

# Probiotics: An Update to Past Researches

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Received August 20, 2020

Accepted September 20, 2020

Published online 30 September 2020



## Please cite this article

as follows: Shirazinia R, Golabchifar AK, Panahi Mishkar A, Fazeli MR. Probiotics: an update to past researches. Int J Basic Sci Med. 2020;5(3):68-84. doi:10.34172/ijbsm.2020.14.

## Abstract

Probiotics are beneficial bacteria living in the microbiota ecosystem of the human body playing particular important roles in human health. The increasing rate of various diseases and the studies about the balance of gut microbiome made scientists trying to find novel therapies in this regard and hypothesize the relationships between the imbalance of gut microbiome and spread of various diseases especially in the immune system. Previous studies have indicated that when administrated in specific amounts, probiotics exert beneficial properties for human health such as antibacterial effects, cytotoxic effects, Hypocholesterolemic effects, immunomodulatory effects, wound healing effects etc. Probiotics also are known to produce nourishing healthy supplements for the human body such as vitamin K and B as well as healthy fatty acids. In this regard summarization of scientific evidence may help to familiarize the scientists with this novel area of research helping to find effective therapies for various disease. In this study, we used published literature in scientific databases such as Web of Science, Cochrane Library, Medline, PubMed, Science Direct, Scopus, as well as Google Scholar for data collection. So, the present review describes scientific-based evidence about probiotics and some of their beneficial effects to highlight the path for further researches about these beneficial bacteria.

**Keywords:** Probiotics, Diarrhea, Lactobacilli, Bifidobacterium, Antibiotic-associated diarrhea, beneficial effects

## Introduction

The word 'probiotic' derived from a Greek background means "for life" which is attributed to the non-pathogenic microorganisms associated with the beneficial effects for mankind and animals. If we want to introduce the term probiotics, we can say probiotics are some live strains of bacteria that when administrated in adequate amounts exert beneficial effects on the host. Prebiotics are substances that promote the growth of probiotic bacteria playing a vital role in the modulation of gut microbiome. Synbiotic is a combination of probiotics and prebiotics.<sup>1,2</sup> The term probiotic was first introduced by Vergin when he was studying the effects of microbial substances on the intestine microbial population and also first was used by Lilley and Stillwell to introduce some kinds of microorganisms based products, stimulating the growth of another.<sup>3,4</sup> At present, the most used

definition for probiotics is that of Fuller: living microbial feed supplements

beneficially affecting the host by contribution to intestinal microbial community balance playing a vital role in health maintenance.<sup>5,6</sup> Probiotics consist mostly strains of the genera *Bifidobacterium* and *Lactobacillus*, additionally, strains of *Pediococcus*, *Bacillus* and some yeasts can be introduced as suitable candidates. These strains together play important roles in the protection of the host against pathogen microorganisms, the host's immune system strength, and the persistence of the intestinal microbial balance.<sup>5</sup> Recently remarkable research efforts confirm the significant importance of the microbial population of the gastrointestinal tract (GIT) revealing the great importance of probiotics.<sup>7</sup> Recent pieces of research have expressed some kinds of beneficial effects for probiotics including antibacterial effects, modulation of the immune system, wound healing,



cytotoxic effects, antitoxin effects, hypocholesterolemic effect, effects on dermal and oral health, modulation of the gut-brain axis, and also promising effects on the *Helicobacter pylori* (HP) infection, ulcerative colitis, Crohn's disease, parasitic infections, irritable bowel syndrome (IBS), and other bowel diseases in addition to dental and periodontal diseases as well as halitosis. Nowadays, properties such as treatment of lactose intolerance and simplifying rotavirus diarrhea are widely accepted for probiotics too. Atopy an allergic reaction is said to be relieved using the consumption of probiotics.<sup>8-14</sup>

Based on *in vitro* studies probiotics originally act through different mechanisms including modifying the microflora as antimicrobial agents, secretion of antibacterial products, rivaling with pathogens to attach the adhesion sites which is presented on the intestinal epithelium, competition for necessary nutrient substances for pathogens survival, production of antitoxin substances and relieve of some alterations induced by infection in the intestinal epithelium including neutrophil migration as well as secretory changes.<sup>15,16</sup> Probiotics have also exhibited anticancer effects. Beneficial effects of the probiotics may proceed beyond the GIT to the urogenital and respiratory mucosa.<sup>17</sup> Some kinds of proteins produced by probiotics can inhibit inflammation and reduce epithelial cells apoptosis,<sup>18,19</sup> for instance, some kinds of DNA extracted from probiotics can reduce the colitis induced complications in several *in vivo* models. The bacteria can also be programmed for antigen delivery.<sup>20,21</sup>

After the inception of the golden era of antibiotics in 1928, the field of medicine underwent a huge alteration due to increment of life expectancy in addition to the improvement of human life quality as well as decreasing the mortality rate throughout the world.<sup>22</sup> But the development of antibiotics caused major problems including disruption of the gut bacterial ecosystem leading to extensive effects such as superinfection and drug resistance. So, it is more reasonable to find agents with low side effects helping antibiotics as an adjuvant or alternative medicine to cover all undesirable effects induced by antibiotic therapies.<sup>23</sup> So, the present investigation aims to make an update to past researches for providing convincing evidence about some desirable properties of probiotics on the health status of the human being.

