The Effect of Probiotics on Various Diseases and their Therapeutic Role: An Update Review

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Abstract

Probiotic bacteria play a critical and functional role in clinical and nutritional applications. In the present study, the ability of various probiotics and their metabolites in the prevention and treatment of different diseases, infection and disorders was reviewed. The issues that were noticed are included: Fibrocystic, diabetes, acne, colon cancer, cardiovascular, urinary tract infections, atopic eczema syndrome, food allergies and obesity. Enhancement in using drug treatment has led to the appearance of drug-resistance concern, thus probiotics can be a suitable choice. This review focuses on the effect of probiotic bacteria and their metabolites on immune-boosting, prevention and treatment of these diseases. For this purpose, after a short glance at each disease, infection and disorder, the mechanism of probiotic action and recent studies about that disease are reviewed. It could be recommended that probiotics consumption, perhaps from birth to all stages of life, would be effective in the life-long, development of health effects and disease treatments.

Keywords: Probiotic, disease, fibrocystic, acne, urinary tract infections, atopic eczema syndrome
INTRODUCTION

Governmental guidelines including united nations of Food and Agriculture Organization (FAO) and the World Health Organization (WHO), reported that there are four group of complications in patients with medical conditions, which are: Systemic infections, detrimental metabolic activity, overstimulation of immunocompromised individuals, and gene transfer. Some of disorders side effects have been reported in the gastrointestinal tract, such as vomiting, nausea, spasms, diarrhea, bloating, thirst, and taste disturbances. Some of them can change the natural microbial flora of the skin and irritate the skin rash and acne. The human intestinal flora contains a variety of bacteria species. Environmental stresses and illnesses can lead to disruption in intestinal flora balance. Some of these bacteria are known as probiotic which addition to digestion aid, produce complex compounds such as vitamins and antibiotics and can be helpful for the body. According to WHO and FAO, probiotics are defined as "living microorganisms whose adequate consumption reveals the health effects of the host".

Different mechanisms have been considered for probiotics in treatment or prevention of several diseases. The prevention of bacterial adhesion; increase in mucosal barrier function; modulation of immune systems (dendritic cells and T cells); bioactive metabolites; and regulation of the nervous systems. Probiotics by stimulation of lactase activity and assistance in lactose digestion can be useful against various diarrhea and lactose intolerance diseases. They can use enzymatic mechanisms to block toxin-mediated pathology and modify toxin receptors. Other suggested mechanisms for influencing intestinal microflora include lowering intestinal pH, releasing intestinal protective metabolites, regulating intestinal motility, and mucus production. In addition, Lactobacillus (L.) sp. bind to mutagenic compounds in the gut, preventing or delaying tumor progression and cancer. This ability has been linked to the modification of intestinal microflora and the reduction of beta-glucuronidase and other carcinogetic levels. Furthermore, the most significant property of probiotics is the increase in the amount of IgA-producing cells, which is effective in controlling allergies. The onset of an immune signal appeared when a non-pathogenic probiotic bacterium interacts with intestinal epithelial cells and immune cells. Overall, an ideal probiotic should be generally recognized as safe, resistant to bile, hydrochloric acid and pancreatic water, has anti-cancer activity, reduces intestinal permeability, produces lactic acid, stimulate the immune system, resistant to both acidic (stomach) and alkaline (duodenal) conditions. In order to have a sufficient health benefit, it is better to use a dose of 5 billion colony forming units (CFU) per day for at least 5 days.

Incorporation of probiotics in several foods are reported e.g. doogh, cheese, fermented drink, yogurt, fermented milks, grape drink, chocolate, fruit juice etc. Probiotics also produces many useful metabolites during their growth and metabolism e.g. production of bioactive compounds, conjugated linolenic acid, propionic acid, etc. Recently, reduction of oxidative stress and inflammatory factors, removal of toxins and heavy metals are reported for these amazing microorganisms. Reduction of oxalate by some probiotics propose suggestion of their usage to overcome problem of patients with high risk of oxalate kidney stone due to reduction of oxalate content in colon. Increasing knowledge on human intestinal microbiota and microbiota development enables the design of new more specific and hitherto unknown probiotics and prebiotics. Also, they can be used instead of drug treatments and lead to prevent the drug resistance issue.

Based on research and studies, the aim of the present paper was to evaluate the ability of probiotics on fibrocystic diseases, diabetes, acne, colorectal cancer, skin, cardiovascular, urinary tract infections, atopic eczema syndrome and also their roles in weight loss, dentistry and prevention of food allergies and lactose intolerance.

