Chapter

Therapeutic Potential of Probiotics and Prebiotics

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Abstract

Advancement in technology is continued as the time is passed. The biological active ingredients technology is the challenging issues for both the researchers and manufacturers. In last decade, much research has been happened about the potential health benefits of pro and prebiotic ingredients. *Probiotics* are the live microorganisms when given in adequate amount confer health benefits but the prebiotics are indigestible ingredients that enhance the activity of one or more probiotics in the colon. The therapeutic potential of these two biological active ingredients is the outcome of emerging field of biotechnology. A number of studies indicating therapeutic potential of probiotics regarding gastrointestinal health, cancer, constipation, immunomodulation, *Helicobacter pylori*, liver disease and urogenital infection have been documented. Similarly, prebiotics also improved helpful for many communicable and non-communicable diseases. It can be seen that advancement in the biotechnology field offer great choice to deliver a marvelous health advantages. Although the market for probiotic and prebiotic food and supplements has been increased in this new era but still need to develop food and supplements containing these two active ingredients with the cooperation of legal bodies of the country.

Keywords: therapeutic, probiotics, prebiotics

1. Introduction

This chapter criticizes and presents the role of different probiotics and prebiotics in the prevention of various ailments and improvement of consumer's health. Scientist worked and explored the action of beneficial live microorganisms and non-digestible food components for the improvement of human health. The chapter highlights various sources and mode of action of probiotics and prebiotics. Disease prevention and health intriguing aspects of these therapeutic components is also addressed in this chapter.

2. Probiotics

The term probiotics was characterized by Parker [1] as life forms and some substances which are responsible for the equalization of the intestinal microorganisms. Fuller [2] defined probiotics as feed supplements in the form of live microorganisms which valuably influences the host creature by enhancing the microbial balance in the intestines. Subsequently, Moriarty [3] recommended that the meaning

of probiotics be reached out to microbial water added substances. Administering probiotics in water has been appeared to enhance water quality by decreasing the centralizations of nitrogen and phosphorus [4]. Probiotics directed in water or eating routine likewise may hinder the development of pathogenic microorganisms, contribute stomach related proteins to expand feed usage, give other development advancing components, and restoring the immune response of the living beings.

Hill et al. [5] updated the probiotics as live microorganisms when given in adequate amount confer health benefits.

2.1 Probiotics: selection criteria

For the living organisms to be termed as probiotics the given criteria should be fulfilled:

1. It must get separated from the same species from its expected host.

2. It ought to have an clear favorable impact on its host.

3. It should not produce any symptoms of disease.

4. It ought to have the capacity to survive the conditions gastrointestinal tract and can easily be passed through it.

5. During storage, greater number of practical microscopic organisms must have the capacity to endure extended lengths of time [6, 7].

2.2 Probiotics: mechanism of action

Mechanisms for the advantages of probiotics are not completely understood. However, generally it includes [8].

- Adherence and colonization of the gut.
- Suppression of development or epithelial authoritative/intrusion by pathogenic microscopic organisms and generation of antimicrobial substances.
- Improvement of intestinal hindrance work.
- Controlled exchange of dietary antigens.
- Stimulation of host mucosal and systematic immunity [9].

2.3 Standardization of probiotics

In Europe health claims of probiotics are assessed by the "European Food Safety Authority" (EFSA). For the selection guidance of probiotics European Commission published probiotics health claims [10] this meant that probiotics are not considered as nutrition claim but it is a health claim. It is further clarified that this general health claim is not mention for any body functions because the health claim of probiotics and strain specific. Consequently, probiotics term is banned with regard to advertising and labelling as food supplement in Europe.

In USA probiotic companies face legal encounters. In the research of probiotics, there are also FDA's restrictions for human trials. The study with regard to human trial must be filed as "Investigative New Drug," which appears redundant and costly obligation.

In Canada, the government has also issued regulatory documents for the use probiotics in food. Canada has a list of 17 probiotic species that can make nonspecific health claims, but no strain-specific probiotic claims have been approved [11].

In 2012, the Chinese Food and Drug Administration (CFDA) issued "Requirements on and a Guide to the Naming of Health Foods" and this year, provision for health food registration and filing was released. Currently, there are 27 health food categories based on health effects recognized in China, including enhancing immunity, the maintenance and relief of constipation, and modulating the intestinal bacteria. The health claim of any probiotics are governed an approval process involving technical review of safety, scientific substantiation of the health effect (based on animal and/or human studies), quality control, quantitative assessment and assessment of the product formulation [12].

2.4 Commonly used probiotics

A portion of the widely utilized probiotic microorganisms are *Lactobacillus rhamnosus, Lactobacillus reuteri, bifidobacteria* and certain strains of *Lactobacillus casei*, *Lactobacillus acidophilus*-groups, *Bacillus coagulans, Escherichia coli* strain Nissle 1917, certain enterococci, particularly *Enterococcus faecium (SF68)*, and the yeast *Saccharomyces boulardii*. Bacterial spore formers, for the most part of the class Bacillus influence the scene. The given probiotics are being used in variety of food products such as fermented milks either independently or in mixes. With the new research endeavors new genera and strains of probiotics are being developed.

Probiotic can either include a single stain or a blend of at least two strains. For example, VSL3 is a probiotic that comprises of blend of eight different strains. The effects of probiotics are strain specific and cannot be summed up. A one strain may display diverse advantages when utilized exclusively and in mix. The benefits arising from the use of probiotics vary according to patient group. Constrained studies showed the adequacy of use of multiple probiotic strains [13].

FAO and WHO have mutually introduced advanced rules with a specific end goal to establish the systematic outlook for a successful Probiotic assessment probiotics in nourishments to support the health cases and other advantages. The standard rules on probiotics developed by FAO/WHO could be used worldwide for assessing probiotics in nourishment that can lead to the supporting of health claims. According to the rules following activities must be fulfilled:

1. Identification of strain.

2. Functional portrayal of the strains and safety properties.

3. Proving the medical advantages in human examinations.

4. Labeling of the adequacy claims and the shelf life of the substance must be honest and should not be deceiving.

2.5 Therapeutic potential of probiotics

The probiotics have most imperative and recorded helpful impacts that incorporate the prevention from various diseases including diarrhea, increasing the

effectiveness of antibacterial activity, reduction in the symptoms of constipation, changes in the conjugation of bile and salts. Moreover, they are also involved in nutrient formation and in enhancing their utilization by the body; a few probiotics are thought to have anti-oxidant action as entire cells or lysates. Probiotics have additionally exhibited their intrinsic impacts in reducing manifestations of allergy, cancer AIDS, various infections of respiratory system and urinary tract. There are different random reports on their advantageous impacts on autism, fatigue, type 2 diabetes, aging, fatigue, obesity and osteoporosis [14].

2.5.1 Diarrhea

The Diarrhea is defined by World health Organization as three to four watery stools in the period of 24 hours. Over the period of more than 20 years several examinations have been done on the microorganisms by several in vitro studies, animal models and some other suitable clinical investigations have confirmed the role of probiotics in reducing the severity of various type of diarrhea [15] *Saccharomyces boulardii* is the only yeast probiotic that is used for treating the diarrhea.

2.5.1.1 Acute infantile diarrhea

Rotavirus is the major cause of acute infantile diarrhea and is the most concentrated gastrointestinal condition and it requires quick oral rehydration as an essential treatment. Along with the oral rehydration therapy Probiotics are thought to have beneficial effects. Although further data is needed to confirm the investigations however 10 billion CFU is the minimum potent dose in kids within the 48 hours [16]. A trial was conducted on *C. difficile*-related colitis and results showed that *S. boulardii* reduce the onset of infection in the patients who had more than one consecutive *C. defficile* disease. *S. boulardii* is yeast which produces proteases that inhibit the *C. defficile* toxins and also blocks its receptors in the intestines. The yeast *S. boulardii* discharges a protease that separates *C. difficile* poisons and hinders the poison intestinal receptors. The Probiotic additionally found to activate particular antitoxin A which is an immunoglobulin that attacks the factor involved in increasing the risk of diarrhea [17, 18].

2.5.1.2 Antibiotic associated diarrhea

Disruption of the natural micro flora is due to the use of anti-microbial medications, i.e., antibiotics frequently prompts diarrhea. The principle component by which antimicrobials cause loose bowels is through weakened protection against pathogens because of disruption of gut micro flora and as a result there is a modification in the digestion of sugars bile acids and unsaturated fatty acids resulting modifications in the digestion of sugars, short-chain unsaturated fats, and bile acids [19]. Probiotics are more powerful in reducing the onset of diarrhea as a result of use of antibiotic medications and these includes strains of *L. acidophilus*, yeast *S. boulardii, L. delbrueckii, L. rhamnosus GG, L. fermentum,* etc. [18]. However, further studies are needed to confirm the beneficial role of probiotics in various diseases, which probiotic is more potent and their recommended dosages [20].