## Methods

To perform this review, the available data about the probiotic bacteria, efficacy in different pathological conditions, most available and studied strains until September 06, 2020 was used. Scientific databases including Web of Science, Cochrane Library, Medline, PubMed, Science Direct, Scopus, and Google Scholar were used for data collection. The search keywords included probiotics, lactobacilli, *Bifidobacterium*, pharmacological

properties, immunomodulation, antibacterial, diarrhea, atopic dermatitis, cancer, IBS, *Helicobacter pylori*, which combination of them were used. Overall, 300 articles from 1975 until 2019 were obtained of which 272 were used in our study. The inclusion criteria for studies were being English language and the accessibility to full text.

## Microorganisms Considered as Probiotics

The number of microorganisms with probiotic characteristics is large, but some of them are more important including *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*, that present in the novel yoghurt-like commodities.<sup>24-26</sup> It has been revealed that probiotics have been used for thousand years and thought to have beneficial effects, but in 1900s scientists started to explore the reasons for these beneficial effects. So far Several strains of bacteria known to be probiotics, for instance: *Bifidobacterium*, *Lactobacillus*, *Pediococcus*, *Leuconostoc*, and *Enterococcus*, but the main species that possess probiotic properties are *Bifidobacterium spp.*, *Lactobacillus acidophilus*, and *L. casei*. Consumption of dairy products containing the genera *Lactobacilli* and *Bifidobacterium* which are also found in the gastrointestinal microflora has great beneficial health effects. So far, some pieces of literature have documented the desirable effects of probiotics, for instance, *L. rhamnosus* GG(ATCC 53103), *L. johnsonii* La1, *L. acidophilus* (NCFB 1478), *L. casei* Shirota, *Bifidobacterium animalis* Bb12 and *L. reuteri* as probiotics with beneficial effects.<sup>26</sup>

## Lactobacilli

First isolated from a human source, *L. acidophilus* a gram-positive and homofermentative, microorganism with the bacteriocins belonging to class II a. This is the most widely considered organism for dietary use. *L. acidophilus* inhabit in a wide variety of environments from dairy products to GIT.<sup>27-29</sup> This microorganism ferments the sugar and produces lactic acid using the Embden Meyerhof-Parnas pathway.<sup>30</sup>

The word homofermentative refers that *L. acidophilus* utilizes glycolysis pathway to ferment hexoses leading to the production of D and L-lactic acids while heterofermentatives follow the phosphoketolase pathway to ferment hexoses and pentoses.<sup>31</sup> *L. acidophilus* can ferment various carbohydrates such as fructose, galactose, lactose cellobiose, amygdalin, maltose, glucose, stachyose, but mellibiose, raffinose, melezitose, mannitol, and arabinose are the kinds of carbohydrates that can't be fermented by this microorganism. Some strains of *L. acidophilus* have the ability to ferment mannitol, fructooligosaccharides, and inulin.<sup>32</sup> *L. acidophilus* has a desirable rate of survival after even 21 days of storage in dairy products including milk and acidified milk which propose this microorganism as a favorable option for the production of dairy probiotic supplements.<sup>33</sup> *L. acidophilus* is isolated from many fermented foods such as yoghurt

and can produce high amounts of lactic acid.<sup>30</sup> One of the important aspects about *L. acidophilus* is its antimicrobial resistance. Some studies have demonstrated that *L. acidophilus* has the genes associated with antimicrobial resistance and the ability to spread among other species and bacteria colonized in the GIT.<sup>34</sup>

So far, many studies have indicated the desirable and promising effects of *Lactobacillus* for the treatment of the diseases associated with diarrhea.<sup>35</sup> The published data and other pieces of evidence revealed the effectiveness of *Lactobacillus* on health.<sup>36</sup> Drinking yoghurt fortified with *L. acidophilus* reduced the cholesterol up to 7 percent in comparison to the ordinary yoghurts.<sup>37-39</sup> It has been expressed that a combination therapy containing *L. acidophilus* and other probiotics reduce the diarrhea induced by radiotherapy in cancer patients.<sup>40</sup> The data obtained about the *Lactobacillus* as a probiotic is making promising evidence for beneficial properties of this bacteria, but obviously, more investigations are needed.

### Bifidobacterium

Bifidobacteria are anaerobe bacteria possessing strains that most of them cannot grow at the conditions containing 90% air and 10% CO<sub>2</sub>. *Bifidobacterium* forms convex, creamy or white, smooth, glossy, neat edged, sticky and soft colonies in agar plates; these bacteria comprise the dominant population in the human gastrointestinal microbiome as well as a range of about 90% of the total population in breastfed infants microbiome.<sup>41</sup> These bacteria were first isolated from infant feces and attracted attention due to significant beneficial properties in the human microbiome. So far, bifidobacteria are isolated from six different niches including the human gut and oral cavity as well as animals' intestine (bovine, rabbit, murine, chicken and insect) while other contaminations (sewage, blood, and food) may be due to the contamination by GIT.<sup>42</sup> Important species are isolated from the GIT are *B. longum*, *B. infantis*, *B. adolescentis* and from the oral cavity: *B. dentium*, *B. breve*, *B. inopinatum*, and *B. denticolenu*.<sup>43</sup> The studies demonstrated to date that about 31 species have been isolated from the genus *Bifidobacterium* with nine of them (*adolescentis*, *angulatum*, *bifidum*, *breve*, *catenulatum*, *dentium*, *gallicum*, *longum*, and *pseudocatenulatum*) isolated from human feces and oral cavity.<sup>44</sup>

