Chapter

Probiotic, Prebiotic and Synbiotic Products in Human Health

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Abstract

The health benefits imparted by probiotics and prebiotics as well as synbiotics have been the subject of extensive research in the past few decades. What is the real role of probiotics strains, prebiotics and synbiotics in influencing a health? To battle the increase in health care costs, in recent years has been developed a preventive approach to medicine with the development of new probiotics and prebiotics or symbiotic products. Many studies suggest that probiotics, prebiotics and synbiotics supplementation may be beneficial in prevention and management of nutritional and health. While these studies show promising beneficial effects, the long-term risks or health benefits of prebiotics, probiotics and synbiotics supplementation are not clear. In this chapter review the literature regarding available information and summarises the current knowledge on the effects of probiotics, prebiotics, and synbiotics on human health and explore recent trends and developments in this field.

Keywords: probiotics, prebiotics, synbiotics, health, functional food

1. Introduction

Probiotic, prebiotic and synbiotic are words of the modern era, bookmark "for life" and is in use to define bacterial association with beneficial effects on human health. In the world of highly processed food, both at the industrial and nutritional level clear consideration are paid to the composition and safety of the intake products. The nutrition quality is essential for human health because of the food poisoning, obesity, allergy, cardiovascular diseases, and cancer, that is consider the plague of the twenty-first century. Worldwide, many research reports underline the health advantages of using probiotics, prebiotics and also, synbiotics in human consumption [1]. In early 1990s, Metchnikoff [2] defined probiotics in a scientific context as the microorganisms that alter of floral/microbial diversity in human bodies and replaces the harmful microbes with useful ones. However, Tissier detected that the microbial population of a particular type of bacteria in stool samples of infected diarrheic children was significantly lower comparing to healthy children [3]. He suggested that patients with diarrhoea (infantile diarrhoea) should oral administration of live organisms (bifidobacteria) and in this way a healthy gut flora was restored. Havenaar and Huis in't Veld [4] have given the modern definition of probiotic: as a viable mono or mixed culture of bacteria which, when applied to animal or man, affects the host beneficially by improving the properties of the indigenous flora. In 2002, Food and Agriculture Organisation of the United Nations (FAO) and World Health Organisation (WHO) defined probiotics as being "live strains of strictly selected microorganisms which, when administered in adequate

amounts, confer a health benefit on the host" [5]. The definition was preserved also, by the International Scientific Association for Probiotics and Prebiotics (ISAPP) in 2013 [6]. The vast majority of results of the clinical research underline the positive effect of the probiotics on the gastrointestinal diseases, such as: irritable bowel syndrome, gastrointestinal disorders, elimination of *Helicobacter*, inflammatory bowel disease, diarrhoeas, and allergic diseases, like as atopic dermatitis. Also, numerous clinical reports have demonstrated the efficiency of the probiotics for the treatment of diseases such as obesity, insulin resistance syndrome, type 2 diabetes, and non-alcoholic fatty liver disease. Increasing the body's immunity (immunomodulation) was the positive effect of probiotics on human health. Majority of scientific reports also show the benefits of the prophylactic use of probiotics in different types of cancer and side effects associated with cancer [1].

In 1995, Gibson and Roberfroid defined prebiotics were by as non-digested food components that, through the stimulation of growth and/or activity of a single type or a limited amount of microorganisms which residing in the gastrointestinal tract, improve the health condition of a host [7]. Instead, in 2004, prebiotics were described as selectively fermented compounds permitting precise changes in the composition and/or activity of the gastrointestinal tract microorganisms, these changes being useful for the host's health and wellbeing [8]. Recently, in 2007, FAO/WHO experts, designated prebiotics as a nonviable food constituent that confers a health advantage on the host linked to the microbiota modulation [9]. However, in the literature it is specified that prebiotics can be used as a probiotics substitute or as a supplementary support for them. Instead, numerous prebiotics can improve the growth of indigenous gut bacteria and have tremendous potential for changing the gut microbiota, but these variations occur just at the level of individual strains. Worldwide, numerous scientific studies underline the positively effects of the prebiotics for human health.

