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Beneficial Effects of Probiotics in Some of the Important Human Disorders: A narrative review

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ABSTRACT

Probiotics were first proposed by Metchnikoff as contributing factors to health. These living microorganisms, which mainly belong to the microflora bacteria of the gastrointestinal tract, can have beneficial effects on human health if consumed in moderation. The most studied probiotics are lactic acid bacteria, which include *Lactobacillus* and *Bifidobacteria*. The present study is an overview of some studies conducted on the effects of using probiotics and their possible patterns in the prevention or reduction of certain human diseases and disorders. The available data suggest that probiotics can play a role in improving constipation and liver enzymes level and functions, and have significant effects on rooting and improving the symptoms of *Helicobacter pylori*. It was concluded that probiotics have positive effects in metabolic syndrome treatment, preventing gestational diabetes, and improving oral health. Since many probiotics are microorganisms familiar to the gastrointestinal tract, if consumed in moderation, there are no side effects for the host. Using them as complementary therapies for some diseases related to the gastrointestinal tract microflora bacteria can be an effective and low-cost approach to alleviating the annoying symptoms of such diseases.

Keywords: Probiotics, Constipation, Helicobacter Pylori, IBS, Metabolic Syndrome, Gestational Diabetes Mellitus, NAFLD, Infantile Colic

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Introduction

The history of discovery, production, and use of fermented milk products dates back to ten thousand years BC, in the Middle East, the Balkans, and among the Aryan tribes of present-day Iran and Turkey. Elie Metchnikoff, a Russian biologist who won the Nobel Prize in 1908, for the first time invented what Western dominance has scientifically witnessed. He used *Bacillus bacteria*, which are endospore-producing bacteria, in modern yogurt production. This simple and comforting technology made its way to Europe during World War II and introduced this beneficial food to the poor residents of this continent. Thus, the collection of organisms that interfere with the fermentation process maintaining the health and stability of the gastrointestinal microflora was later called probiotics (1).

Probiotics are live microorganisms that, if consumed by human beings or animals, can cause beneficial effects on the host's health. Most probiotics belong to a large group of the main bacteria of the human gut microbial flora that have harmless companionable livings.

The most common probiotic microorganisms are divided into two groups: bacteria and fungi. Some of these microorganisms are selective strains of *Lactobacillus* and *Bifidobacterium*. However, species of *Enterococcus*, *Streptococcus*, and *Escherichia coli* are also used as probiotics. Yeasts also include *Saccharomyces cerevisiae*, *Saccharomyces boulardii*, and *Candida intolerance* (2).

From the time of discovery to date, probiotics have attracted researchers and public interest in their potential health benefits. Several reviews and meta-analyses in different contexts have been conducted investigating the beneficial properties of probiotics (3-5). This study aimed to collect evidence on beneficial effects as well as any side effects of probiotics on human health.

Materials and Methods

To cover a wide area of information, the electronic search was performed in two steps. First, the general keywords including probiotics, human, health, uses of probiotics, and therapeutic uses of probiotics were searched. Simultaneously Persian equivalents of the mentioned keywords were also searched in Persian databases. In the next step and after reviewing the search results, nine of the therapeutic uses of probiotics were selected which were associated with constipation, Helicobacter pylori, irritable bowel syndrome symptoms, metabolic syndrome, gestational diabetes mellitus, non-alcoholic fatty liver disease, infantile colic, and oral health. After that, a separate database search was conducted for each of the therapeutic uses, using the following keywords: probiotics in constipation, probiotics in Helicobacter pylori, probiotics in irritable bowel syndrome symptoms, and probiotics in metabolic syndrome, etc.