Some species and subspecies including *animalis* spp. *animalis*, *lactis*, *breve*, *longum* spp. *Longum*, and *longum* spp. *Infantis* are considered as probiotics.<sup>45</sup> Bifidobacteria are widely used in food products, for instance, infant formulas, milk, cheese, yoghurt and dietary supplements,<sup>46</sup> and possess a wide range of beneficial effects including hypocholesteric effects, improvement of gut microbiome especially in preterm infants, treatment of lactose intolerance, protection against infectious diseases like diarrhea, cancer prevention, modulation of mucosal barrier function and stimulation of calcium uptake by

enterocytes.<sup>44</sup> It must be emphasized that when a strain is called probiotic, this fact is only referred to the same strain and not for other genus or the other members of the family.<sup>45</sup> There are various data about the significance of the effect of bifidobacteria on gastrointestinal health and some evidence on the *Bifidobacterium* association with various diseases.<sup>47-50</sup> Some strains of *Bifidobacterium* have shown beneficial effects in the healing of pain and bowel movement difficulties as bloating versus placebo and a *Lactobacillus* species.<sup>51</sup> The role of bifidobacteria for the production of beneficial substances including B vitamins and healthy fatty acids has been proven.<sup>52,53</sup> In a huge follow-up study, the *Bifidobacterium* consumption significantly reduced the pain and other complication associated with IBS.<sup>54</sup>

As mentioned before, the beneficial properties of probiotics for the human being health are under investigation and need more and more researches, but obviously, there are promising reasonable pieces of evidence for pharmacologic and beneficial properties of probiotics, especially bifidobacteria and *Lactobacillus* probiotic strains, in promoting the human health.

### Beneficial Effects of Probiotic Bacteria

#### Balance of the Gut Microbiome

Brown et al in their study conducted for evaluation the beneficial effects of probiotics declared the fact that probiotics can restore the natural balance of the gut microbiome.<sup>55</sup> As mentioned before, the imbalance in probiotics results in various pathologic conditions such as celiac disease, gastric cancer, autism, obesity, anorexia, inflammatory bowel diseases (IBD, Crohn's disease), IBD (General), and type 2 diabetes.<sup>56</sup> It is also clarified that gut microbiome can produce desirable substances such as vitamin B. The role of probiotics to improve digestion and promote the nerve function and angiogenesis has been proven too.<sup>57</sup> Effect of composition and activity of microbiome on the health status of various systems of the body including neural, cardiovascular, metabolic, and immune systems is expressed also. The altered balance of the microbiome is associated with various pathologic conditions for instance type 2 diabetes mellitus, cancer, cardiovascular diseases, malignancy, colitis, obesity, psychiatric and gut-brain axis related diseases as well as numerous immunological disorders.<sup>58-63</sup>

Modulation and changes in the gut microbiome are involved in various health problems. In a research conducted by Liang et al, the results showed that oral administration of probiotics ameliorated the dysbiosis partly due to the modulation of the gut microbiome in addition to short-chain fatty acid and their receptor, GPR 43, in rats with non-alcoholic fatty liver leading to the inhibition of lipid deposition and chronic metabolic inflammation.<sup>64</sup> Chen et al showed that supplementation with *L. rhamnosus* (hsryfm1301) in hyperlipidemic rat model improved lipid metabolism due to regulation and

modulation of rat microbiome balance.<sup>65</sup> So, these shreds of evidence reveal that probiotics play very important roles in the balance of gut microbiota ecosystem in humans and animals.

### Diarrhea

Sazawal et al performed a study and expressed that probiotics reduced the risk of acute diarrhea of diverse causes by 34% as well as administration of probiotics caused the reduced risk of acute diarrhea among adults by 26% and among children by 57%.<sup>35</sup> Phavichitr et al also exhibited that the consumption of probiotics was associated with reduced duration of diarrhea by an average of one day.<sup>66</sup> The effects of probiotics on diarrhea after three days were assessed too, and 55% of people who received probiotics improved after 3 days.<sup>67</sup> In a meta-analysis performed by McFarland, several probiotics including a mixture of *B. bifidum* and *L. acidophilus* in addition to *Saccharomyces boulardii* had significant efficacy for prevention of traveler's diarrhea.<sup>68</sup>

The role of probiotics for amelioration and treatment of acute pediatric diarrhea has been proven too.<sup>69</sup> *S. boulardii*, a probiotic that is routinely used, was shown to exhibit convincing efficacy in the treatment of various chronic and acute gastrointestinal disorders including *Clostridium difficile* (CD) infection, acute or persistent diarrhea as well as human immunodeficiency virus (HIV) related diarrhea enteral nutrition-related diarrhea and Traveler's diarrhea.<sup>70-104</sup>