The effect of probiotics on different diseases

Cystic fibrosis disease

Fibrosis cyst (CF) is a genetic disease which is triggered by a mutation in fibrocytic membrane regulator gene. It develops from the epithelium of various body organs including the respiratory and gastrointestinal tracts. This disorder causes weakness and adhesion of the mucosa and also lead to inflammation and chronic...
infection in the lungs, which associated with gradual destruction of lung function. The same pathophysiology occurs in the gastrointestinal tract. Pancreatic insufficiency, malabsorption, immobility, functional symptoms lead to increase in small intestinal bacteria, which caused to intestinal obstruction. By using live bacteria such as probiotics, they can alter the host’s epithelial and immunological responses or affect the function of microbiota. Probiotics can help to improve microbial balance which altered by continued use of antimicrobial drugs to prevent and treat respiratory exacerbations. In order to determine the effect of probiotics on pulmonary exacerbations and inflammatory characteristics of the sputum, a study was conducted in 2010 in 10 CF patients, for 6 months. Two tablet of mixed probiotics (L. acidophilus, L. bulgaricus, Bifidobacterium (B.) bifidum, Streptococcus (S.) thermophiles) with each tablet containing 6 × 10^{9} CFU, prepared for intake by patients each day. Results indicated probiotics could lessen pulmonary exacerbations rate and may have a inhibition action for pulmonary deterioration in CF patients.

Possible mechanisms of action can help fibrocystic patients by affecting intestinal microbiota including changes in intestinal motility, improving intestinal barrier function, inhibiting the colonization of pathogenic bacteria, improving metabolic processes, and intestinal modulation. In other study 20 patients with cystic fibrosis exposed with L. rhamnosus LGG 10^{11} CFU, twice daily for a month. Results reported improvement in abdominal comfort (81%), reduction in number of stools (56%) and stool fat and sugar. Probiotics lead to improvement in both clinical and biochemical gas trointestinal function in CF patients.

Probiotic diminish fecal calprotectin (abdominal inflammation marker) due to CF. It could lessen the CF side effects including vomiting, diarrhea and allergic responses. Literatures suggests that probiotics could be useful in controlling the gastrointestinal inflammation in CF disease and improve the intestinal.

Diabetes

Diabetes is a disease that occurs in high level of blood sugar. Insulin, a hormone made by the pancreas, is require to enter the food glucose to cells to use as energy. In diabetes, body does not get enough insulin and does not use insulin well and then glucose remains in blood freely, without reaching to the cells. Type 1 diabetes is an organ-specific autoimmune disease that occurs in people with a genetic history. The second type is a metabolic illness and is associated with elevated blood glucose, relative insulin deficiency or insulin resistance. In the type I, which are endogenous antigens of β- pancreatic cells, are identified and acted upon directly or indirectly. Therefore, strategies should be developed to delay or prevent the autoimmune destruction of beta cells. Literatures indicate the gastrointestinal contribution in the autoimmune disorders. Oral administration of probiotic bacteria modulates local and systemic immune responses. The effects of oral administration of probiotic compound on lean (non-obese) diabetic rats showed that beta cell destruction was reduced and diabetes was prevented. Lean diabetic mice developed a spontaneous form of autoimmune diabetes. It is very similar to human disease and could represent a model for examining possible therapeutic approaches. In the type II diabetes, high level of blood glucose causes spontaneous oxidation of sugars, leading to the production of reactive oxygen species (ROS) and the end products of glycosylation, which exposes the body to oxidative stress and inflammation which resulted in high rise of insulin. This issue has important effect in the progress of type 2 diabetes and its cardiovascular disorders. Literatures have indicated that probiotics can lower the level of insulin and glucose in diabetic mice and delay the problems and complications of diabetes. In addition, several studies have shown the effect of lowering blood glucose in humans by probiotics. Ejtahed et al., prepared yogurt by L. acidophilus and B. lactis in 3.98×10^{9} CFU and used for 6 weeks in type 2 diabetes mellitus. Results indicated that it can have medication use by its antidiabetic effect. In other study, intake of soy milk enriched with the L. plantarum A7 (2 × 10^{7} CFU) at 200 ml/day among 20 person with type 2 diabetes mellitus, could decrease the fasting plasma glucose rather than control group. Furthermore, consumption of probiotic supplement including L. acidophilus, L. casei, L. lactis, B. bifidum, B. longum, and B. infantis at 3 × 10^{10} CFU in 250 ml water twice daily for 12 weeks, among 68 adult with type 2 diabetes
mellitus, lead to reduction in “fasting plasma glucose, fasting plasma insulin, haemoglobin A1c, homeostatic model assessment of insulin resistance”46. Preventing the occurrence or reduction of inflammation is related to reducing the amount of gram-negative pathogenic bacteria in the intestine47. Thus, it can be concluded that probiotics can have medication use on type 1 and type 2 diabetes by reducing the destruction of beta cells and reducing inflammation, respectively.