The citations found in the second step and some of the citations from the first step were entered to Endnote X8, and duplicates were removed. Over 234 studies were analyzed and 80 papers were selected to be reviewed in the present study. There were no limitations in the date and language of the studies. Excluded studies were the irrelevant studies, letters, and short communications. In addition, to reduce the missed articles, the references of the available systematic reviews related to each discussed section were analyzed. The Characteristics of the clinical studies used in the present review is provided in Table.1

Table 1. Characteristics of the clinical studies used in the present review

Author	Country	Study Design	Disorder	Probiotics Species Used
Jahangiri [1]	Iran	RCT	Constipation	• *Lactobacillus* • *Bifidobacteria* • *Streptococcus thermophilus*
Noor-L-Houda Bekkali [2]	The Netherlands	Pilot study	Childhood constipation	• *Bifidobacteria bifidum* • *Bifidobacteria infantis* • *Bifidobacteria longum* • *Lactobacilli casei* • *Lactobacilli plantarum* • *Lactobacilli rhamnosus*
FAVRETTO [3]	Brazil	RCT	Constipation	• *Bifidobacterium lactis BI-07*
Flavia Indrio [4]	Italy	RCT	Functional constipation	• *Lactobacillus reuteri DSM17938*
Yangwenshan Ou [5]	China	Open trial	Constipation in adults	• *Lactobacillus casei Strain Shirota*
Sanmugapriya Jayasimhan [6]	Malaysia	RCT	Chronic constipation	• *Bifidobacterium* • *Lactobacillus*
Abedini [7]	Iran	RCT	Childhood constipation	• *Lactobacillus casei* • *Lactobacillus Acidophilus* • *Lactobacillus bulgaricus* • *Lactobacillus rhamnosus* • *Streptococcus thermophiles*
Saneeyan [8]	Iran	RCT	Helicobacter pylori	• *Bifidobacterium breve* • *Lactobasillus casei* • *Lactobacillus acidophilus* • *Lactobasillus reuteri* • *Lactobasillus bulgaricus* • *Bifidobacterium bifidum* • *Streptococcus cremoris*
LIONETTI [9]	Italy	RCT	Helicobacter pylori	• *Lactobacillus reuteri*
Pourfarzi [10]	Iran	RCT	Irritable Bowel Syndrome	• *Bifidobacterium bifidum* • *Lactobasillus*
Francavilla [11]	Italy	RCT	Irritable Bowel Syndrome	• *Lactobacillus casei* • *Lactobacillus plantarum* • *Bifidobacterium breve*
Rezazadeh [12]	Iran	RCT	Metabolic syndrome	• *Lactobacillus acidophilus La5* • *Bifidobacterium lactis Bb12*
Bernini [13]	Brazil	RCT	Metabolic syndrome	• *Bifidobacterium animalis*
Stadlbauer [14]	Austria	Randomized pilot study	Metabolic syndrome	• *Lactobacillus casei Strain Shirota*
Leber [15]	Austria	Randomized pilot study	Metabolic syndrome	• *Lactobacillus casei Strain Shirota*
Barreto [16]	Brazil	Clinical trial	Metabolic syndrome	• *Lactobacillus plantarum*
Kijmanawat [17]	Thailand	RCT	Gestational diabetes mellitus	• *Lactobacillus acidophilus* • *Bifidobacterium bifidum*
Jameshorani [18]	Iran	RCT	Non-alcoholic fatty liver disease	• *Lactobacillus* • *Bifidobacterium* • *Streptococcus thermophiles*