Mego et al designed a study in which between January 2011 and December 2013, patients suffering from colorectal cancer were randomized to receive placebo or probiotics. The results revealed that consumption of probiotics in the patients suffering from colorectal cancer and experiencing gastrointestinal toxicity due to irinotecan-based chemotherapy was safe and could reduce the symptoms of chemotherapy.<sup>105</sup>

*Lactobacillus* strains are safe to be used as a cure in infectious diarrhea in children, but as said before more investigations are needed to prove the claim.<sup>106</sup> Huang et al performed a meta-analysis research to evaluate the efficacy of probiotics for treatment of diarrhea, and the results showed that probiotics reduced the diarrhea duration by about one day in children.<sup>107</sup>

A study showed the promising effects of probiotics for the treatment of diarrhea in children and infants, declaring *L. rhamnosus GG* as the most strain of probiotics with the confirmed effects in diarrhea.<sup>108,109</sup> However, there were no demonstrable effects followed by administration of some strains of probiotics such as *L. casei* subspecies *rhamnosus* (LGG) and *L. paracasei* strain *ST11* (*ST11*) in the treatment of children suffering from severe diarrhea.<sup>110,111</sup> Although the second study confirmed the effect of *L. paracasei* *ST11* (*ST11*) for the treatment of nonrotavirus-induced diarrhea.<sup>111</sup> Despite the promising properties of probiotics in various diseases, the data about the diarrhea induced

by nosocomial infections are contradicting, for example, Szajewska et al performed a study in which 89 children aged 1 to 36 months were enrolled in a double-blind trial receiving either *L. rhamnosus GG* or placebo orally twice a day. The data suggested beneficial effects of probiotics especially *L. rhamnosus GG* in the treatment of nosocomial infections in infants, particularly nosocomial rotavirus gastroenteritis.<sup>112</sup> Moreover, a double-blinded randomized study containing 220 children evaluating the same strain of probiotics failed to show promising effects against nosocomial rotaviral infection while breastfeeding was effective.<sup>113</sup> A randomized trial study including 55 infants showed a lower prevalence of nosocomial diarrhea in the infants consuming probiotic-containing formula.<sup>114</sup> In study enrolling malnourished children in Peru, the number of episodes of diarrhea was reduced after using probiotics.<sup>115</sup> Meanwhile, another study in Finland failed to show significant differences among the experimental groups.<sup>116</sup> Children fed with a formula containing *L. reuteri* and *B. lactis* showed lesser and shorter episodes of diarrhea.<sup>117</sup> Growth inhibitory effects of probiotics in the treatment and prevention of vibrio cholera induced acute diarrhea has been proved too, suggesting probiotics as new sources to develop new pharmaceutical preparations for public health promotion.<sup>118</sup> A study performed by Saavedra et al. on infants aged 5-24 months showed that an infant formula containing probiotics could reduce the incidence of acute diarrhea in infants.<sup>119</sup>

Previous studies showed that infant formulas containing either *B. lactis* or a combination of *B. breve* and *S. thermophilus* showed protective effects against acute diarrhea in children.<sup>120,121</sup> Other published studies also showed that *L. reuteri* had significant effects in the reduction of the episodes of diarrhea and respiratory tract infections.<sup>23,122,123</sup> Another impact of probiotics is in the improvement of the complications due to gastroenteritis especially when combined with rehydration.<sup>124</sup> In another study performed by Salazar-Lindo et al for evaluation of the effects of probiotics for the treatment of watery diarrhea, they failed to show any kind of beneficial effects in this regard.<sup>125</sup>

### Prevention of Antibiotic Associated Diarrhea

Diarrhea is one of the most important side effects of antibiotics as a result of an imbalance in good and bad microbiome populations.<sup>126</sup> Consumption of antibiotics is said that can be associated with overgrowth of pathogens in some cases of CD, leading to life-threatening antibiotic associated diarrhea (AAD).<sup>127</sup>

This fact also has been proven in other studies too.<sup>128-130</sup> Hempel et al in a meta-analysis revealed that consumption of probiotics is associated with the reduction of AAD.<sup>129</sup> Many of studies conducted to evaluate the impacts of probiotics on antibiotics associated diarrhea are performed on small sample sizes and possess methodological biases. Studies based on the meta-analysis approaches declared

reduction of AAD by about 60%.<sup>131</sup> effective probiotics in this condition are *S. boulardii* in adults and *L. rhamnosus* GG in children.<sup>132</sup>

Another meta-analysis for evaluating the effectiveness of *S. boulardii* for prevention of AAD in different ages showed the moderate efficacy of this probiotic in the prevention of antibiotic-associated diarrhea.<sup>133</sup> Another meta-analysis conducted by McFarland et al showed that a combination of various probiotics showed their desirable effects in treating AAD and CD. Additionally, three types of probiotics (probiotic mixtures, *L. rhamnosus* GG, and *S. boulardii*) significantly reduced antibiotic-associated diarrhea.<sup>100</sup> Another meta-analysis based study indicated that probiotics reduced the risk of AAD by 52%.<sup>35</sup> Johnston et al showed that Children treated with probiotics showed a lower risk of AAD.<sup>134</sup> Goldenberg et al in another meta-analysis revealed a protective effect induced by probiotics against AAD with no mentionable side effects.<sup>135</sup>