2.5.1.3 Traveler's diarrhea

It has been assessed that around 20–60% of the people traveling around the world are affected by this type of diarrhea. It especially influences individuals those

who travel from the developed or industrialized areas to the backward or remote areas, specifically traveling between tropical regions and other non-tropical areas. The major cases that are recognized are due to the microscopic organisms which accounts for approximately 60–85% of the cases and most causative bacteria for causing this is *E. coli* and *Compylobacter jejuni* and some other species of *Salmonella* and *Shigella* disease is also caused by parasites and viruses which accounts for around 10% and 5% toward causing the infection [21]. It was observed that the bacteria that was effective against Bacterial diarrhea is *S. boulardii* whereas the activity of Lactobacillus *GG* was observed to be more potent against diarrhea caused by the virus and the idiopathic diarrhea [22–24]. Bacterial Strains that are thought to have preventive effect on the traveler's diarrhea include the *Bifidobacteria, Lactobacilli, and Streptococci* and *Enterococci* [18].

2.5.2 Inflammatory bowel disorder (IBD)

IBD is a long term degenerative disease which involves the severe irritation of G.I.T tract that leads of watery and bloody diarrhea along with the abdominal pain IBD affects the small intestines and a portion of large intestines that is colon and it includes three different conditions which are Crohn's disease, ulcerative colitis (UC) and pouchitis. The other factors that are associated with the onset of disease include the genetic factors, ecological factors, oxidative stress and the weakened immune system [25].

Crohn's disease and ulcerative colitis are long term diseases of the gastro-intestinal tracts that are associated with the inflammation of the immune and likely are because there is absence of balance of the natural immunity with the surroundings and the with the advancement of the culture [26]. Intake of probiotic bacteria can possibly balance out the immunological boundary in the gut mucosa by diminishing the production of nearby proinflammatory cytokines [27–29]. *Bifidobacterium infantis* 35,624 helps in elevating the symptoms of abdominal pain, bloating, passage of gas, straining, bowel dysfunction and incomplete evacuation in the patients of IBD. It has been observed through recent studies that Probiotic supplementation is very helpful in elevating the symptoms of IBD and in some cases even the medical therapy can be replaced by probiotic supplementation. However it is not recommended for the Crohn's disease as the data does not support the use of probiotics. Therefore Probiotics have shown promising role in reducing the symptoms of ulcerative colitis but not in the case of Crohn's disease [30].

2.5.3 Ulcerative colitis (UC)

Ulcerative colitis like Irritable bowel disorder fundamentally influences the inner layer of the rectum and that of large intestines. Long-term ulcerative colitis can lead to the development of colon cancer. Use of different probiotics including *S. boulardii, L. casei, Bifidobacterium bifidum* has demonstrated beneficial results in terms of this disease [31]. A Study was conducted and the results demonstrated that the addition of probiotics bacterial strains of *L. acidophilus, B. bifidum*, and *B. breve* in the fermented milks was helpful in mitigating the diseases in patients [32].

2.5.4 Crohn's disease (CD)

It is a type of Irritable bowel syndrome which ordinarily influences the digestive system; however it may affect any organ from the mouth to the end of the end of digestive tract. Crohn's disease leads to the development of the ulcers and irritation that influences the capacity of the body to process food, assimilate nutrients and excretion of unwanted products in a healthful form. The Bacterial strains that

are involved in causing Crohn's disease include *Salmonella, Clostridium difficile, Campylobacter jejuni, Mycoplasma* and *Adenovirus*, There are various reports that influence the efficacy of various probiotics, e.g., *S. boulardii, L. GG, VSL3, E. coli* Nissel 1917, in combating the issues of CD in human beings [33].

The role of probiotics in therapeutic utilization of Crohn's disease is because of its competition with the groups of bacteria, maintaining the immune system and also destroying the various pathogenic microorganisms. Irritable bowel syndrome can additionally be prevented by using the probiotics which help in maintaining the defensive functions of the mucosa of intestines [34].

2.5.5 Pouchitis

Pouchitis is third kind of Irritable bowel syndrome where there is inflammation of ileal pouch particularly after the procedures such as colectomy and the other include anastomosis of ileal pouch. Various Studies were done and it was observed that the blend of probiotic VSL3 plays a significant role in the reduction of this disease [35].

The strains of powerful probiotic stimulate definite IL-10 and IL-4 mucosal cytokine. Also Probiotics may impact the cell to cell association of mucosa and integrity of the cells through upgrading activity of intestinal mucosa through the regulation of phosphorylation and cytoskeletal activity of tight junctional protein and furthermore through the production of enzymes having anti-oxidant nature. For example, catalase and superoxide dismutase hence remediating the symptoms of IBD [36].

Ileal pouch-anal anastomosis (IPAA) is the favored option to proctocolectomy with perpetual ileostomy in ulcerative colitis and the inherited disease in which adenomatous polyps are formed in the epithelial of large intestines. The most as often as possible noticed chronic problem of IPAA is potentially perpetual inflammation of the ileal supply which is either acute or chronic and is called pouchitis. Gionchetti et al. in a randomized, controlled treatment containing placebo preliminary in which VSL3 was regulated to 40 patients quickly after carefully surgical formation of ileal anal pouches, accomplished abeyance of 90% in the group treated with VSL3 versus 60% in the placebo treatment group following a year [37]. These examinations have confirmed the role of VSL3 in the administration of pouchitis [38].

According to the Rome II Crieteria irritable bowel syndrome is defined as syndrome that lasts for greater than 3 months with the implications of either diarrhea or constipation and also accompanied by the abdominal pain. Many studies on the role of probiotics in preventing Irritable bowel syndrome have been conducted [39–43]. Out of five surveys conducted three trials showed a decrease trend in the symptoms of Irritable Bowel Syndrome. As there is a beneficial role of the probiotics but the reduction in the symptoms of disease without the clinical manifestations has not yet confirmed. However, beneficial role of probiotics in terms of clinical improvement can be attained in reducing the symptoms related to the diarrhea. Many new studies are needed to be conducted on variety of bacterial strains to draw any conclusion regarding their beneficial role [44].

2.5.6 Lactose intolerance

It is a type of disorder that comprises of intolerance to the digestion of carbohydrate lactose that is present mainly in dairy products having prevalence of around 7–20% in Caucasians, 90–100% in Asians and from around 50–85% in Africans [45]. Lactose intolerance can be solved by using the probiotics that alleviate

the symptoms by reducing the transit time through gastro-intestinal tract [46]. Probiotics such as *Streptococcus thermophilus* and *Lactobacillus bulgaricus* undergo the process of fermentation and as a result produces an enzyme lactase that helps in the breakdown of lactose into its subunit glucose and galactose. Thus, it is suggested that the intake of probiotics can help in the digestion of lactose inside the gut lumen and reducing the symptoms of lactose intolerance in both children and adults [47].

2.5.7 Colon cancer

The intake of probiotics and prebiotics has several antagonistic effects on mutagens [48, 49]. The link between the colon cancer and diets that are high in fats and oils and low in fiber and some other western diets lead to the alteration in the bacterial enzymes in the feces. The process through which the probiotic bacteria such as lactobacilli reduce the onset of colon cancer may include various modifications on the metabolic pathways of the intestinal microflora, inhibiting and binding of the cancer causing agents, physicochemical alterations in binding to colon, formation of compounds cancer causing agents and several other mutagens. Improving the immune system and physiology of the host. There is a remarkable evidence on the basis of various animal models and controlled studies [50, 51]. However, there is not enough data or studies to confirm the role of probiotics for protection against the onset of colon cancer.

The process through which the probiotics exhibit tumor suppressing activity includes the modification in the immune functions that are related with the various immune responses, Regulating cell differentiation and apoptosis, inhibiting the formation of the enzymes produced from the pathogenic bacteria *E. coli* and *C. perferinges* that includes the ureases different reductases specifically nitroreductases and oxidoreductases, β-glucuronidase and choloylglycine hydrolase. Enzymes such as ureases and beta glucosidases are involved in the conversion of pro carcinogens to the active carcinogens. In a study probiotic namely *Propionibacterium freudenreichii* produced Short chain fatty acids in the culture media and caused the cell death of gastric and colon cancer cells in humans [52, 53].

2.5.8 Constipation

It is common problem among the older population. Several controlled studies showed that in constipation either the bowel movements are increased or there is decrease in the transit time through the gastro-intestinal tract, for this purpose probiotics are utilized in the treatment of constipation [54, 55]. The most frequently used laxative is lactulose which is also a probiotics is not affected by the disaccharidases of the humans and the microflora in the colon, *bifidobacterium* utilizes it as a substrate that breakdown it into the smaller subunits leading to the creation of the osmotic effect. However, larger controlled studies are needed in order to confirm the use of prebiotics and probiotics apart from lactulose [56, 57].

2.5.9 Immunomodulation

Probiotics are involved in the modulation of the immune responses, are anti-inflammatory in nature and also have effect on humoral and cell regulated immunity. Probiotics are thought to involve in secretion of the factors that are responsible for regulating the immunity. For example the factors secreted from the probiotic strain *L. reuteri* limit the gene expression that is dependent on NF-Kb which results in the decrease in cell growth and greater protein kinases activated by nitrogen which leads to the induction of apoptosis [58].

Probiotics are present in greater quantity in fermented milks. During milk fermentation, *L. helveticus* is able to produce factors that are involved in enhancing the expression of calcineurin which is involved in the formation of mast and goblet cells in the gastrointestinal tract of mouse [59]. The intake of probiotic strain VSL3 is involved in down regulation of such immune responses by decreasing the secretion of IL-8, regardless of the presence of the bacterial pathogen *Salmonella dublin* [60].