Table 1. Characteristics of the clinical studies used in the present review

Nabavi [19]	Iran	RCT	Non-alcoholic fatty liver disease	• *Lactobacillus acidophilus* • *Bifidobacterium lactis*
Aller [20]	Spain	RCT	Non-alcoholic fatty liver disease	• *Lactobacillus bulgaricus* • *Streptococcus thermophilus*
Famouri [21]	Iran	RCT	Non-alcoholic fatty liver disease	• *Lactobacillus acidophilus* • *Bifidobacterium lactis* • *Bifidobacterium bifidum*
Rafeey [22]	Iran	RCT	Infantile colic	• *Lactobacillus rhamnosus* • *Lactobacillus casei* • *Lactobacillus rhamnosus* • *Streptococcus thermophiles* • *Bifidobacterium breve*
Chau [23]	Canada	RCT	Infantile colic	• *Lactobacillus acidophilus* • *Bifidobacterium infantis* • *Lactobacillus bulgaricus* • *Lactobacillus reuteri*
Kianifar [24]	Iran	RCT	Infantile colic	• *Lactobacillus casei* • *Lactobacillus rhamnosus* • *Streptococcus thermophiles* • *Bifidobacterium breve*
Saavedra [25]	USA	RCT	Infantile colic	• *Lactobacillus acidophilus* • *Bifidobacterium infantis* • *Lactobacillus bulgaricus* • *Bifidobacterium lactis* • *Streptococcus thermophilus*
Tsubura [26]	Japan	Clinical trial	Oral health	• *Bacillus subtilis*
Hatakka [27]	Finland	RCT	Oral health	• *Lactobacillus rhamnosus* • *Lactobacillus GG*

Effects of probiotics use on constipation

Constipation is the most common problem with the gastrointestinal tract after a stroke, which can increase intracranial pressure. Constipation is defined as difficulty in defecation and infrequent defecation (less than three times a week), with hard and dry stool (6, 7). Constipation may be either transient or chronic. To distinguish chronic from transient constipation, the duration and characteristics of the patient's symptoms must be assessed (8). In a conceptual view, primary (idiopathic) constipation is divided into three main types: normal-transit, slow-transit, and pelvic floor dysfunction (9). Currently, the main treatment for constipation is symptomatic treatment including laxatives and fiber, which are associated with side effects and limitations (10). Therefore, due to the positive effects of probiotics on the gastrointestinal tract, they can be useful. In this regard, the results of a study showed that the consumption of probiotics increases the frequency of defecation in stroke patients. Therefore, probiotics can be used to treat constipation in these patients (10).

Constipation is also a common complaint in children and its prevalence in the general population is 0.9-2.7% (11). A normal child may have a soft, trouble-free defecation every two or three days, but having hard defecation every three days must be treated (12). Since probiotics are living non-pathogenic bacteria that grow in the gut and regulate its microbial flora, using these microorganisms can be helpful, which is consistent with the results of the following studies. A study by Abedini showed that although consumption of seven probiotic species for four weeks caused no

statistically significant difference in painful and hard defecation between the case-control and placebo groups, there was a statistically significant difference between the two groups in terms of abdominal pain in two to four weeks after the intervention (13).

One of the most well-known products with probiotics is Kefir, which is a product of probiotic fermented milk. Kefir was used as a probiotic product in a study by Turan *et al.*, and the results showed that it had positive effects on the symptoms of constipation, and also, accelerated the colonic transfer (14).

A study by Yangwenshan suggests that probiotics may be useful in constipation. They used *Lactobacillus casei* as probiotic and stated that consumption of *Lactobacillus casei* strain Shirota (LcS) increased defecation frequency, improved symptoms related to constipation, and normalized stool consistency. Using metabolic methods PIPA (Pipecolic acid), which is a non-volatile metabolite in the gut, was identified as a potential target for reducing constipation through *LcS*. Also, it could improve constipation symptoms in a mouse model by increasing the rate of small intestine propulsive contractions and the number of fecal pellets (15).

In another study, the prophylactic effectiveness of *L. reuteri DSM 17938* in preventing functional constipation was investigated and it was revealed that its use in the first three months of life reduces gastrointestinal dysfunction and its associated troubles (16).