In a study performed on the hospitalized children under antibiotics treatments, diarrhea was less likely to develop in the probiotic consuming group in comparison with oral rehydration and the risk of AAD, CD associated diarrhea as well as mean duration of diarrhea reduced too. It is noteworthy that a higher recovery rate was observed in children receiving probiotics.<sup>124,136</sup>

Pattani et al stated that probiotics reduce the risk of CD infection and AAD.<sup>137,138</sup> Another systematic review and meta-analysis showed that the people who used probiotics significantly were in lower risk of CD.<sup>128</sup> Moderate quality shreds of evidence exhibit that probiotics significantly reduce the CDD without any kinds of important side effects. Pediatric AAD is also prevented using probiotics, the data also exhibit an insignificant rate of side effect.<sup>139</sup>

Previous studies have indicated that *S. boulardii* and *lactobacilli* are the most used strains of probiotics for the treatment of AAD as well as *L. rhamnosus* GG and *Bacillus coagulans*.<sup>132,140</sup> Cai et al tried to find the effects of probiotics for the management of AAD. The result of this study expressed *L. rhamnosus* GG as the best option in the treatment of AAD.<sup>141</sup> Patients treated with probiotics for 3 days showed a significantly ( $P = 0.009$ ) lower frequency of AAD while cephalosporins, clindamycin or broad-spectrum penicillin were associated with the increased risk of pathologic conditions such as AAD.<sup>142</sup> Another meta-analysis conducted by Szajewska et al shows that probiotics are effective in the prevention of AAD in participants of different ages under treatment of antibiotics.<sup>143</sup> Probiotics are effective in the prevention of AAD in different ages and may be used during antibiotic therapy as well as 14 days after the antibiotic therapy discontinuance.<sup>144,145</sup> *L. reuteri* consumption reduces the duration of diarrhea while increases the chance of treatment in this disease. This probiotic strain potentially reduces the risk of acquired diarrhea in children as well as the frequency and intensity of antibiotics induced side effects during treatment for *H. pylori*.<sup>146,147</sup> This is

mentionable that yogurt containing *L. acidophilus*, *L. rhamnosus* GG and *B. lactis*, was effective for reducing the incidence of antibiotic-associated gastrointestinal disturbance in children.<sup>148</sup> Despite all beneficial effects of probiotics, *L. plantarum* DSM 9843 compared to placebo was not effective in the incidence of diarrhea and abdominal symptoms.<sup>149</sup> Another study to confirm the beneficial effects of drinking probiotics failed to confirm a beneficial effect on the prevention of AAD.<sup>150</sup> Ruszczyński et al showed that consumption of *L. rhamnosus* by children receiving antibiotics based treatments reduced the risk of any diarrhea.<sup>151</sup> A systematic review stated that the administration of probiotics closer to the first dose of antibiotic reduced the risk of CD infection by about more than 50% in patients.<sup>152</sup> In another report, the risk of AAD reduced due to the administration of probiotics.<sup>153</sup> Probiotics especially specific strains for example: *L. rhamnosus* GG had beneficial effects in preventing AAD, but more investigations are still needed in this area.<sup>154,155</sup>

### Cancer

A research by Ostad et al revealed some anticancer effects of probiotics in different cancer cell lines such as HT-29, Caco-2 and T47D in a dose-dependent manner.<sup>11</sup>

Rafter et al. performed a randomized trial aimed on the evaluation of the effects of a synbiotic for on cancer risk biomarkers in 80 patients who received either placebo or synbiotic. The results showed that synbiotic intervention could modulate cancer biomarkers in these patients.<sup>156</sup>

Thirabunyanon et al isolated various strains of probiotics from fermented dairy milks; two of which including *Enterococcus faecium* and *L. fermentum* exhibited antiproliferation effects against colon cancer cells.<sup>157</sup>

In another study, heat killed *L. acidophilus* 606 and *L. casei* ATCC 393 also showed antiproliferative effects in various cell lines, and soluble polysaccharide constituents isolated from *L. acidophilus* 606 showed potent antioxidant properties.<sup>158</sup>

Moreno et al in their study tried to explore anticancer effects of probiotics and stated that *L. helveticus* R389 could delay breast cancer tumor growth through inducing decrement of IL-6 as well as increment of IL-10.<sup>159</sup>

Another study trying to find more reliable shreds of evidence about the role of probiotics in cancer found that mice pre-inoculation with *L. acidophilus* significantly reduced tumor growth by 50.3%. Moreover, administration of *L. acidophilus* NCFM significantly downregulated the CXCR4 mRNA expressions in the extra-intestinal tissue, mesenteric lymph nodes and colon, highlighting the role of this strain of probiotics in triggering the molecular and cellular mechanisms involved in cancer pathogenesis.<sup>160</sup>

Another study stated that through the intervention in inflammatory processes, the probiotic VSL#3 can prevent dysplasia and cancer.<sup>161</sup> Also, it has been noted that the administration of *E. faecium* CRL 183 was associated with

a 50% reduction in the average number of tumors when compared to other groups in 4-week old male Wistar rats as animal models of cancer.<sup>162</sup>