2.5.10 Helicobacter pylori

The most common and worst bacterial infection found in human is the *Helicobacter pylori*. It causes a number of diseases like peptic ulcers, chronic gastritis, lymphoma, gastric adenocarcinoma and number of other diseases not related to gastrointestinal tract. Probiotics prevent the *H. pylori* infection by enhancing the immunoregulation functions that works as antagonistic to infection caused by *H. pylori* [61–63]. Many studies reported that *H. pylori* growth and gastritis infection can be minimized but the causative organism cannot be completely removed. It is noted that prebiotics plays their role for the suppression of *H. pylori* as well as they also enhance the efficacy of eradication therapy by stopping the side effects caused by antibiotics thus improving compliance [64]. *saccharomyces boulardii* is found helpful in reducing the symptoms of *Helicobacter pylori*.

2.5.11 Liver disease

2.5.11.1 Hepatic encephalopathy

By changing the microbiota count in the gut either by using probiotics or fermentable fiber has been related for the treatment of hepatic encephalopathy in experimental studies [65, 66]. This therapy works as it lowers the blood ammonia level due to inhabitation of bacteria that is acid resistant as well as not producing urease Further work on this approach is still under work [67].

2.5.11.2 Nonalcoholic fatty liver disease

Nonalcoholic steatohepatitis is a disease in which patients are not edict of alcohol but showing the systems of liver biopsy. Experiments on model rats suffering from fatty liver disease have been indicated that intestinal microbiota, bacterial endotoxin and tumor necrosis factor α modulate liver damage caused by alcohol. There is a perception that intestinal microbiota produces endogenous signals, which shows a pathologic role in nonalcoholic fatty liver disease, suggests a role for novel probiotic therapy in this not so uncommon condition [68, 69]. Recent studies have showed that nonalcoholic fatty liver disease is also thought to be linked with the dysbiosis of gut microbiota. By restoring and maintaining the gut microbiota, nonalcoholic fatty liver disease can be controlled. However extensive studies on the strains of gut microbiota and tests on various probiotics may be helpful in determining the use of specific probiotic for this disease [70].

2.5.12 Probiotics in infants health

Human milk defends infants from contagious diseases by several mechanisms. Human milk has various components that modulate the intestinal microbiota and *bifidobacteria*. These bacteria are the basic and significant constituent of the infants that are fed with human milk [71, 72]. Human milk can also minimize the incidence and harmful effects of inhabiting pathogens [73, 74]. Consequently,

it has been observed that a balanced increased in bifidobacterial concentration and reduction in enteric bacterial count and luminal factors of host may show a positive role in defending premature offspring and infants from diarrheal disease. Alteration of the intestinal microbiota by improving the prevalence of nonpathogenic bacteria is an effective method to attain a therapeutic treatment against enteric pathogens [75].

2.5.13 Urogenital infections and HIV

Various urinary tract infections like yeast vaginitis, Bacterial vaginosis and frequent urinary tract infections are major problems faced by the patients. In premenopausal women normal microflora consist of lactobacilli that protect host from infections but various patho-physiologic causes can results infection due to unstable microflora. A very few studies that reports the importance of probiotics for urogenital health [76, 77]. The awesome practices have reported that *L. acidophilus* has positive effect in urogenital health. Promising studies showed evidence that probiotics are also important in preventing recurrent urinary tract infection in women [78]. The women suffering from human immunodeficiency virus infection, prevention of bacterial vaginosis is very important. Previous literature indicates that women that have improper balance of lactobacilli (vaginosis) are in a great risk of human immunodeficiency syndrome [79, 80]. Therefore an adequate level of lactobacilli and preventing bacterial vaginosis is a best method to reduce the risk of getting human immunodeficiency virus infection, gonorrhea and trichomoniasis. One of the recent study shown that a probiotic strain (Lactobacillus reuteri RC-14) specific for human vagina can give strong protection from virus that can reduce the transmission of sexual immunodeficiency virus infection. Still, further work is required to approve these results before the extensive use of probiotics for the treatment of these diseases can be suggested [81].

2.5.14 Breast cancer

Several studies have been conducted on animal and human models to check the effect of probiotics in breast cancer. Several in vitro studies have shown that probiotics are involved in reducing the tumor size and stopped the growth of tumour. In Human studies it was observed that the use of probiotic *Lactobacillus casei shirota* prevented the onset of breast cancer. Also the use of fermented dairy products such as yogurt and fermented milk was inversely linked with the onset of breast cancer. Probiotics can be used for both preventive and treatment purposes of breast cancer. However more studies are needed in order to confirm the safety and efficacy of probiotics in breast cancer [82].

2.5.15 Type 2 diabetes mellitus

Experiments have shown that Type 2 Diabetes Mellitus can be result of dysbiosis of gut microbiota. This microbiota is involved in the permeability of gut mucosa and immune system of host which are linked to the type 2 diabetes mellitus. Different type of probiotic strains either single or multiple can be used for intervening type 2 diabetes mellitus. Probiotics that are mainly used to treat the symptoms of type 2 diabetes are *Lactococcus*, *Bifidobacterium* and *Lactobacillus*. After the oral probiotic administration can be helpful in modulating the immune function, gut microbiota and balancing the energy metabolism. Therefore it was suggested that probiotics are involved in reducing the incidence, delaying and reversing the complications of Type 2 diabetes [83].

3. Meat and dairy products as a functional agent

3.1 Dairy Products

Authors have considered different traditional dairy products such as yogurt, milk and cheese as a functional products as these are rich source of various vitamins and minerals and other constituents that can be used as functional agents [84]. Such as conjugated linoleic acid (CLA) and Selenium, that play an important role in lowering the serum cholesterol level thus preventing the atherosclerosis and other cardiovascular diseases also having antioxidant functions in the body [85].

Yogurt is a traditional dairy product that was prescribed by physicians in Middle East as a treatment of gastrointestinal diseases [86]. Yogurt is manufactured using *Streptococcus thermophilus and Lactobacillus bulgaricus* which both work in synergism. Health benefits of yogurt can be enhanced by the addition of probiotic bacteria in yogurt such as *Bifidobacterium, Lactobacillus acidophilus* and *L. rhamnosus* [87]. Yogurt has been used a food source consisting of probiotic organism throughout the world.

A wide variety of fermented milks have also been developed and various health benefits were linked with the consumption of fermented milks such as lowering of cholesterol. They also contain the important probiotics strains that are involved in improving the health [88].

Probiotic cheeses are available in soft as well as hard varieties. Various Probiotic Strains such as *Bifidobacterium and L. rhamnosus* are readily used in such cheeses and these cheeses can be beneficial source of Probiotics [89].

3.2 Meat products

Meat products are good source of protein and fat along with water and other vitamins which are highly bioavailable. Meat products can be made highly beneficial for health either by incorporating any ingredient in it that is considered healthy or eliminating or reducing any component that can be considered harmful [90].

Fatty acid and cholesterol level of meat can be modified by selecting different breeds, modifying the feed patterns, addition of some feed additives and several interventions regarding animal metabolism [91].

Similarly addition of olive oil to variety of meat products was thought to be associated with the high biological value and decrease onset of breast cancer and heart diseases [92].

Soy protein can also be added into the meat products. In 1999, US FDA stated that any product low in saturated fats and cholesterol containing 25 g of soy proteins may be helpful in preventing the cardiovascular diseases [93].

Lipid oxidation is the major issue in meat products thus instead of using synthetic antioxidants that pose toxicity and other harmful effects can be replaced by the antioxidants from the plat source such as rosemary, tea, etc. Green tea is associated with reducing the level of Cholesterol in body as well as increasing the portion of High density Lipoproteins and decreased the oxidation of lipoproteins [90, 94, 95].

Addition of salt for the preservation purpose can lead to high percentage of salt intake and can lead to the development of hypertension. Several substitutes were assessed and one of the best substitute was the addition of calcium ascorbate. This substitute causes higher acidification due to the fermentation by lactic acid bacteria. Replacement of salt with Calcium ascorbate helped in reducing the sodium chloride level as well enriching the meat with nutrition [96].

4. Prebiotics

Prebiotics are the food that is not digested in the human gut but food ingredients boost the growth and activity of bacteria that are good for our intestine, consequently they balance the intestine of an organism [97]. The most commonly used bacteria that are good for our health is amplified by prebiotics comprise of genus *Bifidobacterium* and *Lactobacillus,* which control the growth of harmful bacteria. Most commonly used prebiotics are mannan-oligosaccharides, galactoglucomannans, lactose, inulin and oligofructose. Short chain carbohydrates used as prebiotics consist of three to ten sugar units derived from the cell wall of yeast and plants. Prebiotics functionality are not alter by any food processing treatment and require little or no regulatory requirements, hence making their consumption more easy as compare to chemical treatment.