**Skin diseases (anti-aging)**

Skin aging includes a complex interaction of intrinsic (genetic and hormonal effects) and external aging (exposure to environmental causes such as ultraviolet (UV) ray, smoking, pollution). Changes in skin aging at the molecular level includes rise in the pH of skin which reduces its ability to suppress ROS and increases metalloproteinase activity. Preliminary studies have suggested that probiotics and their metabolites may play different roles in skin aging48,49.

Most probiotics increases the skin's acidic molecules through their metabolism, which in turn reduce the pH of their environment, which helps in preventing the dominance of pathogenic bacteria, regulate enzyme activity, and maintain a healthy environment48,50. The importance of this issue becomes more apparent when people enter the age of 70 and their skin pH increases significantly45. Furthermore, the antioxidant defense systems could be disrupted due to aging and breakdown several attacks in the environment, free radicals, ROS and cellular damage48. Studies show that probiotics can slowdown skin aging by restoring the balance between free radicals and their carriers49,52. So one of the strongest environmental factors is ultraviolet radiation exposure which has increased due to photography. This effect occurs in the form of wrinkles and increased fragility in the skin. Its more acute effects are suppression of the immune system53. Studies have indicated the effect of probiotics in decreasing the harmful effects of ultraviolet radiation and can be anti-aging 54. As an example, the *L. johnsonii* and carotenoids were administered for 10 weeks to persons and then were exposed to both simulated and natural sunlight. Results indicated that experimental supplementation reduced the UV-induced in "Langerhans cell density" in comparison to placebo, beside augmented the recovery of immune system homeostasis after exposure to UV-ray54. Intake of *L. plantarum* HY7714 (10^10 cfu/day) for 12 weeks in human volunteer could reduce the skin wrinkle depth, improved the skin gloss, and moisture content and also lead to significant improvement in skin elasticity55.

**Acne**

Acne is a medical term that describes what happens when skin follicles (the part of the skin that connects pores to the sebaceous glands) become clogged. It is an inflammatory disorder of the plasma that results from "enlarged endogenous sebum production, inflammation, keratinization, and bacterial colonization of hair follicles" in the face, neck, and chest56. The effects of an oral probiotic (*L. acidophilus* and *L. bulgaricus*) in 300 patients were studied57. Preliminary studies show that probiotics are involved in building the immune system, treating acne, protecting against aging and photography, and reducing the signs of aging skin58. *Enterococcus faecalis* 6400 AU twice a day for 8 week in acne patients, could reduce amount of acne lesions58. *L. plantarum* 1% and 5% twice a day lead to reducing erythema, repairing the skin barrier and reducing skin microflora to lessen acne at 5%59. Jung et al. (2013) in a clinical trial showed that oral antibiotics (minocycline) and probiotics (combination of *L. acidophilus* 10^9 CFU, *L. delbrueckii* 10^9, and *B. bifidum* 20 x 10^9) can provide synergistic benefits in 12 weeks follow up, especially for inflammatory acne60.