*Bacillus polyfermenticus* a probiotic bacterium inhibited tumor growth partly due to the inhibition of the ErbB receptors. This study showed that ErbB2 and ErbB3, as receptors that are involved in the cancer pathogenesis, are suppressed by this probiotic.<sup>163</sup>

Nami et al evaluated the effects of *L. acidophilus* 36YL on four cancer cell lines (HeLa, AGS, HT-29, and MCF-7) and a normal cell line that was HUVEC cell line. The results revealed apoptotic effects of this probiotic on cancer cell lines and negligible toxicity against normal cells.<sup>164</sup>

A bunch of studies also show the probiotics effectiveness in various extraintestinal and gastrointestinal cancers especially colon and colorectal cancers, but there is a great need for more clinical trial-based shreds of evidence highlighting a direct effect for probiotics in the treatment of cancer.<sup>165-190</sup>

### Antibacterial Effects

Traditional yoghurts containing some strains of *Lactobacillus* showed antimicrobial effects against *Escherichia coli* and *Salmonella typhi*. The most antimicrobial effects were observed by *L. casei*.<sup>9</sup> Some other studies showed the antibacterial and antioxidant effects of probiotics too.<sup>191</sup> A study on kefir, another probiotic product, showed desirable anti-pseudomonal effects as well as a significant improvement of wound healing.<sup>10</sup>

### Irritable Bowel Syndrome

Another kind of abnormalities whose response to probiotics is tested is IBS. Various data suggests the beneficial effects of probiotics, but data is hard to compare partly due to differences in the dose of probiotics, duration of therapy, and the study design. A double-blinded randomized clinical trial showed that probiotics are not likely to heal IBS but the symptoms were reduced.<sup>192</sup>

Francavilla et al performed a randomized double-blind trial in which children received either *L. rhamnosus* GG or placebo for the duration of 8 weeks and the results showed that this probiotic was significantly effective to reduce the severity in addition to the frequency of abdominal pain in children with IBS.<sup>193</sup>

Horvath et al. in a study to evaluate the effects of *L. rhamnosus* GG for treating abdominal painful disorders in children observed that supplementation with this probiotic strain leads to a significantly increase in the rate of treatment responders when compared with placebo. Moreover a randomized cross-over trial among 59 patients conducted for the duration of six weeks to compare VSL#3 and placebo showed a significant effect for VSL#3 in symptom relief and abdominal pain/discomfort as well as abdominal bloating/gassiness.<sup>194</sup>

There is no data on prevention of IBS by prebiotics, but consumption of a prebiotic-containing whey-based formula in a controlled trial including 224 infants showed lesser gastrointestinal discomforts.<sup>195</sup> Korterink et al in a meta-analysis based study showed that probiotics reduce abdominal pain in related disorders, especially in patients with IBS.<sup>196</sup>

### *Helicobacter pylori*

The use of probiotics in the treatment of HP is a controversial topic, but the beneficial characteristics of probiotics for the treatment of HP have been exhibited in various animal models. *Bifidobacterium* and *Lactobacillus* are specific bacteria with desirable effects in the treatment of HP *in vitro* through the production of bacteriocins or organic acids in addition to the inhibition of its adhesion to epithelial cells and reducing the load of HP.<sup>197,198</sup> It is noteworthy that some studies exhibit higher eradication rate of HP due to consumption of probiotics in association with antibiotics and proton pump inhibitors that are normal drugs for treating HP.<sup>199</sup> Using in association with the normal therapy of HP, probiotics can reduce the side effects of antibiotic treatments especially diarrhea in children.<sup>200-203</sup> A study conducted to evaluate the effects of probiotics in the treatment of HP showed the desirable effects that may be partly due to the eradication of the risk of disorders associated with gastric inflammation.<sup>204</sup>

In concordance with the above studies, Losurdo stated that probiotics in the treatment of HP showed a direct effect in its clearance and eradication.<sup>205</sup> This is noteworthy that in HP infection, combined therapy with probiotics can protect and restore the microbiome of the intestine.<sup>206</sup> So probiotics both alone and in combination with antibiotics and other HP treatments may alleviate the infection's symptoms as well as reduce drug side effects.<sup>207</sup>

### Constipation

Constipation is a disorder in GIT associated with infrequent stools, difficult stool passage as well as pain and stiffness.<sup>208</sup> Children 3-16 years of age experiencing constipation were randomized in a pilot study and consumed one sachet containing  $10^8$ - $10^{10}$  CFU *B. breve* daily. The data of this study showed the positive effect of this strain of probiotic.<sup>209</sup> Another study conducted by Zhao et al to evaluate the effect of probiotics on constipation showed the positive effects of a mixture containing, *B. longum*, *B. bifidum*, *B. infantis*, *L. plantarum*, *L. casei*, and *L. rhamnosus* on the constipation.<sup>210</sup> Administration of *L. rhamnosus* (Lcr35) to children with chronic constipation showed desirable effects of this probiotic.<sup>211</sup> There are pieces of evidence for some strains stating failure of showing efficacy in the treatment of constipation, for example, *L. rhamnosus* failed to show desirable effects.<sup>212,213</sup> Due to the consumption of *L. reuteri*, bowel frequency improved in infants with functional constipation.<sup>214</sup> Improvement of defecation frequency and abdominal

pain was accomplished due to the consumption of yogurt supplemented with *B. longum*.<sup>215</sup> A dairy product containing *B. animalis* increased stool frequency in children experiencing constipation.<sup>216</sup> Santhosh Jose evaluated the effects of probiotics consumption on the treatment of constipation and exhibited the desirable effects of probiotics in this condition.<sup>217</sup>