4.1 Mode of action of prebiotics

Important modes of action of prebiotics are:

- These are non-digestible carbohydrates that are not digested by the upper gastrointestinal tract and travel in the ileum and colon where fermented by the resident microbes.
- Prebiotics do cause intestinal homeostasis.
- Host surface receptors are coated by prebiotics.
- They produce bateriocins.
- Favorable bacteria produce short chain fatty acids with the help of non-digestible carbohydrates.
- Short-chain fatty acids are the energy source of epithelial cells.
- They regulate metabolic function and modulate immune system [98].

4.2 Targets for prebiotics: gut microbiota and intestinal health

Fermentation of resistant starches and dietary fiber caused by bacteria in colon release short chain fatty acid metabolites (SCFA). SCFA are well known for gut health as well as their part in provision of supplementary energy to the host in fatness is in debate. On contrary, 10% of entire energy in humans is provided by SCFA. According to energy yield hypothesis, dysbioticmicrobiomes have an amplified capacity to remove energy from the food, so that the bacterial conversion of non-digestible carbohydrates and dietary fiber to SCFAs could give additional energy to the host and result fatness of individual over time. Likewise, G-protein coupled receptors (GPR) can sense SCFAs that tie them with lipid and glucose breakdown. SCFAs activate the two major proteins, GPR41 and GPR43 which are expressed on adipocytes and enter endocrine L cells. Peptide YY is released by stimulation of intestinal GPR41 which enhances gut passage time and increase satiety. Inflammation lessens by activation of intestinal GPR43 as well as it simulates glucagon-like peptide (GLP), a hormone which contributes in regulation of insulin secretion. Enteroendocrine L cells express GLP-1 as well as secrete the gut-trophic

hormone GLP-2. Chief stimulus for GLP-2 secretion is nutrient consumption. SCFAs maintain the release of GLP-2 which is important in regulation of the gut fence system and decreases lipopolysaccharide translocation [99].

4.3 Healthy diet for probiotic

4.3.1 Dietary fiber

Diet is an element on which unequal antagonism exists between the microflora of gut and specific group of bacteria get their nutrition. It also serve as direct medium for the gut microflora since it may act as a direct substrate for the microbiota through its indigestible constituents and some by-products of digestion. Among all the nutritional constituents, dietary fibers are vital as they cannot be absorbed in the upper part of the digestive system; although they can be fermented in the lower part of the gut by the intestinal microbiota [100].

4.3.2 Prebiotics

Prebiotics are a subcategory of nutritional fibers that is not affected by the gastric acidity and the enzymes present in the digestive system of mammals which is very crucial for our health [101]. The main distinguishing benefit of prebiotics is their stimulation in growth of intestinal bacteria connected with fitness and comfort [102].

4.3.3 Complex carbohydrate

Some complex carbohydrates include resistant starch and plant cell-wall polysaccharides are not digested by the gut microflora. Polysaccharides comprising of cellulose, hemicelluloses (xylan, xyloglucan, mannan, β-glucan) and pectin. These all complex carbohydrates have positive simulative effect on microbial populations in the gut [103]. A number of bacteria present in human gut that possess genes programming with carbohydrate-active enzymes (CAZymes) in their genomes. These bacteria can digest such compound carbohydrates.

4.3.4 Prebiotic carbohydrates

Prebiotics definition is fulfilled by resistant starch [101]. In the colon prebiotic type of fermentation is provided by it and has lots of metabolic advantages, for instance it increase the bile salt production and laxation, lowers the danger of gastrointestinal tract cancers, and lowers the after meal glucose stimulus and blood lipid levels [104, 105]. Farther more it assists in growing of epithelial cells and propagation by increased butyrate concentration via its fermentation by the gut microbiota [106].

4.3.5 Algal (AGAL) polysaccharides

AGAL polysaccharide provides with dietary fiber, e.g., alginates, agars and carrageenan from seaweeds, consumed in food industry as thickeners and stabilizers or emulsifiers [107]. Many health benefits provided by dietary fibers due to its gel-forming ability and other physicochemical properties, including ability to ferment by the alimentary canal microbiota [108]. These benefits include controlled appetite, type 2 diabetes and obesity by increasing satiation, refining of gut barrier working and lessening the ad worse effects of luminal components.

Gut bacteria cause fermentation of compound carbohydrates that has beneficial affect for the host. This activity makes complex carbohydrate as potential prebiotics. Proteolytic activity produce potential harmful product and the fermentation of complex carbohydrates reduce risk caused by these harmful metabolites [109]. Furthermore, some useful metabolites with anti-cancer and anti-inflammatory activities, like phenolic substances and short chain fatty acids are also produced by the microbial fermentation of complex carbohydrates in the gut [110].

Chemically, inulin-type fructans are a linear polydisperse carbohydrate material consisting mainly, if not exclusively, of β-(2–1)-fructosyl-fructose glycosidic bond linkages [81]. Fructans are proposed to be classified as "functional fiber" according to recent concepts drawn from physiological effects on human individuals [111].

Guar galactomannan was enzymatically hydrolyzed to obtain partially hydrolyzed guar gum which can be utilized as prebiotic source. Partially hydrolyzed guar can be considered as potential prebiotic compound that may further stimulate the growth of potentially probiotic bacteria or native gut microflora [112].

4.3.6 Herbal prebiotics

Some herbs are used for the treatment of inflammatory immune diseases that also have prebiotic effect in the host. These herbs include *Ocimum sanctum*, *Piper nigrum* and *Zingiber officinale*. *Zingiber officinale and Ocimum sanctum* exhibited greater prebiotic activity, with higher growth of *Lactobacillus* and *Bifidobacterium* as compare to most commonly used prebiotic, fructo-oligosaccharide (FOS). However, *Piper nigrum* have similar prebiotic activity as that of most commonly used prebiotic FOS. These herbs used to regulate gut microbiota which ultimately prevent systemic swelling and related disorders [113].

4.3.7 Fractionated lotus seed resistance starch

Fractionated lotus seed resistance starch (LRS3) was fractionated and tested for its structural properties and prebiotic activities. LRS3–20% showed higher prebiotic activity against these bacteria *Bifidobacterium adolescentis* and *Lactobacillus acidophilus as* compared to LRS3–30% and high concentration of amylose maize starch [114].

4.3.8 Cereal grain fraction

Most commonly used cereal grains to develop new classes of prebiotic are corn, rice, wheat, barley and oats which also have high economic value [115].

4.3.9 Burdock root

It is rich source of fructo-oligosaccharides and phenolic compound but its use in food products are limited. It is widely used in bakery product for consumers that search for functional foods of health benefits. Burdock roots are effective alternative for functional foods with health benefits [116].

4.3.10 Lentil

Lentil food are rich source of prebiotic carbohydrates which have raffinose family oligosaccharides, fructooligosaccharides, sugar alcohols and resistance starch.

4.4 Therapeutic potential of prebiotics

4.4.1 Prebiotic impact on intestinal micro flora

Dietary fibers which are part of prebiotic play positive impact on intestinal micro flora [117]. In cholesterol metabolism prebiotic fibers play a very unique action specifically on fermentation of products and modulation of micro flora. Some research show both probiotics and prebiotics (in which non digestible food ingredients are more beneficial for host which stimulate the growth of colonic bacteria) to suppress tumor and preneoplastic lesions in the colons of animal treated with carcinogenic chemicals [118]. The presence of beneficial bacteria in gut of infants fed with human breast milk is supported by the metabolism of the complex mixture of oligo saccharides present in the milk. More mature gut microbiota is found in the formula milk. In adults formulation infants is used to achieve a type of intestinal microbiota. Improper gut microbiota (dysbiosis) can cause autoimmune disorders, infections and allergic reactions in old age [59].

4.4.2 Colon cancer and prebiotics

Aberrant crypt foci (ACF) is the first detectable abnormal growth of cells appears as lesions in the large intestine. To identify ACF lesions chromoscopic colonoscopy of high magnification is used, generally it appear as colonic mucosa. They comprised of crypts that are raised on upper side of normal mucosa. It consists of extremely condensed epithelia and has changed luminal openings visibly confined from the normal neighboring crypts. The development of the ACF to polyp, adenoma and adenocarcinoma equivalents buildup of numerous genetic and biochemical modifications. A little amount of ACF can be a cause of colon cancer. Presently, it is unidentified that which crypts are responsible for the development of tumor. Though, various researches support the idea of development of colon cancer from ACF [119]. Perrin et al. [120] reported that some fibers which stimulate the formation of stable butyrate-producing colonic ecosystem. This type of colonic environment diminished the rate of ACF. Therefore it is clear that colonic ecosystem that produces stable butyrate decreases the risks of developing colon cancer.

4.4.3 Prebiotics modulation of immune function

Immunological functions are modulated by our diet and affect resistance of host by various ways. Along with essential food components non-essential nutrients like non-digested carbohydrates also play an important role in controlling the immunological responses, particularly lymphoid tissues of the gut. Bodera [121] reviewed the previous literature by various scientist on the effects of prebiotics in enhancing the immunity of host and observed that there is sufficient proof indicating prebiotics such as inulin helps in the modulation of immunological functions. He suggests to take prebiotics for the modulation of immunological parameters in gut associated lymphoid tissues, secondary lymphoid tissues and peripheral circulation. First line defense is provided by the innate immune system and prevent the entry of contagious agents or eradicating entering pathogens. It encompasses physical fences like skin and mucous membranes, blood cells and tissue, such as phagocytes, natural killer cells and soluble mediators, like supplement proteins and cytokines.