**Colon cancer**

Cancer is a multifactorial disease in which irregular and uncontrolled cell growth is one of its most prominent features. Colorectal cancer is the growth of cancer cells in the colon or rectum (part of the large intestine)61. Various pathogenic bacteria such as *Escherichia coli* and *Clostridium perfringens* have mutagenic effect and are associated with the progression of colon cancer62. The intestinal microbiota is responsible for the metabolism of nutrients, the production of vitamins, endogenous hormones, and toxic products that can be referred to as carcinogens63. On the other hand, this disease occurs due to the abnormal growth of cells that can invade other tissues in the body (metastasize) or multiply in them. So the imbalance of the microbial balance of the colon can increase the growth of carcinogenic bacteria64. Probiotics such as *Bifidobacterium*
| Disease          | Probiotic & Dosage                                                                 | Patients included | Consumption period (M) | Result                                                                                                      | Ref.  |
|-----------------|-----------------------------------------------------------------------------------|-------------------|------------------------|-------------------------------------------------------------------------------------------------------------|-------|
| Fibrocystic     | L. reuteri -10^9 CFU                                                             | 39                | 6                      | Reduction in calprotectin, improve in gastrointestinal quality                                             | 147   |
|                 | L. reuteri-10^{10} CFU                                                            | 61                | 6                      | Reduction in exacerbations                                                                                    | 148   |
|                 | L. rhamnosophy GG-6 × 10^9 CFU                                                    | 43                | 6                      | Increase in forced expiratory volume, reduction in exacerbations and hospitalisations                         | 149   |
|                 | Mix: L. rhamnosophy, L. acidophilus, L. casei, L. bulgaricus, B. breve, B. infantis, S. thermophiles-10^8 CFU | 47                | 1                      | Reduce in calprotectin                                                                                     | 150   |
| Diabetes        | L. acidophilus, L. rhamnosus, L. casei, L. bulgaricus, B. longum, S. thermophiles - 3.92×10^{10} CFU | 27                | 2                      | Antidiabetic (type 2) medication use                                                                         | 42    |
|                 | L. sporogenes-1.30×10^{10} CFU                                                    | 26                | 2                      | Antidiabetic (type 2) medication use                                                                         | 151   |
|                 | L. Bb12, L. acidophilus-1.11×10^{9} CFU                                           | 20                | 2                      | Antidiabetic (type 2) medication use                                                                         | 152   |
|                 | L. acidophilus, L. rhamnosophy L. casei, L. bulgaricus, L. rhamnosophy, L. bulgaricus-9.5×10^{8} CFU | 31                | 6                      | Antidiabetic (type 2) medication use                                                                         | 153   |
| Skin            | S. epidermidis                                                                    | -                 | -                      | Growth inhibition of Propionibacterium acnes and Acne Vulgaris by competitive exclusion                   | 154   |
|                 | L. reuteri                                                                        | -                 | -                      | Improvement of eczema, blocks integrin, decrease cell death due to S. aureus infection                     | 155   |
|                 | L. casei, L. rhamnosus S. thermophiles B. breve, L. acidophilus, B. infantis, L. bulgaricus-1×10^9 cfu (twice daily) | 40                | 2                      | Improvement of atopic dermatitis                                                                          | 156   |
|                 | L. rhamnosophy GG ATCC 53103-5 × 10^8 cfu (twice daily)                           | 925               | 6                      | Decrease in eczema, no effect on cumulative incidence of allergic diseases, although tended to reduce IgE-associated (atopic) diseases inducing apoptosis, reducing expression of Bcl-2, decrease in activity of matrix metalloproteinase (which is associated with the invasion of colon cancer cells) | 157   |
| Colon cancer    | L. delbrueckii                                                                    | In vitro          | -                      |                                                                                                                                                                    | 158   |
| Disease                      | Probiotic & Dosage                                                                 | Patients included | Consumption period (M) | Result                                                                                                                                                                                                 | Ref. |
|-----------------------------|------------------------------------------------------------------------------------|-------------------|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| Cardiovascular disease      | *L. rhamnosus* GG CGMCC 1.2134 (LGG)                                               | 16 rat            | 6.25                   | Reduce in the expression of β-catenin and the inflammatory proteins, the anti-apoptotic protein Bcl-2. Increase in the expression of the pro-apoptotic proteins; inducing apoptosis and ameliorating inflammation, and may hold a promise as bio-therapeutic dietary agent. LGG have a potential protection effect against colon carcinogenesis | 70   |
|                            | *L. acidophilus* 6.4 × 10^1 cfu, *B. bifidum*, and *B. infantum*-9 × 10^10 cfu (0.9 g/ kg body weight) | 40 rats           | 6.25                   | Administration of LBB modulates the gut microbiota and reduces colon cancer development by decreasing tumor incidence.                                                                                   | 74   |
|                            | *L. reuteri* NCIMB 30242                                                          | 127 healthy       | 2.25                   | Reduction in LDL-C, TC, Non-HDL-C, apolipoprotein B-100, apolipoprotein B-100/apolipoprotein A-1, Fibrinogen, No difference: HDL-C and TAG                                                            | 159  |
|                            | *L. acidophilus* La5 and *B. lactis* Bb12-4 × 10^6 CFU/g for each probiotic strain | 60 type 2 diabetic men and women | 1.5                    | Reduction in LDL-C, TC. No difference: HDL-C and TAG                                                                                                                                             | 160  |
|                            | *L. acidophilus* La5 and *B. lactis* Bb12-3.9 × 10^7 CFU/g                         | 59 normocholesterolemic, women | 1.5                    | No difference: LDL-C, TC, HDL-C, TAG, and TC:HDL-C                                                                                                                                            | 161  |
|                            | *L. acidophilus* and *B. lactis* 10^8 CFU/g                                        | 14 healthy        | 1.5                    | Reduction in TC, No difference: LDL-C, HDL-C, TAG, and LDL-C:HDL-C                                                                                                                           | 162  |
| Urinary tract infections    | *L. rhamnosus* GR-1 and *L. reuteri* RC-14-109 CFU twice a day                    | 280 post-menopausal women | 3                      | Positive effect similar to antibiotic therapy                                                                                                                                                    | 163  |
| Disease                  | Probiotic & Dosage                                                                 | Patients included | Consumption period (M) | Result                                      | Ref. |
|-------------------------|----------------------------------------------------------------------------------|-------------------|------------------------|---------------------------------------------|------|
| **Food allergy**        | **L. acidophilus; 1 ×10⁸ CFU; twice a day**                                        | 113               | 6                      | Recurrent UTI                               | 164  |
|                         | **Saccharomyces boulardii- 5 ×10⁷ CFU; twice a day**                               |                   |                        | UTI; Recurrent UTI                          | 165  |
|                         | **L. acidophilus, L. delbrueckii subsp. bulgaricus, L. casei, L. plantarum, B. longum, B. infantis, B. breve, S. salivarius subsp. thermophilus L. brevis, L. casei and B. longum** | Shrimp tropomyosin |                        | Reduction in clinical symptoms, histamine levels, tropomyosin-specific IgE, increase in tropomyosin-specific IgG2a | 166  |
|                         | **L. acidophilus LaVK2, B. bifidum BbVK3, Lactococcus lactis ssp. cremoris NCDC-86, and Lc. lactis ssp. Lactis biovar diacetylactis NCDC-60 L. acidophilus, L. casei, B. bifidum, and E. faecium** | Casein/Whey protein-mice |                        | Mild relief in clinical symptoms, reduction in total IgE, IgG2a, OVA-specific IgE, IgG1 IgG2a, increase in IFN-γ, reduction in IL-5, IL-5, IL-6, and IL-10 | 167  |
| Lactose intolerance     | **L. plantarum 10¹⁰ CFU + B. animalis 10¹⁰ CFU**                                  | Peanut extract-mice | 1.5                    | No observable clinical symptoms, No change in body weight of treated group, increase in IgE levels, CD4+CD25+ splenic lymphocyte | 169  |
|                         |                                                                                  |                   |                        | No significant differences                  | 170  |
bacteria can selectively inhibit the growth of these pathogenic bacteria and create a favorable environment that modulates bacterial enzymes. Pure Bifidobacterium has antimutant activity and activate phagocytes, which affect the immune response and destroy tumor cells in the early stages of growth. For this reason, natural resources that have anti-cancer effects for colon cancer, eg. probiotics, have received considerable attention, recently. Numerous papers have shown that consistent use of probiotics, can advance the quality characteristics of intestinal microbiota and reducing the carcinogenic compound. Literature reported various effects of probiotics on colonic cancer including “promotion of epithelial repair and barrier”, “increased tumor cells apoptosis”, “prevention of dysbiosis and restoring eubiosis”, “upregulation of cytokines promoting tissue repair and antitumor responses”, “production of metabolites with positive effects on the epithelium and immune cells (SCFAs, acetate, propionate, butyrate)”, “inhibition of biofilm formation and thus cell proliferation via Toll-like receptors” and “improvement of adverse events during chemotherapy and radiation therapy”. They can also have synergistic effect with anti-cancer and immunological drugs. The influencing factors which affect their impact are included: strain, host and their reach route to the large intestine. A study conducted by Hataoka et al., 2008 showed that promoting the consumption of definite strains of probiotics could prevent colon cancer by lessen the activity of harmful bacterial enzymes. Drago, 2019 stated that some selected probiotics can exert anti-cancer activity by physiological mechanisms that are effective in preventing bowel cancer and reducing anti-cancer side effects. Thus, the interaction between probiotics and intestinal microbiota can lead to: neutralizing cancer, improving intestinal barrier function, vitamins and short-chain fatty acids synthesis, altering the intestinal microflora, inhibiting tyrosine kinase, increasing the production of cytokines, antioxidants and anti-angiogenic agents and reducing gastric pH etc.