For the simultaneous use of probiotics and prebiotics high potential is attributed. In 1995, Gibson and Roberfroid introduced the term "synbiotic" to describe union between probiotics and prebiotics synergistically acting of health [7]. Synbiotic is a designated compound that introduced in the gastrointestinal tract can careful stimulates the growth and/or activates the metabolism of physiological intestinal microbiota, thus conferring beneficial result to the host's health [10]. As the word "synbiotic" is a synergy, the term can be attributed only to the products where a prebiotic compound selectively improves a probiotic microorganism [11]. The main aim of this type of combination is the improvement of probiotic microorganism's survival in the gastrointestinal tract. Therefore, synbiotic have both probiotic and prebiotic assets and were designed in order to solve the probiotics survival in the gastrointestinal tract [12]. An adequate combination of both components (prebiotic and probiotic) in a single product should guarantee a superior effect, compared to the action of the probiotic or prebiotic alone [13, 14].

Besides basic role of the nutrition consisting in the supply of necessary nutrients for growth and development of the organism, some additional aspects are becoming increasingly important, including the maintenance of health and counteracting diseases. The introduction of probiotics, prebiotics, or synbiotics into human diet is favourable for the intestinal microbiota and the human health. They may be consumed in the form of dairy products, raw vegetables and fruit or fermented pickles. Another source of probiotics, prebiotics, or synbiotics may be pharmaceutical formulas and functional food. Although probiotics, prebiotics and synbiotics have considerable potential in nutritional and clinical applications, considerable researches are required for the implementation of probiotics into human health, nutrition and regulation of different abnormalities. The screening of probiotics, prebiotics and synbiotics and their amounts is essential in gaining a therapeutic effect in health. However, further research focused on discovering new probiotic strains,

the assortment of probiotics and prebiotics for synbiotics, dose setting, safety of use, and clinical trials is necessary. Also, the health benefits should be established in properly scheduled clinical trials conducted by independent research centres.

This chapter is an attempt to emphasise the possible benefaction of probiotics, prebiotics and synbiotics for improving human health and regulation of common metabolic disorders or abnormalities.

2. Probiotics

Gut bacterial colonisation starts since at birth when new-borns are exposed to a nonsterile climate. Henceforth, it changes and transforms over a lifetime, depends on a complex and dynamic interaction between the diet, genome, and lifestyle of the host, as well as antibiotic consumption. Remarkable bacterial colonisation of age-specific changes described in gut microbiota configuration include a decrease in the Bacteroidetes/Firmicutes ratio and a reduction in bifidobacteria in people aged over 60 years, when the immune system starts to decline [15]. Normally, the composition of the intestinal microflora is considered to be constantly throughout adulthood period.

Since the beginning of the twentieth century the interest in lactic acid fermentation was expressed by the Russian scientist and immunologist, Ilia Miecznikow, that worked at Pasteur Institute, Paris. In the book "Studies on Optimism" he affirmed that "with various foods undergoing lactic acid fermentation and consumed raw (sour milk, kefir, sauerkraut, pickles) humans introduced huge amounts of proliferating lactic acid bacteria to their alimentary tracts" [16].

2.1 Probiotic strains

The microorganisms that are used as probiotics can belong to different types, such as bacteria, yeast and mould. Selected probiotic bacteria strains can be as following:

a. *Lactobacillus: acidophilus*, *sporogenes, plantarum, rhamnosus, delbrueckii, reuteri, fermentum, brevis, casei, farciminis, paracasei, gasseri, crispatus*;

b. *Bifidobacterium*: *bifidum, infantis, adolescentis, longum, thermophilum, breve, lactis;*

c. *Streptococcus*: *lactis, cremoris, thermophilis, diacetylactis*;

d. *Leuconostoc mesenteroides*;

e. *Pediococcus* spp.;

f. *Propionibacterium* spp.;

g. *Enterococcus—Enterococcus faecium*;

The literature mentions as probiotics the following yeast and mould strains:

a. Yeast: *Saccharomyces cerevisiae, Saccharomyces bourlardii*, *Candida pintolopesii, and Sacaromyces boulardii*

b. Moulds: *Aspergillus niger, A. oryzae* [17].

The type of the microbes used as probiotics increased due to the increase in the research concerning the health but as well as by the increase of the newly discovered and identified microbes, which could be used as probiotics in different food and beverages with huge impact on human body.