4.4.4 Prebiotics as dietary modulators of gut microbiota in obesity

It is suggested that gut microbiota plays an important role in obesity and obesity-associated comorbidities that gut microbiota could be a possible goal for fatness

involvements. It is assumed that microbial dysbiosis is associated with fatness, it is concluded that restoring the potential symbiosis between the gut microbiota and host holds great potential. Prebiotics are consumed so that gut microbiota can be modified. Prebiotics are not capable to be digested by host enzymes although they move in the large intestine and are particularly fermented in the gastrointestinal tract where they help in growth of bacteria particularly *Bifidobacterium* and *Lactobacillus* that have been related with health benefits [122].

4.4.5 Prebiotics assist in the management of cognition

Worldwide, Schizophrenia is the 25 leading cause of disabilities that decrease the life about 10–20 years. Inappropriate treatment like pharmacotherapy in the administration of cognitive defects and weight gain are recognized a significant contributors of these diseases; therefore there is a need to develop such treatments that alleviate one, or both, of these diseases would be very helpful. By using gut microbiome from dietary source like prebiotics for the treatment of these diseases may be one such intervention. Moreover, prebiotics also effect breakdown, and in case of obesity they rise the concentration of anorexigenic gut hormones such as peptide tyrosine tyrosine, glucagon-like peptide 1 and leptin and decrease the amount of orexigenic hormones such as ghrelin [123].

4.4.6 Prebiotics for the improvement of enzyme activity and phosphate uptake

Prebiotics improve the activity of enzymes and phosphate uptake in the intestine. One of study was conducted to recognize the impact of prebiotics supplementation in infant formula on enzyme activity and phosphate uptake in the small intestine of Sprague Dawley (SD) rats. Forty-eight fifteen days old SD rats of similar weight were divided into three groups randomly: A was selected as control group in which SD rats were fed with standard infant formula with no prebiotics treatment. Rats in groups B, C were nourished standard infant formula supplemented with oligosaccharides, and the standard infant formula supplemented with polysaccharides, correspondingly. The results were checked at 28 days. It was observed that as compared to group A, group B and C showed the following: (1) In SD rats group C showed greater activities of sucrose and lactase in the small intestine; (2) In SD rats of group C comparative expressions of lactase gene in the anterior and posterior segments of the small intestine were increased by 1.68 and 2.26, and the *Mgam* gene relative expression in the posterior segment of the small intestine was improved by 0.99 in SD rats of group C; (3) the relative expressions of *Na/Pi-IIb* gene in the anterior and posterior segments of the small intestine were increased by 1.85 and 2.28 in SD rats of group C. These results specify that the supplementation of prebiotics in infant formula can stimulate enzyme movement in the small intestine by improving the relative expression of enzyme gene and *Na/Pi-IIb* gene and by reducing the intestinal injury. The polysaccharides improved to be healthier than that of oligosaccharides [124].

4.4.7 Prebiotics and the bioavailability of minerals and trace elements

Prebiotic carbohydrates have positive influence in the absorption of minerals and trace elements. There exist a promising evidence about the stimulatory impact of prebiotic carbohydrates (non-digestible oligosaccharides and lactulose) on the bioavailability of minerals and trace elements. However, most of the studies is on the rats because, the studies on the human is limited. It has been hypothesized that prebiotics create strong osmotic effect that reduce the pH and stimulate the exchange of

protons and increase level of calbindin and butyrate. Colon surface area also enlarged that is a good source to increase the minerals and trace elements absorption [125].

4.4.8 Prebiotics in diabetes and cardiovascular diseases

Prediabetes is linked with the long term inflammation that is associated with greater risk of developing type 2 diabetes and cardiovascular diseases. Increased concentration of lipopolysaccharides is linked with dysbiosis of the natural microbiota that is involved in the development of type 2 diabetes and cardiovascular diseases. Prebiotics involved in the selective functioning of natural micro biota such as inulin decreases the concentration of endotoxin, reduces permeability of the intestines and limit the metabolic dysfunction in rodents. The impact of prebiotics on the cardiovascular functions in patients at the risk of type 2 diabetes is still unknown. The prebiotic supplementation along with inulin could be used as preventive strategy for limiting the risk of cardiovascular diseases in the patients at risk of type 2 diabetes. This strategy can affect the clinical practices by setting and accepting dietary recommendation of prebiotics by medical and scientific community [126].

4.4.9 Prebiotics and renal profile

It is well documented that prebiotics, probiotics and the symbiotic supplementation had resulted in the improvement of renal function. Firouzi and Haghighatdoost [127] studied renal profile of a meta-analysis of a clinical trial. They pointed out that level of glomerular filtration rate was reduced whereas the concentration of creatinine was increased in the intervention group in comparison to the placebo group and the results were non-significant. The combined effect on the blood urea nitrogen demonstrated that the level declined as compared to the placebo group. Whereas the levels of uric acid increased in intervention group in comparison with the placebo group. The supplementation of prebiotics, probiotics and symbiotic should be limited among those in which renal function is compromised until well designed and large scale randomized controlled trials prove the efficiency and safety of prebiotics, probiotics and symbiotic supplementation for having improved effects on the renal function.

4.4.10 Prebiotics in controlling cancer

A study was conducted to check the impact of prebiotics intake consisting of xylo-oligosaccharides, fructo-oligosaccharides, resistant dextrin and polydextrose on immunity and the structure of gut microbiota in perioperative colorectal cancer patients.

A double blind, randomized clinical trial was conducted that consisted of 140 perioperative colorectal cancer patients involving 50 females and 90 males having age between 40 and 75 years. Patients were divided on random basis into two groups consisting of intervention group that received 30 g/day of prebiotic supplementation for the period of 7 days and control group that did not receive supplementation. The immunological and nutritional indices of both groups were evaluated before and after operation and were compared with their baseline levels. Also the fecal samples of random 40 patients from the both groups were taken to examine the gut microbiota. There was significant reduction in the abundance of intestinal microbiata from pre to post operation in the control group. Intake of prebiotics is recommended to improve immunological indices in patient having colorectal cancer for 7 days before operation. Prebiotics enhanced the concentration of four commensal microorganism containing opportunistic pathogens in patients having colorectal cancer. Surgical stress decreased the population of intestinal microbiota

but increased the population of commensal microbiota and opportunistic microorganisms. *For further research Bacteroides* is considered as a relevant bacterial species on the mechanism of prebiotics [128].

4.4.11 Anxiolytic effect of prebiotics

Long term treatment of prebiotics particularly combination of fructooligosaccharides and galactooligosaccharides have antidepressant effects and also involved in combating the issues related to anxiety. The effect of Galactooligosaccharide (GOS) and the combination of fructooligosaccharides and galactooligosaccharides is involved in reducing the level of corticosterone level in the body by mainly limiting its release. Prebiotics are involved in modifying the expression of specific genes related to the concentration of short chain fatty acids in the hypothalamus and hippocampus. Administration of Prebiotics resulted in the increased level of acetate and propionate and reduction in the concentration of isobutyrate that have significant correlation with the positive effects on behavior. Moreover, the administration fructooligosaccharides and galactooligosaccharides reduced the level of corticosterone and proinflammatory cytokines resulted from the chronic stress as well as normalizing the anxiety and depression like behavior along with mitigating the impact of stress on the microbiota [129].

5. Conclusion

Probiotics and prebiotics are functional foods that have significant biotechnological benefits with wonderful potential for invention. Though probiotics and prebiotics are likely to be used in treating many communicable and non-communicable disorders but it is very hard to draw conclusions from a number of researches that indicating the therapeutic potential of probiotics and prebiotics because scientists used different strains and prescriptions for various disorders. Further research using reliable regulations will permit more decisive results on the effects of probiotics and prebiotics for treatment of various diseases. Although various products with probiotic, prebiotics and symbiotic are usually available in food and supplement formats, in near future these products will target to specific disease and will be available as drug.

