.
- 579 91. Suk, J-H.; Park, J-A.; Kang, S-M. Effects of *Lactobacillus reuteri* Intake to Facial Skin Condition of
580 Women. *J Kor Soc Cosm*. **2018**, 24(4), 661-670.
- 581 92. Kimoto-Nira, H.; Aoki, R.; Sasaki, K.; Suzuki, C.; Mizumachi, K. Oral intake of heat-killed cells of
582 *Lactococcus lactis* strain h61 promotes skin health in women. *J Nutr Sci*. **2012**, 1, e18.
- 583 93. Lee, J.B.; Suk, J. han.; Kang, S.M. Effect of *Lactobacillus rhamnosus* KCTC 5033 on the Appearance of
584 Facial Skin due to the Ingestion of Probiotics and Paraprobiotics. *J Invest Cosmetol*. **2018**, 14(3), 287-296.
- 585 94. McPherson, T. Current understanding in pathogenesis of atopic dermatitis. *Indian J Dermatol*, **2016**, 61(6),
586 649-655.

- 587 95. Czarnecka-Operacz, M.; Sadowska-Przytocka, A. Probiotics for the prevention of atopic dermatitis and
588 other allergic diseases: What are the real facts? *Allergol Pol - Polish J Allergol.* **2017**, *4*(3), 89-92.
- 589 96. Kalliomäki, M.; Kirjavainen, P.; Eerola, E.; Kero, P.; Salminen, S.; Isolauri, E. Distinct patterns of neonatal
590 gut microflora in infants in whom atopy was and was not developing. *J Allergy Clin Immunol.* **2001**,
591 *107*(1), 129-134.
- 592 97. Björkstén, B.; Sepp, E.; Julge, K.; Voor, T.; Mikelsaar, M. Allergy development and the intestinal
593 microflora during the first year of life. *J Allergy Clin Immunol.* **2001**, *108*(4), 516-520.
- 594 98. Matsumoto, M.; Aranami, A.; Ishige, A.; Watanabe, K.; Benno, Y. LKM512 yogurt consumption improves
595 the intestinal environment and induces the T-helper type 1 cytokine in adult patients with intractable
596 atopic dermatitis. *Clin Exp Allergy.* **2007**, *37*(3), 358-370.
- 597 99. Woodfolk, J.A. T-cell responses to allergens. *J Allergy Clin Immunol.* **2007**, *119*(2), 280-294.
- 598 100. Chapat, L.; Chemin, K.; Dubois, B.; Bourdet-Sicard, R.; Kaiserlian, D. Lactobacillus casei reduces CD8+T
599 cell-mediated skin inflammation. *Eur J Immunol.* **2004**, *34*(9), 2520-2528.
- 600 101. Hacini-Rachinel, F.; Gheit, H.; Le Luduec, J.B.; Dif, F.; Nancey, S.; Kaiserlian, D. Oral probiotic control
601 skin inflammation by acting on both effector and regulatory T cells. *PLoS One.* **2009**, *4*(3), e4903.
- 602 102. Weise, C.; Zhu, Y.; Ernst, D.; Ku, A.A.; Worm, M.. Oral administration of Escherichia coli Nissle 1917
603 prevents allergen-induced dermatitis in mice. *Exp Dermatol.* **2011**, *20*, 805-809.
- 604 103. Shah, M.M., Saio, M.; Yamashita, H.; Tanaka, H. Lactobacillus acidophilus Strain L-92 Induces CD4
605 CD25 Foxp3 Regulatory T Cells and Suppresses Allergic Contact Dermatitis. *Biol Pharm Bull.* **2012**, *35*(4),
606 612-616.
- 607 104. Watanabe, J.; Sasajima, N.; Aramaki, A.; Sonoyama, K. Consumption of fructo-oligosaccharide reduces
608 2,4-dinitrofluorobenzene-induced contact hypersensitivity in mice. *Br J Nutr.* **2008**, *100*(2), 339-346.
- 609 105. Flanagan, M. The physiology of wound healing. *J Wound Care.* **2000**, *9*(6), 299-300.