With the development of better culturing methodologies, more affordable genome and metagenome sequencing, the probiotic research is in a fulminant era, one which permits designing adapted probiotics that address specific consumer needs and issues. Also, the data of the conformation and role of the human gut microbiome accelerated by massively parallel sequencing, has extended the range of microorganisms with possible human benefits, although many of these are still at the very early stage of research.

These organisms are sometimes referred to as next-generation probiotics (NGPs), but may also be termed live biotherapeutic products (LBPs). NPGs obviously follow to the standard classification of a probiotic, but mainly referring to those microorganisms that have not been used as agents to promote health till now, and which are more likely to be delivered under a drug regulatory framework. Next-generation probiotics fit well within the US Food and Drug Administration (FDA) definition of a live biotherapeutic products: "a biological product" that: comprises live microoorganisms, such as bacteria; it is not a vaccine; is applicable to the prevention, treatment, or cure of a disease or condition of human beings [18].

Examples of current NGP: *Faecalibacterium* spp., *Akkermansia* spp., *Bacteroides fragilis* strain ZY-312, *Bacteroides xylanisolvens* DSM 23964, *Clostridium butyricum* MIYAIRI 588, *Faecalibacterium prausnitzii* and other.

Probiotics are subject to regulations in the general food law worldwide, conforming to they should be safe for human and animal health. In the Unite State of America, microorganisms that are used for human consumption should have the Generally Regarded As Safe (GRAS) status, regulated by the Food and Drug Administration (FDA). Rather, in Europe, European Food Safety Authority (EFSA) introduced the term of Qualified Presumption of Safety (QPS). The term of QPS it is a concept which involves some additional criteria of the safety assessment of bacterial supplements, including the history of safe usage and absence of the risk of acquired resistance to antibiotics [19, 20]. Until this moment mechanism of action of probiotics has not been clearly understood, but research results are those obtained from animal models and in vitro experiments. From a medical point of view it is considered that action mode of probiotics may improve the barrier functions of the gut mucosa because several strains of *Lactobacillus* spp. and *Bifidobacterium* spp. as well as structural compounds, and microbial-produced metabolites are able to stimulate epithelial cell signalling pathways. Thomas and Versalovic [21] reported that the Nuclear FactorKappa-Light-Chain-Enhancer of activated B cells (NF-kB) pathway is controlled by probiotics at many different levels with effects seen on I Kappa B protein (IKB) degradation and ubiquitination, proteosome function [22] and nuclear-cytoplasmic movement of RelA through a PPAR-gamma dependent pathway. Also, it is known that probiotics can modulate the immune system functions for instance, *L. acidophilus* has been found to modulate toll-like receptors and the proteoglycan recognition proteins of enterocytes. This thing leads to activation of dendric cells and lymphocytes T-helper 1 responds. After stimulation of lymphocytes T-helper 1 cytokines can suppress lymphocyte T-helper 2 responses which provoke the atopic issues [23]. Another possible mechanism of action of probiotics may be their ability to suppress the growth of pathogenic bacteria by producing broad-spectrum bacteriocins [24]. After the latest research on probiotics we can conclude that molecular and genetic research allowed the determination of the beneficial effect of probiotics, involving four mechanisms:

1. Antagonism through the production of antimicrobial compounds [25];

2. Pathogens competition for adhesion to the epithelium and for nutrients [26];

3. Immunomodulation of the host [27];

4. Inhibition of bacterial toxin production [28].

The first two mechanisms are directly related with their effect on other microorganisms. Nevertheless, all four mechanisms, from medical point of view, play an important role in the infections prophylaxis and treatment and also, for maintenance a balanced host's intestinal microbiota [1]. The capability of probiotic strains to co-aggregate, as one of their mechanisms of action, can contribute to the development of a protective barrier preventing pathogenic bacteria from the colonisation of the gut epithelium [29]. Probiotics bacteria are able to adhere to epithelial cells, inhibiting the pathogens. This mechanism plays an important effect on the host's health condition. Also, the adhesion of probiotic microorganisms to epithelial cells can start a signalling cascade, leading to immunological modulation. Otherwise, the discharge of some soluble compounds may cause a direct or indirect (through epithelial cells) activation of immunological cells [30].

Probiotics may have an significant role in: chronic inflammation of the alimentary tract or of a part thereof, the prevention and treatment of contagious diseases, lactose intolerance and lactose digestion, cholesterol reduction, cardiovascular health, urogenital disease, allergic disease, oral health, gastrointestinal disease, obesity but and an possible role in the elimination of cancer cells.