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References

[1] Parker RB. Probiotics, the other half of the antibiotic story. Animal Nutrition and Health. 1974;**29**:4-8

[2] Fuller R. Probiotics in man and animals. Journal of Applied Bacteriology. 1989;**66**:365-378

[3] Moriarty DJW. 2007 Control of luminous *Vibrio* species in penaeid aquaculture ponds. Aquaculture. 1998;**164**:351-358

[4] Wang YB, Xu ZR, Xia MS. The effectiveness of commercial probiotics in Northern White Shrimp (*Penaeus vannamei* L.) ponds. Fisheries Science. 2005;**71**:1034-1039

[5] Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nature Reviews Gastroenterology & Hepatology. 2014;**11**:506-514

[6] Guslandi M, Giollo P, Testoni PA. A pilot trial of *Saccharomyces boulardii* in ulcerative colitis. European Journal of Gastroenterology & Hepatology. 2003;**15**(14):697-698

[7] Mansour-Ghanaei F, Dehbashi N, Yazdanparast K, Shafaghi A. Efficacy of *Saccharomyces boulardii* with antibiotics in acute amoebiasis. World Journal of Gastroenterology. 2003;**9**(13):1832-1833

[8] Steidler L, Hans W, Schotte L, Neirynck S, Obermeier F, Falk W, et al. Treatment of murine colitis by *Lactococcus lactis* secreting interleukin-10. Science. 2000;**16**(289):1352

[9] Sartor RB. Therapeutic manipulation of the enteric microflora in inflammatory bowel diseases: Antibiotics, probiotics and prebiotics. Gastroenterology. 2004;**17**(126):1620

[10] EC (European Commission). Guidance on the implementation of regulation no. 1924/2006 on nutrition and health claims made on foods. Conclusion of the Standing Committee on the Food Chain and Animal Health. [Internet document]. 2007. Available from: http://ec.europa.eu/food/safety/docs/labelling_nutrition_claim_reg-2006-124_guidance_en.pdf [Accessed: 13 May 2016]

[11] Health Canada Guidance document. The use of probiotic microorganisms in food. [Internet document]. 2009. Available from: http://www.hc-sc.gc.ca/fn-an/legislation/guide-ld/probiotics_guidance orientation_probiotiques-eng.php [Accessed: 29 Jan 2019]

[12] Thomas LV. Probiotics—The journey continues. International Journal of Dairy Technology. 2016;**69**(4):469-480

[13] Chapman CMC, Gibson GR, Rowland I. Health benefits of probiotics: Are mixtures more effective than single strains? European Journal of Nutrition. 2011;**50**(1):1-17

[14] Harish K, Varghese T. Probiotics in humans–evidence based review. Calicut Medical Journal. 2006;**4**(4):e3

[15] Narayan SS, Jalgaonkar S, Shahani S, Kulkarni VN. Probiotics: Current trends in the treatment of diarrhoea. Hong Kong Medical Journal. 2010;**16**(3):213-218

[16] Szymański H, Pejcz J, Jawień M, Chmielarczyk A, Strus M, Heczko PB. Treatment of acute infectious diarrhoea in infants and children with a mixture of three *Lactobacillus rhamnosus* strains—A randomized,

double-blind, placebo-controlled trial. Alimentary Pharmacology & Therapeutics. 2006;**23**(2):247-253

[17] Hord NG. Eukaryotic-microbiota crosstalk: Potential mechanisms for health benefits of prebiotics and probiotics. Annual Review of Nutrition. 2008;**28**:215-231

[18] McFarland LV. Meta-analysis of probiotics for the prevention of antibiotic associated diarrhea and the treatment of *Clostridium difficile* disease. The American Journal of Gastroenterology. 2006;**101**(4):812-822

[19] Bartlett JG. Antibiotic-associated diarrhea. The New England Journal of Medicine. 2002;**346**(5):334-339

[20] Sudha RM, Bhonagiri S. Efficacy of *Bacillus coagulans* strain unique IS-2 in the treatment of patients with acute diarrhea. International Journal of Probiotics & Prebiotics. 2012;**7**(1)

[21] Hill DR, Ryan ET. Management of travellers' diarrhoea. British Medical Journal. 2008;**337**:a1746

[22] Katelaris PH, Salam I, Farthing MJ. Lactobacilli to prevent traveler's diarrhea? The New England Journal of Medicine. 1995;**333**(44):1360

[23] Kollaritsch H, Holst H, Grobara P, Wiedermann G. Prevention of traveler's diarrhea with *Saccharomyces boulardii*. Results of a placebo controlled double-blind study. Fortschritte der Medizin. 1993;**111**(43):152-156

[24] Oksanen PJ, Salminen S, Saxelin M, Hamalainen P, IhantolaVormisto A, Muurasniemi-Isoviita L, et al. Prevention of travellers' diarrhea by Lactobacillus GG. Annals of Medicine. 1990;**22**(45):53-56

[25] Moeinian M, FarnazGhasemi-Niri S, Mozaffari S, Abdollahi M. Synergistic effect of probiotics, butyrate and l-Carnitine in treatment of IBD. Journal of Medical Hypotheses and Ideas. 2013;**7**(2):50-53

[26] Matsumoto S, Hara T, Hori T, Mitsuyama K, Nagaoka M, Tomiyasu N, et al. Probiotic Lactobacillus-induced improvement in murine chronic inflammatory bowel disease is associated with the down-regulation of pro-inflammatory cytokines in lamina propria mononuclear cells. Clinical and Experimental Immunology. 2005;**140**(3):417-426

[27] Ishikawa H, Akedo I, Umesaki Y, Tanaka R, Imaoka A, Otani T. Randomized controlled trial of the effect of bifidobacteria-fermented milk on ulcerative colitis. Journal of the American College of Nutrition. 2003;**22**:56-63

[28] Kruis W, Schutz E, Fric P, Fixa B, Judmaier G, Stolte M. Doubleblind comparison of an oral *Escherichia coli* preparation and mesalazine in maintaining remission of ulcerative colitis. Alimentary Pharmacology & Therapeutics. 1997;**11**:853-858

[29] Rembacken BJ, Snelling AM, Hawkey PM, Chalmers DM, Axon AT. Nonpathogenic *Escherichia coli* versus mesalazine for the treatment of ulcerative colitis: A randomized trial. Lancet. 1999;**354**:635-639

[30] Coqueiro AY, Raizel R, Bonvini A, Tirapegui J, Rogero MM. Probiotics for inflammatory bowel diseases: A promising adjuvant treatment. International Journal of Food Sciences and Nutrition. 2018;**28**:1-10

[31] Kelesidis T, Pothoulakis C. Efficacy and safety of the probiotic *Saccharomyces boulardii* for the prevention and therapy of gastrointestinal disorders. Therapeutic Advances in Gastroenterology. 2012;**5**(2):111-125

[32] Asto E, Mendez I, Audivert S, Farran-Codina A, Espadaler J. The efficacy of

probiotics, prebiotic inulin-type fructans, and synbiotics in human ulcerative colitis: A systematic review and meta-analysis. Nutrients. 2019;**11**(2):293

[33] Jonkers D, Penders J, Masclee A, Pierik M. Probiotics in the management of inflammatory bowel disease. Drugs. 2012;**72**(6):803-823

[34] Van Immerseel F, Ducatelle R, De Vos M, Boon N, Van De Wiele T, Verbeke K, et al. Butyric acid-producing anaerobic bacteria as a novel probiotic treatment approach for inflammatory bowel disease. Journal of Medical Microbiology. 2010;**59**(2):141-143

[35] Veerappan GR, Betteridge J, Young PE. Probiotics for the treatment of inflammatory bowel disease. Current Gastroenterology Reports. 2012;**14**(4):324-333

[36] Howarth GS. Inflammatory bowel disease, a dysregulated host-microbiota interaction: Are probiotics a new therapeutic option. Journal of Gastroenterology and Hepatology. 2008;**23**(12):1777-1779

[37] Gionchetti P, Rizzello F, Helwig U, Venturi A, Lammers KM, Brigidi P, et al. Prophylaxis of pouchitis onset with probiotic therapy: A double-blind, placebo-controlled trial. Gastroenterology. 2003;**124**:1202-1209

[38] Lichtenstein L, Avni-Biron I, Ben-Bassat O. The current place of probiotics and prebiotics in the treatment of pouchitis. Best Practice & Research: Clinical Gastroenterology. 2016;**30**(1):73-80

[39] Kim HJ, Camilleri M, McKinzie S, Lempke MB, Burton DD, Thomforde GM, et al. A randomized controlled trial of a probiotic, VSL#3, on gut transit and symptoms in diarrhea predominant irritable bowel syndrome. Alimentary Pharmacology & Therapeutics. 2003;**17**:895-904

[40] Niedzielin K, Kordecki H, Birkenfeld B. A controlled, doubleblind, randomized study on the efficacy of *Lactobacillus plantarum* 299V in patients with irritable bowel syndrome. European Journal of Gastroenterology & Hepatology. 2001;**13**:1143-1147

[41] Nobaek S, Johansson ML, Molin G, Ahrne S, Jeppsson B. Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. The American Journal of Gastroenterology. 2000;**95**:1231-1238

[42] O'Sullivan MA, O'Morain CA. Bacterial supplementation in the irritable bowel syndrome. A randomized double-blind placebo controlled crossover study. Digestive and Liver Disease. 2000;**32**:294-301

[43] Sen S, Mullan MM, Parker TJ, Woolner JT, Tarry SA, Hunter JO. Effect of Lactobacillus plantarum 299V on colonic fermentation and symptoms of irritable bowel syndrome. Digestive Diseases and Sciences. 2002;**47**:2615-2620

[44] Connell M, Shin A, James-Stevenson T, Xu H, Imperiale TF, Herron J. Systematic review and meta-analysis: Efficacy of patented probiotic, VSL#3, in irritable bowel syndrome. Neurogastroenterology and Motilility. 2018;**30**(12):124-128

[45] Scrimshaw NS, Murray AB. The acceptability of milk and milk products in populations with a high prevalence of lactose intolerance. American Journal of Clinical Nutrition. 1988;**48**:1083

[46] Sanders ME. Summary of the conclusions from a consensus panel of experts on health attributes on lactic cultures: Significance to fluid milk products containing cultures. Journal of Dairy Science. 1993;**76**:1819-1828