Also, Dimidi *et al.* reported the beneficial effects of the *B. Lactis* subgroup on intestinal transit and stool frequency and consistency (17). According to a study by Bekkali, performed to determine the effect of a mixture of probiotics containing *Bifidobacteria* and *Lactobacilli* on the treatment of constipation in children, probiotics had a positive effect on the symptoms of constipation (18). In another study, the effect of consumption of freshly fortified cheese with a probiotic on the constipation symptoms was investigated, and it was concluded that consumption of freshly fortified cheese with *Bifidobacterium lactis Bi-07* had beneficial effects on the symptoms of defecation (19). On the other hand, the study of the effect of consumption of microbial cells (Hexbio) containing fructo-oligosaccharide, *Bifidobacteriu*m, and *Lactobacillus* in improving the frequency of defecation and symptoms of chronic constipation, indicates that it is effective in improving stool frequency and consistency. Also, it can reduce the feeling of incomplete evacuation in adults with chronic functional constipation (20). A review by Chengcheng on the studies conducted in this field also shows that consumption of probiotics, especially multispecies probiotics, can significantly reduce Gamma-glutamyl transferase (GGT) and increase stool frequency and consistency (21). Based on the above-mentioned studies, it can be concluded that the use of probiotics in the treatment or improvement of the constipation symptoms can be useful.

Effects of probiotics on the eradication of Helicobacter pylori

Helicobacter pylori (H. pylori) is a spiral and gram-negative bacterium that causes the most common chronic bacterial infection and is found in all parts of the world at all ages, affecting about half of the world's population. In developing countries, the infection occurs at younger ages and its complications include duodenal ulcers, gastrointestinal malignancies, and acute and chronic gastritis (22, 23). The idea of using probiotics as an adjunct in the treatment of *H. pylori* infection is based on the studies that have shown the beneficial effects of *Lactobacilli* or their metabolic products in killing or stopping the growth of *H. pylori* in the laboratory (24, 25). In a study by Saneeyan *et al*. on 50 infected children, using protexin did not increase *H. pylori* rooting, but reduced the side effects of treatment and increased adherence to the treatment diet (26). The probiotics as a single agent for the treatment to eradicate *H. pylori* may not be effective. According to a study by Goderska *et al*., it has been suggested that the use of probiotics alone is not recommended for *H. pylori* eradication, but in combination with standard therapy and as an adjunct, probiotics can improve the eradication rates and reduce the side effects of the treatment (27). Also, in a study by Min-Min, probiotics were used in combination with standard treatment and the results showed increased *H. pylori* eradication and reduced side effects of the treatment in the general population (28).

There is strong evidence that supports the effectiveness of probiotics in the treatment of *H. pylori* infection. The study of Boltin confirms this evidence, however, according to this study

the optimal probiotic species, dosage, and duration of treatment are not yet known and further studies are needed. They also stated that the benefits of a probiotic may depend on the effectiveness of the chosen antibiotic diet as well (29). Therefore, the researchers are trying to find the best dosage of probiotic consumption.

A study by Feng *et al*. showed that probiotics increased rooting speed and reduced side effects in combination with therapies designed to eradicate *H. pylori*. They also stated that using probiotics before and during eradication treatment, as well as consuming them for more than two weeks, have had better effects on the treatment. According to the findings of this study, the best effects of probiotics have been related to *Lactobacillus* and its various strains along with the quadrilateral bismuth diet (a four-drug regimen including omeprazole, amoxicillin, clarithromycin, and bismuth) (30).

Other studies in this field confirm the effectiveness of probiotics. A review by Jouerong showed that probiotic supplementation during anti-H. pylori treatment may be effective in improving *H. pylori* eradication, minimizing the side effects of the treatment, and reducing the clinical symptoms associated with the disease (30).

A study by Fang *et al.* on the effectiveness of Lactobacillus-supplemented triple therapy, suggests that *Lactobacillus (L. reuteri)* as a triple therapy supplement may increase *H. pylori* eradication rate, and also, reduce the incidence of treatment-related diarrhea in children (31), which is consistent with the results of a study by Lionetti's. They reported that children who received *L. reuteri* had fewer symptoms than those who received a placebo (32). In this regard, many studies investigated the effect of probiotics on *H. pylori* cohesion and inhibition of inflammation in gastric epithelial cells in humans. In a study, it was shown that *L. acidophilus* and *L. bulgaricus* were effective in reducing the burden of *H. pylori* and due to the safety and health benefits of probiotics, foods containing these two strains could be used as adjunctive therapy for the eradication of *H. pylori* infection (33). According to the above-mentioned studies, the use of probiotics alone may not be effective for eradicating *H. pylori*, but using them as supplements can be very helpful in reducing the side effects of the treatment.