In another study reported by Choi et al, significant reduction of *Bifidobacterium* and *Bacteroides* species in the feces of the patients suffering from functional constipation was observed.<sup>218</sup> Dimidi et al exhibited that probiotics, particularly *B. lactis*, improved stool consistency, stool frequency and whole gut transit time.<sup>219</sup> It is well understood that altered microbiome precisely contributes to the pathogenesis of constipation, but the specific mechanism of probiotics in the constipation is still unclear, and this effect may be partly due to their impact on the fermentation and gut microbiome, as well as effects on the central and enteric nervous systems and the immune system.<sup>220</sup>

### Atopic Dermatitis and Dermal Health

There is a bunch of studies indicating the beneficial role of probiotics in various conditions of the skin such as atopic eczema, wound, and scar healing as well as a help to skin-rejuvenation.<sup>8</sup>

Consumption of probiotics containing *L. acidophilus*, *L. casei*, *L. salivarius*, and *B. bifidum* was effective to reduce Scoring Atopic Dermatitis (SCORAD) index as well as total serum immunoglobulin E (IgE) and cytokines such as interleukin (IL)-5, IL-6, and interferon (IFN)- $\gamma$  in pediatric patients.<sup>221</sup>

Weise et al showed that *E. coli* Nissle 1917 modulated immune responses through the increment of Foxp3 (+) cells and immunoregulatory cytokine patterns.<sup>222</sup>

In a study by Kukkonen et al, pregnant women carrying infants with a high risk of allergy received a mixture of 4 species of probiotics or placebo for about 4 weeks before delivery and their children received the same probiotics or a placebo daily for 6 months after birth. The data showed that feeding probiotics to newborn infants increased the resistance to respiratory infections during the first 2 years of life as well as a significant reduction in (atopic) eczema.<sup>223</sup> Another study expressed that a great reduction was observed in clinical eczema among children whose mother received probiotic.<sup>224</sup> A meta-analysis based study conducted by Doege et al revealed the fact that administration of probiotics during pregnancy prevented atopic eczema in children with the ages ranging from 2 to 7 years.<sup>225</sup>

It has been declared that when applied on the skin, *B. longum* lysate had beneficial effects on the symptoms of sensitive and reactive skin.<sup>226</sup>

Lew and Liong in their study reported that some bioactive compounds from probiotics such as hyaluronic acid, sphingomyelinase, peptidoglycans and lipoteichoic

acid exert beneficial dermal effects, but the exact mechanism remains unclear.<sup>227</sup>

*Lactobacillus fermentum* is another strain with beneficial effects in children experiencing moderate or severe atopic dermatitis.<sup>228</sup> Probiotics, particularly *L. rhamnosus* GG is effective either for the prevention of atopic dermatitis or healing of the related symptoms.<sup>229</sup> However, there are various studies in which there was no convincing data about the efficacy of some strains of probiotics in the treatment of atopic dermatitis.<sup>230</sup>

A meta-analysis conducted by Pelucchi et al exhibited the role of probiotics for some kinds of dermal conditions such as atopic dermatitis.<sup>231</sup> Consumption of *B. lactis* and *L. rhamnosus* relieved the symptoms of atopic dermatitis only in food sensitized children.<sup>232</sup>

Yeşilova et al reported that probiotics are effective in reducing an indicator of atopic dermatitis that is SCORAD index in the patients as well as serum IFN- $\gamma$ , IL-6, and IL-5 as well as total serum IgE levels.<sup>233</sup>

Another meta-analysis also consisted of about ten studies showed the moderate role of probiotics in the treatment of atopic dermatitis.<sup>234</sup> Based on the data such as reduction of the clinical symptoms as well as local and systemic inflammation, probiotics can be used to alleviate allergic inflammations such as atopic dermatitis.<sup>235</sup> Probiotics are announced as a new strategy in the treatment of atopic dermatitis, their beneficial effects may be partly due to the balance of the gut microbiome, improvement of immunological defense barrier (IgA) in the intestine, modulation of inflammatory responses in addition to the production of inflammatory cytokines.<sup>236</sup> *L. gasseri* is another strain of probiotics assumed to reduce the immune responses induced by inflammatory cytokines for instance IL-17 that is another kind of evidence confirming the desirable effects of probiotics in atopic dermatitis.<sup>237</sup> Meneghin et al studied the effect of probiotics in the atopic dermatitis of children, and the data suggested about the effectiveness of probiotics; moreover, most of the studies about this matter were conducted on a single strain of probiotics other than a mixture, but the effectiveness of the mixture was more.<sup>238</sup> Foolad et al declared the usefulness of probiotics in the treatment of atopic dermatitis. Probiotics induced a long term reduction in the symptoms of atopic dermatitis, and the severity of the symptoms was reduced.<sup>239</sup> In a study in which 88 children were enrolled to evaluate the effectiveness of a single strain of probiotics called *L. sakei*, the results confirmed a significant reduction of symptoms and severity of dermatitis in the intervention group.<sup>240</sup> *L. plantarum* CJLP133 is another strain of probiotics with promising effects in the treatment of atopic dermatitis in children.<sup>241</sup> In a study a combination of *Lactobacillus* strains including *L. reuteri* and *L. rhamnosus* were given to atopic dermatitis experiencing children. the results at the end of the intervention, showed that about 56% of the patients declared the improvement