[47] Oak SJ, Jha R. The effects of probiotics in lactose intolerance: A

systematic review. Critical Reviews in Food Science and Nutrition. 2018;**59**(11):1675-1683. DOI: 10.1080/10408398.2018.14259

[48] Hirayama K, Rafter J. The role of lactic acid bacteria in colon cancer prevention: Mechanistic considerations. Antonie Van Leeuwenhoek. 1999;**76**:391-394

[49] Marotta F, Naito Y, Minelli E, Tajiri H, Bertuccelli J, Wu CC, et al. Chemopreventive effect of a probiotic preparation on the development of preneoplastic and neoplastic colonic lesions: An experimental study. Hepato-Gastroenterology. 2003;**50**:1914-1918

[50] Rafter J. Lactic acid bacteria and cancer: Mechanistic perspective. The British Journal of Nutrition. 2002;**88**:S89-S94

[51] Rafter J. Probiotics and colon cancer. Best Practice & Research: Clinical Gastroenterology. 2003;**17**:849-859

[52] Lee SY, Jeon HM, Ju MK, Kim CH, Yoon G, Han SI, et al. Wnt/Snail signaling regulates cytochrome C oxidase and glucose metabolism. Cancer Research. 2012;**72**(14):3607-3617

[53] Mario U, Giulia M, Francesco B, Velia D, Michele M, Gaetano B, et al. Potential role of probiotics on colorectal cancer prevention. BMC Surgery. 2012;**12**(Suppl 1):S1-S35

[54] Koebnick C, Wagner I, Leitzmann P, Stern U, Zunft HJ. Probiotic beverage containing Lactobacillus casei Shirota improves gastrointestinal symptoms in patients with chronic constipation. Canadian Journal of Gastroenterology. 2003;**17**:655-659

[55] Ouwehand AC, Lagstrom H, Suomalainen T, Salminen S. Effect of probiotics on constipation, fecal azoreductase activity and fecal mucin content in the elderly. Annals of Nutrition and Metabolism. 2002;**46**:159-162

[56] Martínez-Martínez IM, Calabuig-Tolsá R, Cauli O. The effect of probiotics as a treatment for constipation in elderly people: A systematic review. Archives of Gerontology and Geriatrics. 2017;**71**:142-149

[57] McFarland LV. Meta-analysis of probiotics for the prevention of traveler's diarrhea. Travel Medicine and Infectious Disease. 2007;**5**(2):97-105

[58] Delcenserie V, Martel D, Lamoureux M, Amiot J, Boutin Y, Roy D. Immunomodulatory effects of probiotics in the intestinal tract. Current Issues in Molecular Biology. 2008;**10**(1/2):37

[59] Isolauri E, Sherman PM, Walker WA, editors. Intestinal Microbiome: Functional Aspects in Health and Disease, Nestlé Nutr Inst Workshop Series, Nestec Ltd., Vevey/S. Karger AG., Basel, ©. Vol. 88. 2017. pp. 161-170. DOI: 10.1159/000455400

[60] Hardy H, Harris J, Lyon E, Beal J, Foey AD. Probiotics, prebiotics and immunomodulation of gut mucosal defenses: Homeostasis and immunopathology. Nutrients. 2013;**5**(6):1869-1912

[61] Canducci F, Cremonini F, Armuzzi A, Di Caro S, Gabrielli M, Santarelli L, et al. Probiotics and *Helicobacter pylori* eradication. Digestive and Liver Disease. 2002;**34**:S81-S83

[62] Felley C, Michetti P. Probiotics and *Helicobacter pylori*. Best Practice & Research: Clinical Gastroenterology. 2003;**17**:785-791

[63] Hamilton-Miller JM. The role of probiotics in the treatment and prevention of *Helicobacter pylori* infection. International Journal of Antimicrobial Agents. 2003;**22**:360-366

[64] Cremonini F, Di Caro S, Covino M, Armuzzi A, Gabrielli M, Santarelli L, et al. Effect of different probiotic preparations on anti-*Helicobacter pylori* therapy-related side effects: A parallel group, triple blind, placebocontrolled study. The American Journal of Gastroenterology. 2002;**97**:2744-2749

[65] Liu Q, Duan ZP, da Ha K, Bengmark S, Kurtovic J, Riordan SM. Synbiotic modulation of gut flora: Effect on minimal hepatic encephalopathy in patients with cirrhosis. Hepatology. 2004;**39**:1441

[66] Loguercio C, Abbiati R, Rinaldi M, Romano A, Del Vecchio Blanco C, Coltorti M. Long-term effects of enterococcus faecium SF68 versus lactulose in the treatment of patients with cirrhosis and grade 1-2 hepatic encephalopathy. Journal of Hepatology. 1995;**23**:39-46

[67] Dalal R, McGee RG, Riordan SM, Webster AC. Probiotics for people with hepatic encephalopathy. Cochrane Database of Systematic Reviews. 2017;**2**:1465-1858. Art. No.: CD008716. DOI: 10.1002/14651858.CD008716.pub3

[68] Li Z, Yang S, Lin H, Huang J, Watkins PA, Moser AB, et al. Probiotics and antibodies to TNF inhibit inflammatory activity and improve nonalcoholic fatty liver disease. Hepatology. 2003;**37**:343-350

[69] Olah A, Belagyi T, Issekutz A, Gamal ME, Bengmark S. Randomized clinical trial of specific lactobacillus and fiber supplement to early enteral nutrition in patients with acute pancreatitis. The British Journal of Surgery. 2002;**89**:1103-1107

[70] Chen J, Thomeson M, Vitetta L. Interaction of gut microbiota with dysregulation of bile acids in the pathogenesis of nonalcoholic fatty liver disease and potential therapeutic implications of probiotics. Journal of Cellular Biochemistry. 2019;**120**(3):2713-2720

[71] Drasar BS, Roberts AK. Control of the large bowel microflora. In: Hill MJ, Marsh PD, editors. Human Microbial Ecology. Boca Raton, FL: CRC Press; 1990. pp. 87-111

[72] Yoshita M, Fujita K, Sakata H. Development of the normal intestinal flora and its clinical significance in infants and children. Bifidobacteria and Microflora. 1991;**10**:11-27

[73] Maxson RT, Jackson RJ, Smith SD. The protective role of enteral IgA supplementation in neonatal gut origin sepsis. Journal of Pediatric Surgery. 1995;**176**:2313

[74] Steinwender G, Schimpl G, Sixl B, Kerbler S, Ratschek M, Kilzer S, et al. Effect of early nutritional deprivation and diet on translocation of bacteria from the gastrointestinal tract in the newborn rat. Pediatric Research. 1995;**39**:415-420

[75] Xiao L, Ding G, Ding Y, Deng C, Ze X, Chen L, et al. Effect of probiotics on digestibility and immunity in infant: A study protocol for a randomized controlled trial. Medicine (Baltimore). 2017;**96**(14):e5953

[76] Hilton E, Isenberg HD, Alperstein P, France K, Borenstein MT. Ingestion of yogurt containing *Lactobacillus acidophilus* as prophylaxis for candidal vaginitis. Annals of Internal Medicine. 1992;**116**:353-357

[77] Williams AB, Yu C, Tashima K, Burgess J, Danvers K. Evaluation of two self-care treatments for prevention of vaginal candidiasis in women with HIV. Journal of the Association of Nurses in AIDS Care. 2001;**12**:51-57

[78] Falagas ME, Betsi GI, Tokas T, Athanasiou S. Probiotics for prevention of recurrent urinary tract infections in

women: A review of the evidence from microbiological and clinical studies. Drugs. 2006;**66**:1253-1261

[79] Cohen CR, Duerr A, Pruithithada N, Rugpao S, Hillier S, Garcia P, et al. Bacterial vaginosis and HIV seroprevalence among female commercial sex workers in Chiang Mai, Thailand. AIDS Journal. 1995;**9**:1093-1097

[80] Sewankambo N, Gray RH, Wawer MJ, Paxton L, McNaim D, Wabwire-Mangen F, et al. HIV-1 infection associated with abnormal vaginal flora morphology and bacterial vaginosis. Lancet. 1997;**350**:546-550

[81] Liu JJ, Reid G, Jiang Y, Turner MS, Tsai CC. Activity of HIV entry and fusion inhibitors expressed by the human vaginal colonizing probiotic *Lactobacillus reuteri* RC-14. Cellular Microbiology. 2006;**9**(1):120-130

[82] Ranjbar S, Seyednejad SA, Azimi H, Rezaeizadeh H, Rahimi R. Emerging roles of probiotics in prevention and treatment of breast cancer: A comprehensive review of their therapeutic potential. Nutrition and Cancer. 2019;**71**(1):1-12

[83] Sun Z, Sun X, Li J, Li Z, Hu Q, Li L, et al. Using probiotics for type 2 diabetes mellitus intervention: Advances, questions, and potential. Critical Reviews in Food Science and Nutrition. 2019;**59**:1-14. DOI: 10.1080/10408398.2018.1547268

[84] Parodi PW. Anticancer agents in milk fat. Australian Journal of Dairy Technology. 2003;**58**:114-118

[85] Thom E, Wadstein J, Gudmunsden O. Conjugated linoleic acid reduces body fat in healthy excercising humans. Journal of International Medical Research. 2001;**29**:392-396