Effects of probiotics in irritable bowel syndrome symptoms

Irritable bowel syndrome (IBS) is often considered as a functional disorder because no structural, biochemical, or infectious etiology has been found for it. The underlying problem appears to be related to the gastrointestinal (GI) dynamic or sensory dysfunction (34, 35).

Due to the lack of effective treatment and chronicity of the disease, which is usually associated with anxiety in patients, it seems necessary to find a more effective treatment to control patients' symptoms such as abdominal pain and defecation swings. Studies have shown that adding probiotic yogurt to the patients' diet can be effective in improving IBS symptoms, especially abdominal pain and bloating. Given the high prevalence of IBS and the lack of effective treatments, providing a treatment that even slightly improves the symptoms of the disease is an important achievement (36). Several studies have shown an increase in the prevalence of celiac disease in patients with IBS. Examination of probiotic supplements in patients with celiac disease (CD) strictly adherent to a gluten-free diet (GFD), showed that after six weeks of treatment, the probiotics mixture was effective in reducing symptoms and there was a significant reduction in pain (37).

The evidence confirms the potential beneficial effect of *Bifidobacteria*, alone or in combination, on the symptoms of IBS without the induction of significant changes in bowel function. It has also been stated that changes in the intraluminal milieu and secondary effects on colonic transit will lead to beneficial effects for patients (38). Besides, more effectiveness of probiotics compared to placebo has been reported by Didari (39). In another study by Nikfar *et al.*, it was reported that probiotics may improve the symptoms of IBS and can be used as a standard treatment supplement (40).

Effects of probiotics on metabolic syndrome

A set of metabolic abnormalities, such as abdominal obesity, high fasting blood sugar level, high blood pressure, and hyperlipidemia is called metabolic syndrome (MetS), which usually occurs in middle age (41). Several definitions are available for MetS. According to the National Cholesterol Education Program (NCEP), the presence of any three or more following factors is defined to be MetS (42):

1. Blood glucose greater than 5.6 mmol/L (100 mg/dl) or drug treatment for elevated blood glucose
2. HDL cholesterol greater than 1.0 mmol/L (40 mg/dl) in men and greater than 1.3 mmol/L (50 mg/dl) in women or drug treatment for low HDL-C
3. Blood triglycerides greater than 1.7 mmol/L (150 mg/dl) or drug treatment for elevated triglycerides
4. Waist circumference more than 102 cm (men) or more than 88 cm (women)
5. Blood pressure higher than 130/85 mmHg or drug treatment for hypertension

This syndrome, with an increasing prevalence, is a risk factor for type 2 diabetes (T2D) and cardiovascular diseases (43, 44). By changing the intestinal bacterial flora, probiotics can reduce weight and insulin resistance by modulating immune function and reducing inflammation. And since insulin resistance is an etiological factor for the individual components of the metabolic syndrome that plays a key role in the development of diabetes (45), these effects could be used in prevention methods. Improving lipid profiles caused by probiotics arise from reduced cholesterol absorption, the production of short-chain fatty acids, and the breakdown of bile acids. It has also been suggested that probiotics reduce blood pressure by their proteolytic action and releasing angiotensin-converting enzyme inhibitory peptides. Examination of probiotic yogurt's effectiveness on the glycemic index (GI) and endothelial function markers in patients with metabolic syndrome has shown that taking probiotic yogurt improves fasting blood sugar level and leads to partial improvement of serum endothelial function markers (46). It was also reported that *B. Lactis HN019* has potential effects in reducing obesity, hyperlipidemia, and some inflammatory markers in people with metabolic syndrome, which may lower the risk of cardiovascular diseases in such patients (47).