- 610 106. Rieger, S.; Zhao, H.; Martin, P.; Abe, K.; Lisse, T.S. The role of nuclear hormone receptors in cutaneous
611 wound repair. *Cell Biochem Funct.* **2015**, *33*(1), 1-13.
- 612 107. Canesso, M.C.; Vieira, A.T.; Castro, T.B.; Schirmer, B.G.; Cisalpino, D.; Martins, F.S.; Rachid, M.A.; Nicoli,
613 J.R.; Teixeira, M.M.; Barcelos, L.S. Skin Wound Healing Is Accelerated and Scarless in the Absence of
614 Commensal Microbiota. *J Immunol.* **2014**, *193*(10), 5171-5180.
- 615 108. Robson, M.C. Wound infection: A failure of wound healing caused by an imbalance of bacteria. *Surg*
616 *Clin North Am.* **1997**, *77*(3), 637-650.
- 617 109. Oryan, A.; Jalili, M.; Kamali, A.; Nikahval, B. The concurrent use of probiotic microorganism and
618 collagen hydrogel/scaffold enhances burn wound healing: An in vivo evaluation. *Burns.* **2018**, *44*(7),
619 1775-1786.
- 620 110. Sikorska, H.; Smoragiewicz, W. Role of probiotics in the prevention and treatment of meticillin-resistant
621 Staphylococcus aureus infections. *Int J Antimicrob Agents.* **2013**, *42*(6), 475-481.
- 622 111. Karska-Wysocki, B.; Bazo, M.; Smoragiewicz, W. Antibacterial activity of Lactobacillus acidophilus and
623 Lactobacillus casei against methicillin-resistant Staphylococcus aureus (MRSA). *Microbiol Res.* **2010**,
624 *165*(8), 674-686.
- 625 112. Prince, T.; McBain, A.J.; O'Neill, C.A. Lactobacillus reuteri protects epidermal keratinocytes from
626 Staphylococcus aureus-induced cell death by competitive exclusion. *Appl Environ Microbiol.* **2012**, *78*(15),
627 5119-5126.
- 628 113. Jones, M.; Ganopolsky, J.G.; Labbe, A.; Gilardino, M.; Wahl, C.; Martoni, C.; Prakash, S. Novel nitric
629 oxide producing probiotic wound healing patch: preparation and in vivo analysis in a New Zealand

- 630 white rabbit model of ischaemic and infected wounds. *Int Wound J.* **2012**, *9*(3), 330-343.
- 631 114. Isenberg, J.S.; Ridnour, L.A.; Espey, M.G.; Wink, D.A.; Roberts, D.D. Nitric oxide in wound-healing.
632 *Microsurgery.* **2005**, *25*(5), 442-451.
- 633 115. Codex Alimentarius. Codex Standards for fermented milks. In Milk and Milk Products. 2nd ed. **2011**, 6-
634 16.
- 635 116. Farnworth, E.R. Kefir a complex probiotic. *Food Sci Technol Bull Funct Foods.* **2006**, *2*(1), 1-17.
- 636 117. Satir, G.; Guzel-Seydim, Z.B. How kefir fermentation can affect product composition? *Small Rumin Res.*
637 **2016**, *134*, 1-7.
- 638 118. Irigoyen, A.; Arana, I.; Castiella, M.; Torre, P.; Ibáñez, F.C. Microbiological, physicochemical, and
639 sensory characteristics of kefir during storage. *Food Chem.* **2005**, *90*(4), 613-620.
- 640 119. Chen, H.C.; Wang, S.Y.; Chen, M.J. Microbiological study of lactic acid bacteria in kefir grains by culture-
641 dependent and culture-independent methods. *Food Microbiol.* **2008**, *25*(3), 492-501.
- 642 120. Rahimzadeh, G.; Fazeli, M.R.; Mozafari, A.N.; Mesbahi, M. Evaluation of anti-microbial activity and
643 wound healing of kefir. *Int J Pharm Sci Res.* **2015**, *6*, 286-293.