Cardiovascular disease
Cardiovascular disease is a group of illnesses that occur in the heart or arteries (arteries, capillaries, and veins) and affect the circulatory system. Various methods are used to control this disease, including medication, surgery, and lifestyle changes. Probiotics containing materials are one of the special foods that can help in cardiovascular diseases by affecting the health of microorganisms living in the intestine and maintaining the balance between species of symbiotic bacteria and pathogens. One of the key and important factors in treatment and prevention is controlling the level of blood lipids and inflammatory factors that low density lipoprotein-cholesterol (LDL-C) has been named as the main risk factor. In earlier, probiotics were shown to be effective in lowering cholesterol in tribes that used fermented yogurt. These bacteria, along with other useful components of food, cause changes in metabolic pathways by fermenting dietary fiber and producing short-chain fatty acids, reduce the synthesis of endogenous cholesterol. Other effects include reducing and controlling the level of inflammation in inflammatory markers. Literatures have revealed that probiotics could reduce the cholesterol levels. As example, live L. fermentum 11976 led to significant reductions in total cholesterol, triglyceride and LDL-C levels of hypercholesterolemic hamsters. Similar results were observed in rats fed a high cholesterol diet supplemented with lyophilized L. plantarum MA2 led to significant decrease in their total cholesterol, LDL-C and triglyceride levels rather than rat fed only by high cholesterol diet. Recent studies have linked the mechanism of inflammation reduction to improve lipid profile levels. Studies showed that dysbiosis in the pathogenesis is directly related to the level of ischemic heart disease and inflammatory cytokines.