2.2 Probiotics in human health

2.2.1 Probiotics in prevention and treatment of acute diarrhoea and diarrhoea associated with antibiotics

Diarrhoea induced by antibiotics is a very common complication in the hospital setting, representing a percentage by 13–60% and disease caused by Clostridium difficile is also a significant cause of nosocomial diarrhoea and colitis that prolongs the hospital stay by 3–7 days and increases the risk of new nosocomial infections with 20–65%, costs, and mortality (2- or 3-fold depending on reports) [31]. The roles of the probiotics used to treat these patients are:

1. restoration intestinal microflora;

2. increase immune response;

3. compete with pathogenic bacteria;

4. remove their toxins.

Saccharomyces boulardii, Lactobacillus acidophilus, Lactobacillus bulgaricus, Lactobacillus rhamnosus, Lactobacillus paracasei, Bifidobacterium longum, Bifidobacterium breve there were some of the most widely studied probiotics for treatment of acute diarrhoea. In a recent meta-analysis of 21 studies (4780 patients), the administration of *S. boulardii* decreased the risk of antibiotic-induced diarrhoea in both children and adults from 19 to 8.5%, with a relative risk of 0.47. In another meta-analysis of 82 randomised clinical trials using diverse species (usually

Lactobacillus spp., alone or combined with bifidobacteria, enterococci, or *S. boulardii*), a reduced risk of antibiotic-induced diarrhoea was also established, with a relative risk of 0.58 [31].

Floch et al. [32] reported that for the primary prevention of disease caused by *C. difficile* in patients treated with antibiotics, probiotics also decrease the incidence of such disease, especially when strains of *S. boulardii*, and possibly other *Lactobacillus*, such as GG, are administered. Instead, a recent meta-analysis settled that only four probiotic strains (not including *Lactobacillus* GG) have been shown to significantly decrease the incidence of diarrhoea induced by *C. difficile*, such as follows: *S. boulardii* (2×10^{10} CFU/day), *L. casei* DN114001 (probiotic drink twice daily), a mixture of *L. acidophilus* and *Bifidobacterium bifidum* (2×10^{10} CFU/day), and a mixture of *L. acidophilus*, *L. casei*, and *L. rhamnosus*) [33].

For patients that intake antibiotics to eradicate *Helicobacter pylori*, studies have been conducted based on probiotics adding in order to increase eradication rates and also to prevent side effects such as antibiotic-induced diarrhoea. Numerous meta-analyses showed that the addition of probiotics may increase the efficacy of eradication with an odds ratio (OR) ranging from 1.2 to 2 times compare to the control group. Although additional studies are needed, it appears that the most effective strains are *L. acidophilus* (1.25×10^9 CFU) (OR: 1.24), milk fermented with *L. casei* DN-114001 (2 packs daily) (OR: 1.47), yogurt with *Lactobacillus gasseri* (OR: 1.19) (2 packs daily), and *Bifidobacterium infantis* (2×10^9 CFU) (OR: 1.21) [31]. Also, in supplementary clinical researches where antibiotics are used, probiotics appear to decrease the incidence of diarrhoea (with an OR ranging from 0.16 to 0.47) [34].

Also, the efficiency of probiotic strains in the next therapy's: nosocomial, non-nosocomial, and viral diarrheas have been studied. The conclusion was as follows: it turns out that probiotics may increase the amount of IgA antibodies, which leads to the decrease number of a viral infection [35].