- 644 121. Serafini, F.; Turrone, F.; Ruas-Madiedo, P.; Lugli, G.A.; Milani, C.; Duranti, S.; Zamboni, N., Bottachini,
645 F.; van Sinderen, D.; Margolles, A.; Ventura, M. Kefir fermented milk and kefir promote growth of
646 *Bifidobacterium bifidum* PRL2010 and modulate its gene expression. *Int J Food Microbiol.* **2014**, *178*, 50-
647 59.
- 648 122. Huseini, H.F.; Rahimzadeh, G.; Fazeli, M.R.; Mehrzama, M.; Salehi, M. Evaluation of wound healing
649 activities of kefir products. *Burns.* **2012**, *38*(5), 719-723.
- 650 123. Tsiouris, C.G.; Kelesi, M.; Vasilopoulos, G.; Kalemikerakis, I.; Papageorgiou, E.G. The efficacy of
651 probiotics as pharmacological treatment of cutaneous wounds: Meta-analysis of animal studies. *Eur J*
652 *Pharm Sci.* **2017**, *104*, 230-239.
- 653 124. Rodrigues, K.L.; Gaudino Caputo, L.R.; Tavares Carvalho, J.C.; Evangelista, J.; Schneedorf, J.M.
654 Antimicrobial and healing activity of kefir and kefir extract. *Int J Antimicrob Agents.* **2005**, *25*(5), 404-
655 408.
- 656 125. Jung, G.W.; Tse, J.E.; Guiha, I.; Rao, J. Prospective, Randomized, Open-Label Trial Comparing the Safety,
657 Efficacy, and Tolerability of an Acne Treatment Regimen with and without a Probiotic Supplement and
658 Minocycline in Subjects with Mild to Moderate Acne. *J Cutan Med Surg.* **2013**, *17*(2), 114-122.
- 659 126. Wang, Y.; Kuo, S.; Shu, M.; Yu, J.; Huang, S.; Dai, A.; Two, A.; Gallo, R.L.; Huang, C.M. Staphylococcus
660 epidermidis in the human skin microbiome mediates fermentation to inhibit the growth of
661 *Propionibacterium acnes*: Implications of probiotics in acne vulgaris. *Appl Microbiol Biotechnol.* **2014**,
662 *98*(1), 411-424.
- 663 127. Kang, B.S.; Seo, J.G.; Lee, G.S.; Kim, J.H.; Kim, S.Y.; Han, Y.W.; Kang, H.; Kim, H.O.; rhee, J.H.; Chung,
664 M.J.; Park, Y.M. Antimicrobial activity of enterocins from *Enterococcus faecalis* SL-5 against
665 *Propionibacterium acnes*, the causative agent in acne vulgaris, and its therapeutic effect. *J Microbiol.* **2009**,
666 *47*(1), 101-109.
- 667 128. Al-Ghazzewi, F.H.; Tester, R.F. Effect of konjac glucomannan hydrolysates and probiotics on the growth
668 of the skin bacterium *Propionibacterium acnes* in vitro. *Int J Cosmet Sci.* **2010**, *32*(2), 139-142.
- 669 129. Bateni, E.; Tester, R.; Al-Ghazzewi, F.; Bateni, S.; Alvani, K.; Piggott, J. The Use of Konjac Glucomannan
670 Hydrolysates (GMH) to Improve the Health of the Skin and Reduce Acne Vulgaris. *Am J Dermatol*
671 *Venerol.* **2013**, *2*(2), 10-14.
- 672 130. Drust, B.; Cable, N.T.; Reilly, T. Investigation of the effects of the pre-cooling on the physiological

- 673 responses to soccer-specific intermittent exercise. *Eur J Appl Physiol Occup Physiol*. **2000**, 81(1–2), 11-17.
- 674 131. Tett, A.; Pasolli, E.; Farina, S.; Truong, D.T.; Asnicar, F.; Zolfo, M.; Beghini, F.; Armanini, F.; Jousson, O.;
675 De Sanctis, V.; Bertorelli, R.; Girolomoni, G.; Cristofolini, M.; Segata, N. Unexplored diversity and strain-
676 level structure of the skin microbiome associated with psoriasis. *NP J Biofilms Microbiomes*. **2017**, 3(1), 14.