Urinary tract infections
The urinary tract includes the urinary tract and the reproductive tract, and both systems are exposed to the external environment and capable of infection, both external and internal. Infections are due to an imbalance in the microorganisms of the urinary tract. The resulting infections involve children to adults and affect the bladder, kidneys, urethra, vagina and cervix. It is one of the most common infections in women and is a global and important problem. Bacterial species in the vaginal mucosa is different between postmenopausal and premenopausal women, and the healthy flora of the premenopausal vaginal mucosa is surrounded by Lactobacillus species.
Their defensive role depends on their ability to produce antibacterial agents to limit pathogen growth, biosurfactant production, and to form defense system. They produce the biosurfactants that prevent the attachment and binding of pathogens93. The production of lactic acid and the production of an acidic environment in the vagina is another characteristic of them and reduces autophagy in the epithelial cells. This leads to the destruction of intracellular microorganisms and the promotion of homeostasis94. Also, the presence of Bifidobacterium strains in the vagina can lead to production of lactic acid and hydrogen peroxide, which act against local infections95. Studies have shown that lactobacilli are effective in preventing infections of the urinary tract in women. Lactobacillus. and Bifidobacterium. strains are of the predominant species in probiotics and can use to prevent and treat urinary tract infections96. A hospital study of elderly patients admitted to the ICU showed that probiotics (5×10⁷ CFU of L. acidophilus, L. rhamnosus, L. gasser and L. Plantarm for twice a day for seven days), could prevent urinary tract infections. Its administration causes a significant change in the microflora of the urinary tract and reduces the colonization of pathogens97. The study of meta-analysis findings indicate that probiotics as monotherapy could not have noteworthy effects but its use as adjuvant therapy to antibiotics could have a moderate efficacy on preventing the recurrence of UTI98.

**Atopic eczema syndrome**

Atopic eczema is an irritated skin disease with an early development. It has increased in occurrence in recent years and affects up to 25% and 10% of teenagers and adults, respectively99. Atopic eczema may be inherited, or occur due to contact with allergens or stimulants. Congenital trauma to the fetus may also be a strong indicator of atopic development100. This is one of the most usual inflammatory skin disorder in children. Its symptoms include irritate itching, skin damage, pain, lack of sleep, etc.101 Literatures show a decrease in the amount of Bifidobacterium in the infant, young children and adults with this disease102,103. One of the methods used to treat this disease is to change the mixture of intestinal bacteria and reduce inflammation in the intestine with probiotics104. Based on the study conducted by105, intake of L. johnsonii twice a day for 21 days, on atopic dermatitis patients lead to decrease in Staphylococcus aureus and improve in atopic dermatitis scores105. Beside, consumption of Vitreoscilla (V.) filiformis in cream twice a day for 1 month and also Streptococcus thermophilus 1.7 g/5 mL in 20 mL lotion, lead to increase in skin ceramides and improvement in all aspects of atopic dermatitis patients106,107. Based on the findings of the study it has been found that probiotics can be effective in chronic inflammatory skin disease, atopic eczema by altering the microbial flora of the intestine.