In a much broader study, the effect of probiotics on abnormalities such as obesity, insulin resistance syndrome, T2D, and non-alcoholic fatty liver disease was investigated. The results showed significant reductions in abdominal fat and body mass index (BMI) for obese and overweight people who received probiotic and synbiotic supplements. They also stated that probiotics improved carbohydrate metabolism and reduced metabolic stress in patients with T2D and insulin receptor substrate (IRS) (48). Stadlbauer *et al.* reported that using *Lactobacillus casei Shirota* in 28 patients with MetS did not cause any changes in blood pressure (BP), waist circumference (WC), triglyceride (TG), and TC blood levels (49). In a study by Leber *et al*., similarly, there were no changes in BP, WC, TG, TC, and fasting glucose levels reported (50). However, some studies reported a significant reduction in blood glucose levels (46, 51).

According to scientific findings, the role of gut microbiota in regulating plasma glucose, appetite, serum lipids, and inflammation has been proven. On the other hand, according to the results of a study by Shay, prebiotics or probiotics, which are widely used to promote microbiota, can reduce low-grade intestinal inflammation by improving intestinal glucose integrity and reducing serum lipids, weight, and insulin resistance (52). Although clinical trials have often failed to achieve the beneficial effects of probiotics on metabolic syndrome components, most studies have reported positive results regarding these microorganisms. Therefore, the use of probiotics can be considered as a new approach in the prevention or improvement of metabolic syndrome components (44).

Effects of probiotics on gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is the most common disorder during pregnancy (53). At the end of pregnancy, the number of *Proteobacteria* and *Acinetobacteria* increases and bacterial enrichment reduces (54). Therefore, consuming probiotic products to increase and improve intestinal microflora can be useful. According to studies, probiotics can boost the antioxidant system of beta cells and promote glucose homeostasis by reducing the rate of insulin removal (55). According to available results, probiotic supplementation may reduce the risk of high blood sugar in newborns and improve glycemic control, blood lipid profiles, inflammation, and oxidative stress in pregnant women with GDM (56). Kijmanawat *et al.* examined the effectiveness of probiotics on insulin resistance in patients with GDM and found that the use of probiotic supplements for four weeks in women with diet-controlled gestational diabetes leads to a decrease in fasting blood glucose level and an increase in insulin sensitivity in the late second

trimester and early third trimester (57). It is worth mentioning that Taylor reviewed the studies conducted in this field and stated that while probiotic supplementation has significantly reduced insulin resistance in pregnant women with GDM, there was no significant effect on their fasting blood glucose levels and LDL-Chol levels (58). Non-effectiveness of probiotics on fasting blood sugar levels was also reported by Pan *et al*., but the reducing effect of probiotic supplementation on insulin resistance and fasting serum insulin, compared with the control group, was significantly observed (59). In general, according to a review by Hajifaraji, the available data suggest that manipulation of gut microbiota in women at risk of or with GDM can probably have significant benefits on improving metabolic profiles and pregnancy outcomes (60).

Effects of probiotics on non-alcoholic fatty liver disease

Today, non-alcoholic fatty liver disease (NAFLD) is a major burden on the health systems of various countries, and due to the lack of an effective and special treatment for it, using probiotics has recently been considered. For example, in a study by Jameshorani et al.(61) on 90 patients, the percentage changes in BMI, blood pressure, fasting serum glucose levels, triglyceride (TG) and cholesterol level, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were compared between study and control group after consumption of Familact. The results showed that the safe and effective Familact synbiotic improved blood sugar level, body mass index (BMI), and fat profile except for high-density lipoprotein (HDL) and reduced liver transaminases in patients with NAFLD (61). Beneficial effects of consuming probiotic yogurt on the levels of serum liver enzymes, TC, and LDL-C have also been reported in a study, in which samples consumed probiotic yogurt containing *Lactobacillus acidophilus La5* and *Bifidobacterium lactis Bb12* (62). Also, in a study by Aller *et al.*, an improvement was observed in liver aminotransferase level using *Lactobacillus bulgaricus* and *Streptococcus thermophilus* bacteria (63). Changes in the intestinal flora and endotoxemia may play a role in the development of NAFLD. On the other hand, Xue *et al.* found that probiotics can regulate serum levels of lipopolysaccharide (LPS) and toll-like receptor 4 (TLR4) in the liver, and may delay NAFLD development by signaling LPS/TLR4 (64). In a study by Xue et al. (64), the possible mechanism of probiotics in NAFLD was explained by showing that probiotics can reduce liver aminotransferase, total cholesterol, tumor necrosis factor-alpha (TNF-α), and improve insulin resistance in patients with NAFLD (65). Besides, since TNF-α is a systemic inflammation factor, which can accelerate atherosclerosis pathogenesis (66), probiotics may also help to prevent such chronic disease.