- 677 132. Chang, H.W.; Yan, D.; Singh, R.; Liu, J.; Lu, X.; Ucmak, D.; Lee, K.; Afifi, L.; Fedrosh, D.; Leech, J.;
678 Vasquez, K.S.; Lowe, M.M.; Rosenblum, M.D.; Scharschmidt, T.C.; Lynch, S.V.; Liao, W. Alteration of
679 the cutaneous microbiome in psoriasis and potential role in Th17 polarization. *Microbiome*, **2018**, 6(1),
680 154.
- 681 133. Eppinga, H.; Thio, H.B.; Schreurs, M.W.J.; Blakaj, B.; Tahitu, R.I.; Konstantinov, S.R.; Peppelenbosch,
682 M.P.; Fuhler, G.M. Depletion of *Saccharomyces cerevisiae* in psoriasis patients restored by
683 Dimethylfumarate therapy (DMF). **2017**, *PLoS One*, 12(5), e0176955.
- 684 134. Thio, H.H. The microbiome in psoriasis and psoriatic arthritis: The skin perspective. *J Rheumatol Suppl*.
685 **2018**, 94, 30-31.
- 686 135. Vijayashankar, M.; Raghunath, N. Pustular psoriasis responding to Probiotics – a new insight. *Our*
687 *Dermatol Online*. **2012**, 3(4), 326-328.
- 688 136. Groeger, D.; O'Mahony, L.; Murphy, E.F.; Bourke, J.F.; Dinan, T.G.; Kiely, B.; Shanahan, F.; Quigley, E.M.
689 *Bifidobacterium infantis* 35624 modulates host inflammatory processes beyond the gut. *Gut Microbes*.
690 **2013**, 4(4), 325-339.
- 691 137. Manning, T.S.; Gibson, G.R. Microbial-gut interactions in health and disease. Prebiotics. *Best Pract. Res.*
692 *Clin. Gastroenterol*. **2004**, 18(2), 287-298.
- 693 138. Daehn, I.S.; Varelias, A.; Rayner, T.E. Sodium butyrate induced keratinocyte apoptosis. *Apoptosis*. **2006**,
694 11(8), 1379-1390.
- 695 139. Staiano-Coico, L.; Khandke, L.; Krane, J.F.; Sharif, S.; Gottlieb, A.B.; Krueger, J.G.; Heim, L.; Rigas, B.;
696 Higgins, P.J. TGF- α and TGF- β expression during sodium-N-butyrate-induced differentiation of human
697 keratinocytes: Evidence for subpopulation-specific up-regulation of TGF- β mRNA in suprabasal cells.
698 *Exp. Cell Res*. **1990**, 191(2), 286-291.
- 699 140. Elder, J.T.; Zhao, X. Evidence for local control of gene expression in the epidermal differentiation
700 complex. *Exp. Dermatol*. **2002**, 11(5), 406-412.
- 701 141. Leon Carrion, S.; Sutter, C.H.; Sutter, T.R. Combined treatment with sodium butyrate and PD153035
702 enhances keratinocyte differentiation. *Exp. Dermatol*. **2014**, 23(3), pp. 211-214.
- 703 142. Vinolo, M.A.R.; Rodrigues, H.G.; Nachbar, R.T.; Curi, R. Regulation of inflammation by short chain fatty
704 acids. *Nutrients*. **2011**, 3, 858-876.
- 705 143. Codoner, F.M.; Ramirez-Bosca, A.; Climent, E.; Carrion-Gutierrez, M.; Guerrero, M.; Perez-Orquin, J.M.;
706 Horga de la Parte, J.; Genoves, S.; Ramon, D.; Navarro-Lopez, V.; Chenoll, E. Gut microbial composition
707 in patients with psoriasis. *Sci Rep*. **2018**, 8, 3812.