**Food allergy**

Food allergy is definite as an adverse immune reaction to dietary proteins and includes a variety of disorders. It affects 6% of children and 3% to 4% of adults. This disease may be caused by Ig-E and non-Ig-E mediated mechanisms by cellular mechanisms108. After eating sepecific foods such as tomato, soya bean, egg or etc., Ig-E causes acute allergic disorders due to the involvement of arm cells, cell tissue and blood basophilis. Re-exposure to this factor due to the binding of food proteins to specific Ig-E molecules causes the release of mediators such as histamine, which mediate these symptoms. The disease affects various target organs such as the “skin (urticaria, angioedema), the respiratory system (rhinitis, asthma), the gastrointestinal tract (pain, protrusion, and diarrhea) and the cardiovascular system (anaphylactic shock)”. The most severe form of intestinal food allergy in infants is “food protein-induced enterocolitis syndrome” which has different symptoms including vomiting, scattered diarrhea, increased neutrophil count, and shock, and is potentially similar to sepsis with dehydration, acidemia, and methaemoglobinaemia109.

Probiotics are one of the treatments used to manage patients with food allergies. The exact mechanisms of the effects of probiotics on the disease are unclear. Study on animals showed that that in addition to modulating intestinal microbiota, could improve intestinal mucosal barrier function, reduce leakage of antigens via mucosa, and reduce exposure110. Direct modulation of the immune system may be mediated by increased in production of Ig-E or induction of anti-inflammatory cytokines111. According to Liu et al., usage of B. infantis lead to reduction in β-Lactoglobulin, total IgE and
IgG1, signs of inflammation, IL-4, IL-10 and IL-13\textsuperscript{112}. Probiotic enzymes reduce the load and antigens exposure by enzymatically degrading food antigens\textsuperscript{113}. Mechanism of action of probiotics are involved in reducing the immune system’s exposure to dietary antigens. Due to the positive role of probiotic bacteria in creating a coherent relationship with the immune system and regulating immune responses to reduce the host sensitivity as well as reducing the symptoms of inflammation, is considered as a new strategy in improving food allergies\textsuperscript{114}.

**Lactose intolerance**

Researchers have found that many people who think they have a food allergy actually have food intolerances, which are different with each other. Food intolerances do not include Ig-E antibodies. Intolerance may occur due to protein, chemicals, carbohydrates, enzyme deficiencies or decreased intestinal permeability\textsuperscript{115}. Lactose intolerance is a common gastrointestinal disorder which is caused by lack of the lactase enzyme in the intestinal wall or an inability to digest lactose into glucose and galactose. Its level estimated at 50% in Asia\textsuperscript{116}. Lactose intolerance can be observe after consuming lactose containing foods, by symptoms such as abdominal pain, diarrhea, bloating, nausea, vomiting and swelling\textsuperscript{117}. The unabsorbed lactose has an osmotic charge and causes the secretion of fluids and electrolytes until it reaches equilibrium. Osmosis dilates the intestines and eventually accelerates the transit of the small intestine. This free lactose is fermented in the large intestine by colon bacteria to produce short-chain fatty acids and hydrogen gas\textsuperscript{118}. Also, fermented and non-fermented milk products which containing probiotics can reduce its symptoms and be effective in treating lactose intolerance\textsuperscript{116}. Furthermore, dairy products containing probiotics improve lactose digestion by slowing the passage of food through the gastrointestinal tract\textsuperscript{119,120}, intake of *L. reuteri* (8 × 10\textsuperscript{8} CFU/day) by 40 lactose intolerant patients, caused to improvement in abdominal pain, bloating, diarrhea, and flatulence\textsuperscript{120}. The results showed that probiotics can be effective in treating and preventing lactose intolerance by increasing the enzyme lactase, but still need further investigation.

**Probiotics in dentistry**

Dentistry includes the study, diagnosis, inhibition and management of oral diseases and the related disorders. Tooth decay is a multifactorial disease and the most common chronic disease, begins with the dissolution of the mineral part of the tooth and progresses to the local alignment of the enamel and dentin. If caries does not prevent and treat, it will lead to inflammation of the pulp and periapical. This disease has four main causes: bacteria, sugars, predisposing factors and time. The most important pathogens for the initial growth of tooth decay are *S. mutans* and the most important pathogen in the development of caries lesions is *Lactobacillus*. *S. mutans* are important because of their characteristics such as their acidity, ability to survive in acidic environments, biofilm formation and cariostatic activity\textsuperscript{121,122}. On the surface of the mouth, there are a number of different probiotics that reduce the incidence of tooth decay, gum disease, reduce bad breath and fight oral infection by *Candida albicans*\textsuperscript{123}. The most common strains in the oral cavity, are *Lactobacillus* and *Bifidobacterium* strains\textsuperscript{124,125}. The mechanism of action of probiotics in the oral cavity is similar to that of intestinal probiotics. Environmental conditions can disrupt the balance of oral bacteria and lead to defect in oral health\textsuperscript{126-128}.