The available evidence had shown the role of oxidative stress and related markers in the pathogenesis of NAFLD. The effects of probiotics on oxidative stress are one of the important factors that studies have announced. The study by Ipar *et al.* suggested that using probiotics caused a reduction in TC, LDL-C, and total oxidative stress serum levels (67). Similarly, Rajkumar *et al*. reported improvements in lipid profile and insulin sensitivity and a reduction in C-reactive protein levels in 60 overweight subjects (68).

The studies confirm that intestinal bacteria induce endogenous signals that are effective on hepatic insulin resistance and NAFLD (69) and since the main role of probiotics is to modulate the intestinal bacterial flora, they can be considered beneficial. Famouri *et al.* also supported the hypothesis that probiotics can be advantageous. They suggested that a course of probiotic compound could be effective in improving pediatric NAFLD (70). On the other hand, the meta-analysis of data from a study by Gao showed the role of probiotics in improving hemostasis, total cholesterol, HDL, and TNF-α, however, it should be noted that in this study, no improvement was observed in BMI, glucose, or insulin levels in adult patients with NAFLD (71). The overall results of these studies indicate positive effects of probiotics in improving liver function and enzymatic levels.

Probiotics for infantile colic

Infantile colic, characterized by intense crying for no apparent reason, is a common phenomenon that causes parental anxiety. Colic is defined as crying for more than three hours a day and for more than three days a week, lasting at least a week (72). It has recently been suggested that probiotics may play a role in relieving symptoms.

In a study by Rafi, the combined effect of probiotics on infantile colic was compared with conventional therapy. The results showed that probiotic therapy was at least as effective as conventional infantile colic therapy. The probiotics were even better than conventional therapy in terms of reducing the need to use antifreeze (73). Examination of effectiveness of *L. reuteri DSM17938* on infantile colic compared with placebo showed an improvement in symptoms by reducing crying time in Canadian breastfed infants with infantile colic (74). Synbiotic, a combination of probiotics and prebiotics, has been also studied. For example, Kianifar *et al.*, instead of using a single probiotic strain, used a synbiotic (a mixture of 7 different probiotics and FOS) and the results showed a significant improvement in colic symptoms compared with placebo (75). In a study by Saudra, long-term consumption of formula supplemented with *B. lactis* and *S. thermophilus* by infants caused a decrease in colic and irritation reports and reduced the rate of antibiotics use (76). Also, a review by Schreck Bird *et al*. on five studies conducted with different probiotic strains, suggested that supplementation with probiotic *L. reuteri* in breastfed infants appears to be safe and effective for treating infantile colic (77).

However, the data of some studies, while accepting the case effectiveness, have not made these results generalizable. As Sung reported, *L. reuteri DSM17938* may be effective only for certain subgroups of infants with colic, probiotics are not recommended to treat infantile colic in formula-fed infants, and they cannot be used to prevent infantile colic (78). Also, Anabrees *et al.* in a review of the studies, stated that although *L. reuteri* may be effective as a treatment strategy for crying in infants with colic who are exclusively breastfed, there is still no evidence confirming the effectiveness of probiotics in treating infantile colic or crying in formula-fed infants (79).