2.2.2 Probiotics in in diseases of the gastrointestinal apparatus

Inflammatory bowel disease (IBD) is a recurrent chronic condition in which an abnormal interaction exists between intestinal flora and the host. Patients with IBD have an increased risk of colorectal cancer [31]. Due to the growing area of disease spreading and ageing societies, the use of probiotic bacteria for human health is becoming increasingly important. The consumption of pre-processed food (fast food), often containing excessive amounts of fat and insufficient amounts of raw fruits and vegetables, is another factor of harmful modification of human intestinal microbiota. It seems that the system of intestinal microorganisms and its desirable modification with probiotic formulas and products may protect people against enteral problems, and improve health [1]. *L. plantarum* is a probiotic that has been used with good results in the management of some symptoms in patients with IBD. It has been reported that the DSM 9843 strain significantly reduced flatulence, and the LPO 1 and 299 V strains significantly reduced abdominal pain [36]. In many studies it has been reported that probiotics may be helpful in the treatment of inflammatory enteral conditions, Crohn's disease, ulcerative colitis, and non-specific ileitis. The aetiology of those diseases is not completely understood, but it is evident that they are associated with recurrent infections or chronic inflammations of the intestine. Using a complex probiotic, such as: VSL#3, which contains 4 lactobacilli strains—*L. acidophilus*, *L. casei*, *Lactobacillus delbrueckii* sp. *bulgaricus*, and *Lactobacillus plantarum;* 3 bifido bacterial strains: *B. longum*, *B. infantis*, and *Bifidobacterium breve;* and *Streptococcus salivarius* sp. *thermophilus*, revealed to decrease activity of pouchitis (a non-specific inflammation of the ileal pouch) in ulcerative colitis (UC) and after ileal anastomosis [37]. The frequent

doses recommended in pouchitis are 2–4 sachets daily (each sachet contains 450,000 million live bacteria 4.5×10^{11} CFU; but there are also capsules containing 112,000 millions of bacteria) [31]. However, in additional research was described lower improvements in the reduction of disease in association with conventional treatment in patients with UC, and minor to moderate contribution, with the use of probiotic VSL#3, *Escherichia coli* Nissle, *Lactobacillus* GG, or milk fermented with bifidobacteria and/or lactobacilli (whether or not compared to placebo or other treatments, such as mesalazine) [38]. In trials with probiotics on remission induction or maintenance in Crohn's disease (using several strains such as *Lactobacillus* GG, VSL3, *L. johnsonii* LA1, *Escherichia coli* Nissle 1917, *S. boulardii*) have been reported less satisfactory results than in UC [32].

In a 2007 [39] demonstrated that administering probiotics may improve the rate of eradication and reduce the incidence of adverse events in case of infection with *Helicobacter pylori*. Zhang et al. [40] informed that the using the probiotics for standard eradication therapy in patients infected with *H. pylori* may increase the rate of eradication of the microorganism by approximately 13% and decrease the overall rate of adverse effects by approximately 41%, based on the patient's age, gender or probiotics dose. The probiotic used to improve the results of eradication therapies was *Lactobacillus reuteri*. In these therapies which demonstrated an ability to inhibit the colonisation of the human gastric mucosa with *H. pylori*, in addition to an ability to produce reuterin, a broad-spectrum antibiotic active against *H. pylori*, DSM 17648 strain of *L. reuteri* seemed especially effective for eradication therapies [36]. Also, *S. boulardii* seemed to significantly increase the rate of eradication, although under the desired success level (80% versus 71% in the control group) [36].

Few studies are, so far available, and, consequently much clinical evaluation is needed in the future of the most effective strains and of how host factors (such as the genetic characteristics of patients) influence therapeutic response.

2.2.3 Probiotics in liver disease

The researchers reported that probiotics can be useful in treating hepatic diseases due to their potential ability to modulate alterations in the gut microbiota, intestinal permeability, and immune and inflammatory responses. More studies based on murine and *in vitro* models show the role of probiotics in several liver diseases [41]. From medical point of view the pathogenic mechanism involved in liver damage secondary to alcohol abuse is endotoxemia. Researchers reported that through using *L. plantarum* encapsulated alginate beads induce a dose-dependent reduction of endotoxin level in rats exposed to alcohol [41].

Domingo [36] suggests that non-alcoholic fatty liver disease (NAFLD) comprises a varied range of pathological circumstances, from simple steatosis to cirrhosis, through steatohepatitis and fibrosis. It is known that probiotics (VSL#3) can modulate the intestinal flora, influencing the bowel-liver axis and improving NAFLD. Xu et al. [42] reported in a study that compared two types of probiotics (*L. acidophilus* and *B. longum*), neither improved intestinal permeability, but *B. longum* probiotic attenuated hepatic fat accumulation. However there are few human studies on the efficacy of probiotics in the prevention or treatment of NAFLD.