- 708 144. Sokol, H.; Pigneur, B.; Watterlot, L.; Lakhdari, O.; Bermudez-Hanaran, L.G.; Gratadoux, J.; et al.,
709 *Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium identified by gut microbiota
710 analysis of Crohn disease patients. *Proc Natl Acad Sci USA*. **2008**, 105, 16731-16736.
- 711 145. Lopez-Siles, M.; Khan, T.M.; Duncan, S.H.; Harmsen, H.J.M.; Garcia-Gil, L.J.; Flint, H.J. Cultured
712 representatives of two major phylogroups of human colonic *Faecalibacterium prausnitzii* can utilize pectin,
713 uronic acids, and host-derived substrates for growth. *Appl Environ Microbiol*. **2012**, 78, 420-428.
- 714 146. Eppinga, H.; Weiland, C.J.S.; Thio, H.B.; van der Woude, C.J.; Nijsten, T.E.C.; Peppelenbosch, M.P.; et
715 al., Similar depletion of protective *Faecalibacterium prausnitzii* in psoriasis and inflammatory bowel

- 716 disease, but not in hidradenitis suppurativa. *J Crohns Colitis*. **2016**, *10*, 1067-1075.
- 717 147. Tobin, D.J. Introduction to skin aging. *J Tissue Viability*. **2017**, *26*(1), 37-46.
- 718 148. Sugimoto, S.; Ishii, Y.; Izawa, N.; Masuoka, N.; Kano, M.; Sone, T.; Chiba, K.; Miyazaki, K.; Ishikawa, F.
- 719 Photoprotective effects of Bifidobacterium breve supplementation against skin damage induced by
- 720 ultraviolet irradiation in hairless mice. *Photodermatol Photoimmunol Photomed*. **2012**, *28*(6), 312-319.
- 721 149. Satoh, T.; Murata, M.; Iwabuchi, N.; Odamaki, T.; Wakabayashi, H.; Yamauchi, K.; Abe, F.; Xiao, J.Z.
- 722 Effect of Bifidobacterium breve B-3 on skin photoaging induced by chronic UV irradiation in mice. *Benef*
- 723 *Microbes*. **2015**, *6*(4), 497-504.
- 724 150. Kim, H.M.; Lee, D.E.; Park, S.D.; Kim, Y-T.; Kim, Y.J.; Jeong, J.W.; Jeng, S.S.; Ahn, Y.T., Sim, J.H., Huh,
- 725 C.S.; Chung, D.K.; Lee, J.H. Oral administration of lactobacillus plantarum HY7714 protects hairless
- 726 mouse against ultraviolet B-induced photoaging. *J Microbiol Biotechnol*. **2014**, *24*(11), 1583-1591.
- 727 151. Ra, J.; Lee, D.E.; Kim, S.H.; Jeong, J.W.; Ku, H.K.; Kim, T.Y.; Choi, I.D.; Jeung, W., Sim, J.H.; Ahn, Y.T.
- 728 Effect of oral administration of Lactobacillus plantarum HY7714 on epidermal hydration in ultraviolet
- 729 B-irradiated hairless mice. *J Microbiol Biotechnol*. **2014**, *24*(12), 1736-1743.
- 730 152. Hong, K.B.; Jeong, M.; Han, K.S.; Hwan Kim, J.; Park, Y.; Suh, H.J. Photoprotective effects of galacto-
- 731 oligosaccharide and/or Bifidobacterium longum supplementation against skin damage induced by
- 732 ultraviolet irradiation in hairless mice. *Int J Food Sci Nutr*. **2015**, *66*(8), 923-930.
- 733 153. Moczar, E.; Yvetter, S.G.; Robert, L.; Robert, A. USE OF OLIGOSACCHARIDES IN THE PREVENTION
- 734 AND TREATMENT OF THE AGING OF TISSUES. **1999**, United States Patent No: 5,910,490.
- 735 154. Strickland, M.F.; Pelley, P.R.; Kripke, L.M. Cytoprotective oligosaccharide from aloe preventing damage
- 736 to the skin immune system by UV radiation. **1998**, United States Patent No: 5,824,659.
- 737
- 738



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