Effect of probiotics on oral health

The probiotic mechanism of action in the mouth may be the same as that in the gastrointestinal tract, but there is still insufficient information on this view and no study has confirmed that probiotic species can regulate and improve conditions in the oral cavity. In addition, it should be noted that the oral cavity is different from the gastrointestinal tract. These differences exist in immune response, mucosal epithelial structure, resident microbial flora, and the chemical composition of gastrointestinal tract secretions that differ from saliva in the mouth. Therefore, the results of studies on probiotics and their role in gastrointestinal diseases cannot be applied directly to the oral cavity and dentistry, and further studies are needed to investigate the effect of probiotics on the oral cavity (80). Here, there are some examples of studies in which different probiotics were used:

To inhibit the growth of *Streptococcus mutans*, Busscher *et al.* used *L. Acidophilus*, *L. rhamnosus GG*, and *L. casei* bacteria and reported a positive relationship between inhibition of *Streptococcus mutans'* growth and use of these bacteria (81). Haukioja *et al.* investigated the effects of *L. casei Shirota*, *L. rhamnosus GG*, *B. lactis*, and *L. reuteri Bb12* on the protein composition of saliva and other oral bacteria bindings. It was concluded that these bacteria inhibit the binding of other bacteria and improve the protein composition of saliva (82). In addition, a study by Hataka confirmed the possible effectiveness of probiotics in reducing oral candidiasis in the elderly and concluded that they can be used to prevent and even treat this disorder. They also stated that since probiotic consumption can reduce the feeling of dry mouth, it can be beneficial for oral health (83).

The results of a study by Tsubura *et al.* showed the effectiveness of *Bacillus subtilis* as oral lavage in people with periodontitis (84), which is consistent with the results of a review by Matsubara *et al.* According to this study, probiotics can be used as adjuncts to the usual periodontitis treatment without any side effects (85). Stamatova *et al.* also reported that probiotics may control common oral infections but the molecular mechanisms of probiotics in the mouth are still unclear and the consumption dosage should be determined for each symptom (86). There is growing evidence suggesting that certain types of probiotics, especially from dairy products, can be effective in improving oral health by preventing the growth of harmful microflora (87).

The most common adverse effects

Despite the high extent of beneficial and health-promoting effects of probiotics, several adverse effects are reported for them. Three case-report studies reported that L. rhamnosus caused bacteremia in the infant population (88-

90). One of the prevalent reported side effects of probiotics was fungemia, which was described as a result of consuming *S. boulardii* in more than 20 case-report studies (91-93).

Strengths and limitations

The present study had several limitations. First, this study was a narrative review and the outcomes were not analyzed statistically. There were numerous available studies in each section and it was not possible to review them all. However, to perform a high-quality study, a high number of studies were reviewed and the studies with high quality were included. Besides, the available systematic reviews and their references were evaluated in each section to reduce missed studies. In addition, a narrative review checklist was provided.

Conclusion

Fermented foods, especially dairy-based foods, are known to be a good source of various probiotics (94). Milk-based fermented foods such as cheese, yogurt, and curd are rich sources of *Lactobacillus* (95). Foods provided from soybean fermentation such as cheonggukjang are good sources of *B. subtilis* (96).

Although the discovery and identification of probiotics date back to many years ago, their possible different effects and mechanisms are not yet well understood. The beneficial effects of probiotics are obvious to everyone but their benefits depends on a variety of factors including selected strain, consumption quantity, duration of use, and the physiological characteristics of individuals. Therefore, researchers are increasingly trying to find the most efficient combination of these factors in their research. Although the vast majority of researchers advocate these microorganisms in diet, they never consider them as complete alternatives to existing treatments. Thus, they can be considered as a complementary therapy. Finally, performing more studies, especially systematic review and meta-analysis in each section, is suggested in order to provide more reliable results.

Authors' Contributions

B.T and S.R designed and supervised the project, B.T and S.R contributed to data collection and conception. B.T and S.R written the first draft of the manuscript. All authors performed their duty under the supervision of B.T as the main author. Also, all authors approved the final version of the manuscript.

Conflict of interests

The authors declare that there is no conflict of interests.

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