A probiotic must be able to adhere to the surface of the tooth and integrate into the bacteria that make up the biofilm, and be able to fight off pathogenic bacteria and prevent them from multiplying. According to\textsuperscript{129} using *S. thermophiles* and *L. lactis* ssp. which are used in dairy industry, can integrate into surface biofilms and interfere with the development of *S. sobrinus* species\textsuperscript{129}. Other study have shown that Weissella cibaria species have the ability to integrate biofilms produced by *S. mutans* and inhibit the reproduction of this bacterium\textsuperscript{130}. The application of probiotics may be different, such as chewing gum, milk, cheese, yogurt, ice cream, drops, mouthwash, etc.\textsuperscript{123} In periodontal disease, clinical study has shown the noticeable improvement by using chewing gum or tonsils containing probiotics\textsuperscript{131}. There are various studies with proven probiotic activity on oral pathogens including *L. casei* LC-11 in lessening of cariogenic biofilm potential\textsuperscript{132}, *L. paracasei* in caries management\textsuperscript{133},
**B. animalis** subsp. Lacis improved resistance to oral infections\textsuperscript{134} etc. Probiotic techniques for oral health are still a promising area of research. Obviously, more research on the concentration and methods of probiotic uptake is needed to more fully evidence in the beneficial effects of probiotics on oral health.

**Obesity**

Probiotics are believed to help obesity and weight management by acting an important role in gut. Obesity is caused by an imbalance between energy intake and consumption, which lead to fat accumulation in body\textsuperscript{135}. Two groups of beneficial bacteria residing in the human gut are bacterioids and firmomycetes, and body weight appears to be related to the balance of these two groups of bacteria\textsuperscript{136,137}. Studies in humans and animals have shown that the intestinal bacteria of normal-weight individuals are more diverse than those of overweight individuals, and that obese individuals have more firmomycetes and fewer bacterioids than normal-weight individuals\textsuperscript{138-140}. Several animal studies have shown that if the intestinal bacteria of obese mice transfer to the intestines of lean mice, obesity occurred in second group\textsuperscript{140}. Therefore, strengthening the intestinal microbiota can play an effective role in weight loss. As mentioned previously in the effect of probiotics on bowel cancer in above, probiotics can alter and improve the gut microbiota. Probiotics can affect weight loss in several ways include: 1. Some species of the *Lactobacillus* family prevent the absorption of dietary fat in the body and thus increase the fat excreted in the feces\textsuperscript{141,2}. They help to secrete an appetite suppressant hormone called GLP-1. When the level of secretion of this hormone increases, the level of calorie burning and fat burning in the body also increases\textsuperscript{142,3}. Increase the level of ANGPTL4 protein and reduce fat storage\textsuperscript{143,4}. In addition, there is some evidence linking obesity to inflammation of the brain. Probiotics can reduce inflammation in various organs of the body, such as the brain, and prevent obesity by improving intestinal health\textsuperscript{144}. According to literatures, *L. gasseri* SBT2055 (LG2055) and *L. plantarum* TENSIA lead to reduction in abdominal adiposity and body weight\textsuperscript{145,146}. Although many studies confirm the effect of probiotics on obesity, more research is needed on their mechanism of action.

**CONCLUSION**

Probiotics and their metabolites as biological control agents play an important role in prevention and treatment of various diseases, especially those related to the gastrointestinal tract. This role of probiotics became more important with the industrialization of the world, increase ready to eat food consumption, stressful condition, heavy metal contamination of water and weather, which lead to reduction of some beneficial bacteria. In other hand, development in using drug treatment for different diseases lead to enhancement of drug-resistant issue which can result in some problems including treatment failure, increased mortality as well as treatment costs, reduced infection control efficiency, and spread of resistant pathogens from hospital to community. Probiotic consumption in different ways, could be a safe choice for boosting immune system, prevention and treatment of different diseases including fibrocystic, diabetes, acne, colon cancer, cardiovascular, urinary tract infections, atopic eczema syndrome, food allergies and obesity which are focused in present study. Based on study on literatures, probiotics had important role in inhibition or treatment of various diseases. Although, some papers indicate no significant effect associate to probiotic role. Certainly, future research is suggest to determining the best probiotic and its ideal dose for each disease.

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**CONFLICT OF INTEREST**

The authors declare that there is no conflict of interest.

**AUTHORS’ CONTRIBUTION**

KK conceptualize and supervised the study. FH applied methodology and did the investigation. MS contributed to software work and wrote the draft. SE did the validation and grammatical editing. FT performed the formal
analysis. ADT administered the project. AS completed the final review and edited the manuscript. All listed authors have read and approved the final manuscript for publication.

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DATA AVAILABILITY
All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT
Not applicable.

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