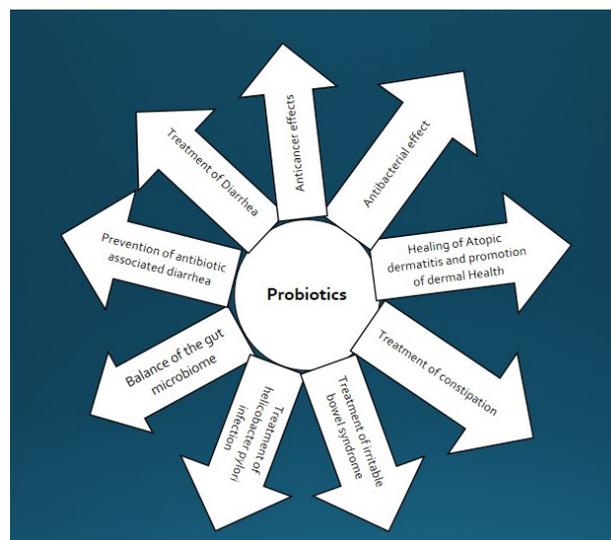
of eczema symptoms.<sup>242</sup> Niccoli et al also reported the effectiveness of *L. salivarius* LS01 in children with atopic dermatitis.<sup>243</sup> A meta-analysis on the data published during February 1997 and May 2007 provided more convincing evidence about the effectiveness of probiotics in the treatment of some kinds of dermal disorders such as atopic dermatitis.<sup>244</sup> Consumption of probiotics has shown promising effects in adults too. For instance, in a study conducted on 38 patients suffering from atopic dermatitis, the results showed that *L. salivarius* LS01 significantly improved the clinical manifestation and quality of life that may be partly due to the modulation of Th1/Th2 cytokine profiles.<sup>245</sup> A combination of *B. lactis*, *L. acidophilus* and fructooligosaccharides administered to preschool children experiencing atopic dermatitis showed significant improvement of clinical symptoms in the intervention groups.<sup>246</sup> Improvement and stabilization of intestinal mucosal barrier is associated with the pathogenesis of atopic dermatitis, and probiotics may stabilize this barrier in the intestine.<sup>247</sup>

Göbel et al expressed that the consumption of probiotics decreased the levels of IFN- $\gamma$  and IL-10 leading to the beneficial effects of probiotics in young children experiencing atopic dermatitis.<sup>248</sup> A meta-analysis suggests that probiotics may be an option for the treatment of atopic dermatitis including moderate to severe atopic dermatitis in the children and adults.<sup>249</sup> Another meta-analysis also exhibits that probiotics have a protective role in the pre and postnatal period in all risky population.<sup>250</sup> Iemoli et al conducted another study in which a combination of *L. salivarius* LS01 and *B. breve* BR03 exhibited beneficial effects in the treatment of atopic dermatitis in adults.<sup>251</sup> Likewise, 53 children enrolled in an eight week supplementation period during which a probiotic (*L. fermentum*) (n=26) or a placebo (n=27) was administered, and improvement in atopic dermatitis severity with probiotic treatment was observed.<sup>228</sup>

Grüber et al declared that there are not enough shreds of evidence on the beneficial effects of probiotics in the treatment of atopic dermatitis in children.<sup>252</sup> Atopic eczema/dermatitis syndrome was alleviated after the administration of *L. rhamnosus* GG for 4 weeks; the observed data also exhibited the beneficial effects of this probiotic in IgE-sensitized infants but not in non-IgE-sensitized infants (Figure 1).<sup>253</sup>

## Conclusion

This review aimed to briefly introduce probiotics as well as some of their beneficial effects including antibacterial effects, balance of the gut microbiome, prevention of AAD, and treatment of some pathologic conditions such as diarrhea, cancer, IBS, HP infection, constipation and atopic dermatitis. In our review, the most known health properties of probiotics are found to be the prevention of diarrhea due to the balance of the gut microbiome. Despite these beneficial effects, some strains of probiotics



**Figure 1.** Summarization of Some Beneficial Effects of Probiotics.

failed to show efficacy in various pathologic conditions that highlight this fact that the beneficial effects exerted by probiotics are limited to precise strains of these bacterial communities. Regarding the vast developments in this area of research, there is more and more requirements for investigations on this interesting area of research to find biological products with more efficacy and less side effects.

## Conflict of interests

The authors declare no conflict of interests.

## Ethical Approval

This review was based on the previously published articles and no ethical approval is provided.

## Authors' contribution

AAG designed the study and scientifically revised the manuscript. RS drafted and wrote the manuscript and performed the searching of databases. APM drafted the manuscript and performed the searching of databases. MRF scientifically revised the manuscript.

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