[86] Metchinkoff E. The Prolongation of Life, Optimistic Studies (English translation edited by PC Michelle). New York, London: G.P Putnam's and Sons; 1998

[87] Zouhari A, Accolas JP, Desmazeaud MJ. Metabolism and biochemical characteristics of yogurt bacteria. A review. Lait. 1992;**72**:1-34

[88] Playne MJ. Functional dairy foods and ingredients. Australian Dairy Foods. 2003;**58**(3):242

[89] Playne MJ. Researching, developing and commercializing probiotic cheese. Australian Dairy Foods. 2002;**23**(2):28-30

[90] Fernández-Ginés JM, Fernández-Lopez J, Sayas-Barberá E, Pérez-Alvarez JA. Meat products as functional foods: A review. Journal of Food Science. 2005;**70**(2):R37-R43

[91] Chizzolini R, Zanardi E, Dorigoni V, Ghidini S. Calorific value and cholesterol content of normal and low-fat meat and meat products. Trends in Food Science and Technology. 1999;**10**:119-128

[92] Pappa IC, Bloukas JG, Arvanitoyannis IS. Optimization of salt, olive oil and pectin level for low-fat frankfurters produced by replacing pork backfat with olive oil. Meat Science. 2000;**56**:81-88

[93] Sadler MJ. Meat alternatives - market developments and health benefits. Trends in Food Science and Technology. 2004;**15**:250-260

[94] Ferrari CKB, Torres EAFS. Biochemical pharmacology of functional foods and prevention of chronic diseases of aging. Biomedicine and Pharmacotherapy. 2003;**57**:251-260

[95] Tang S, Kerry JP, Sheehan D, Joe Bukley D, Morrissey PA. Antioxidative effect of added tea catechins on susceptibility of cooked red meat,

poultry and fish patties to lipid oxidation. Food Research International. 2001;**34**:651-657

[96] Ruusunen M, Vainionpaa J, Poulanne E, Lyly M, Lähteenmäki L, Niemistö M, et al. Physical and sensory properties of low-salt phosphate free frankfurters composed with various ingredients. Meat Science. 2003;**63**:9-16

[97] Gibson GR, Roberfroid MD. Dietary modulation of the human colonic microbiota—Introducing the concept of prebiotics. The Journal of Nutrition. 1995;**125**:1401-1412

[98] Yoo JY, Kim SS. Probiotics and prebiotics: Present status and future perspectives on metabolic disorders. Nutrients. 2016;**8**(3):173

[99] den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. Journal of Lipid Research. 2013;**54**(9):2325-2340

[100] Markowiak P, Śliżewska K. Effects of probiotics, prebiotics, and synbiotics on human health. Nutrients. 2017;**9**(9):1021

[101] Slavin J. Fiber and prebiotics: Mechanisms and health benefits. Nutrients. 2013;**5**:1417-1435

[102] Gibson RG, Probert HM, Van LJ, Rastall RA, Roberfroid MB. Dietary modulation of the human colonic microbiota: Updating the concept of prebiotics. Nutrition Research Reviews. 2004;**17**:259-275

[103] Flint HJ. The impact of nutrition on the human microbiome. Nutrition Reviews. 2012;**70**:3-10

[104] Bindels LB, Walter J, Ramer-Tait AE. Resistant starches for the administration of metabolic diseases. Current Opinion in Clinical Nutrition & Metabolic Care. 2015;**18**:559-565

[105] Fuentes-Zaragoza E, Sánchez-Zapata E, Sendra E, Sayas E, Navarro C, Fernández-López J, et al. Resistant starch as prebiotic: A review. Starch/Staerke. 2011;**63**:406-415

[106] Lesmes U, Beards EJ, Gibson GR, Tuohy KM, Shimoni E. Starch type III polymorphseffects on human colon microbiota and short chain fatty acids in human alimentary canal. Journal of Agricultural and Food Chemistry. 2008;**56**:5415-5421

[107] Brownlee IA, Allen A, Pearson JP, et al. Alginic acid salt or ester as a dietary fiber. Critical Reviews in Food Science and Nutrition. 2005;**45**:497-510

[108] Dettmar PW, Strugala V, Craig RJ. Important part alginates contributes in health. Food Hydrocolloids. 2011;**25**:263-266

[109] Russell WR, Gratz SW, Duncan SH, et al. High-protein, reduced-carbohydrate weight-loss diets promote metabolite profiles likely to be detrimental to colonic health. The American Journal of Clinical Nutrition. 2011;**93**:1062-1072

[110] ElKaoutari A, Armougom F, Gordon JI, Raoult D, Henrissat B. The abundance and variety of carbohydrate-active enzymes in the human gut microbiota. Nature Reviews. Microbiology. 2013;**11**(7):497-504

[111] Madrigal L, Sangronis E. Inulin and derivates as key ingredients in functional foods. Archivos Latinoamericanos de Nutrición. 2007;**57**(4):387-396

[112] Mudgil D, Sheweta B, Ami Rameshbhai P, Nihir PS. Partially hydrolyzed guar gum as a potential prebiotic source. International

Journal of Biological Macromolecules. 2018;**112**:207-210

[113] Liu Y, Sun M, Yao H, Liu Y, Gao R. Herbal medicine for the treatment of obesity: An overview of scientific evidence from 2007 to 2017. Evidence-Based Complementary and Alternative Medicine. 2017;**17**. Article ID: 8943059

[114] Zeng H, Peilin C, Chuanjie C, Cancan H, Shan L, Baodong Z, et al. Structural properties and prebiotic activities of fractionated lotus seed resistant starches. Food Chemistry. 2018;**15**(251):33-40

[115] Zhuang X, Zhao C, Liu K, Rubinelli P, Ricke SC, Atungulu GG. Chapter 10. Cereal grain fractions as potential sources of prebiotics: Current status, opportunities, and potential applications. In: Ricke SC, Atungulu GG, Park SH, Rainwater CE, editors. Food and Feed Safety Systems and Analysis. San Diego, CA: Elsevier Inc.; 2017. pp. 173-191

[116] Moro TMA, Celegatti CM, Pereira APA, Lopes AS, Barbin DF, Pastore GM, et al. Use of burdock root flour as a prebiotic ingredient in cookies. LWT. 2018;**90**:540-546

[117] DeVrese M, Schrezenmeir J. Probiotics, Prebiotics, and Synbiotics in Food Biotechnology. Berlin, Heidelberg: Springer; 2008. pp. 1-66

[118] Uccello M, Malaguarnera G, Basile F, D'agata V, Malaguarnera M, Bertino G, et al. Potential role of probiotics on colorectal cancer prevention. BMC Surgery. 2012;**12**(1):S35

[119] Alrawi SJ, Schiff M, Carroll RE, Dayton M, Gibbs JF, Kulavlat M, et al. Aberrant crypt foci. Anticancer Research. 2006;**26**:107-119

[120] Perrin P, Pierre F, Patry Y, Champ M, Berreur M, Pradal G, et al. Only fibres promoting a stable butyrate producing colonic ecosystem decrease the rate of aberrant crypt foci in rats. Gut. 2001;**48**(1):53-61

[121] Bodera P. Influence of prebiotics on the human immune system (GALT). Recent Patents on Inflammation & Allergy Drug Discovery. 2008;**2**:19-153. DOI: 10.2174/187221308784543656

[122] Nicolucci AC, Reimer RA. Prebiotics as a modulator of gut microbiota in paediatric obesity. Pediatric Obesity. 2017;**12**:265-273

[123] Chia-Ching KA, Burnet PWJ, Lennox BR. Can prebiotics assist in the management of cognition and weight gain in schizophrenia? Psychoneuroendocrinology. 2018;**95**:179-185

[124] Zhou S, Hang Y, Wang J, Fang R. Enzyme activity and phosphate uptake in the small intestine of Sprague Dawley rats improved by supplementation of infant formula with prebiotics. Animal Nutrition. 2018;**4**(3):300-304

[125] Bongers A, van den Heuvel EGHM. Prebiotics and the bioavailability of minerals and trace elements. Food Reviews International. 2003;**4**(19):397-422

[126] Mitchell CM, Davy BM, Halliday TM, Hulver MW, Neilson AP, Ponder MA, et al. The effect of prebiotic supplementation with inulin on cardiometabolic health: Rationale, design, and methods of a controlled feeding efficacy trial in adults at risk of type 2 diabetes. Contemporary Clinical Trials. 2015;**45**:328-337

[127] Firouzi S, Haghighatdoost F. The effects of prebiotic, probiotic, and synbiotic supplementation on blood parameters of renal function: A systematic review and meta-analysis of clinical trials. Nutrition. 2018;**51-52**:104-113

[128] Xie X, Yaqin H, Hai L, Dong Y, Li N, Ting S, et al. Effects of prebiotics on immunological indicators and intestinal microbiota structure in perioperative colorectal cancer patients. Nutrition. 2019;**61**:132-142

[129] Aurelijus B, Silvia A, Rachel D, Moloney VL, Kiera M, Gerard C, et al. Targeting the microbiota-gut-brain axis: Prebiotics have anxiolytic and antidepressant-like effects and reverse the impact of chronic stress in mice. Biological Psychiatry. 2017;**82**(7):472-487