Hepatitis viruses, especially B and C, are known to cause long-term hepatocellular injury. As in other hepatic diseases, the plasma level of endotoxin increases in these patients because of changes in the gut microbiota [41]. Several studies evaluated the effects of probiotics in patients with hepatitis B virus (HBV) and hepatitis C virus (HCV). A research study achieved with *Bifidobacterium adolescentis* SPM0212 lead to increased expression of myxovirus (Mx) resistance A, an interferon (IFN)-inducible antiviral effector. Further, the extracellular surface

antigen of HBV level decreased depend by the dose up to 50% and gene expression was inhibited by 40% in hepatoma *cell* line HepG2.2.15 [43].

Also, in the literature have been reported studies regarding treatment with probiotic of patients with cirrhosis. Zhang et al. [44] used a cirrhotic-rat model with modified gut microbiota. In this research it was observed that the effects on total bilirubin (BT) and the ratio between aerobic and anaerobic bacteria were similar in healthy and cirrhotic rats. After administration of norfloxacin and probiotics to modify the gut microbiota, BT, liver function and endotoxemia were estimated. Cirrhotic rats showed a higher population of *Enterobacteriaceae* compared to healthy rats. It was concluded that treatment with bifidobacteria decreased the amount of *Enterobacteriaceae* and endotoxin level and increased the amount of *Lactobacillus* compared with healthy rats [44]. There are limited studies suggesting the role of probiotics for hepatocellular carcinoma. Chávez-Tapia et al. [41] reported in his article that clinical data the next probiotics—*L. rhamnosus LC705* and *Propionibacterium freudenreichii subsp. Shermanii,* maybe reduce the biologically effective dose of aflatoxin exposure. Similar data from murine models with *L. rhamnosus GG* were reported. Particularly after aflatoxin exposure, lower expression of c-myc, cyclin D1, bcl-2 and rasp-21/g3pdh were found [41].

In recent years also, several studies have shown that probiotics have beneficial effects and after liver transplantation. In a research by [45] patients who suffered for liver transplant were allocated to groups that received one of three treatments: live *L. plantarum* 299 strain and prebiotics (fibre), heat-killed lactobacilli and fibre, or selective bowel decontamination. Also, all patients received early enteral feeding. Patients who intake live lactobacilli and fibre developed a lower amount of bacterial infections (e.g. 13%) when compared to patients that underwent selective bowel decontamination: 48% [45]. However, probiotic bacteria such as *Saccharomyces cerevisiae* and *Lactobacillus* have been associated in some studies to the development of sepsis but the use of probiotics in patients who underwent a liver transplant requires at this point, a much more careful analysis of their safety [41].

2.2.4 Probiotics in urogenital and vaginal disease

According to the Centers for Disease Control and Prevention (CDCP), more than 1 billion women around the world suffer from non-sexually transmitted urogenital infections, such as bacterial vaginitis (BV), urinary tract infection (UTI) and several other yeast infections [46]. The dominant microflora in a healthy human vagina is comprised from a variety of *Lactobacillus* species with crucial role in protecting women from genital infections. A slight change in lactobacilli concentration can result in microbial disproportion in the vagina, causing a quantitative and qualitative modification from normally occurring lactobacilli to a mixed microflora controlled by anaerobic bacteria such as *Gardnerella vaginalis*, *Bacteroides* spp., *Prevotella* spp., and *Mobiluncus* species [47]. Commane et al. [48] reported in a research study the importance of probiotics in a woman's urogenital wellbeing. It was confirmed that by supplementing with probiotics (*L. rhamnosus* GR-1 and *Lactobacillus reuteri)* it can stimulate the colonisation of beneficial microbiota and may improve the vaginal health. Daily oral consumption of probiotics such as *L. rhamnosus* and *L. fermentum* exhibited the modification of the vaginal flora [48]. It is well-known that there is an association between abnormal vaginal microbial flora and an increased incidence of urinary tract infection (UTI). When administered twice daily orally the only strains clinically shown to have an effect are *L. rhamnosus* GR-1 and *L. reuteri*, these strains reduce recurrences of UTI and restored a normal lactobacilli dominated vaginal flora in patients [49]. The smallest imbalance in the microbial composition greatly influences the health of the vaginal microenvironment, potentially leading to compromised state

of BV and UTI. The primary solution for compromised state would be balancing the number of *Lactobacillus* spp. via the supplementation of probiotics [50].

2.2.5 Probiotics in cardiovascular diseases and lipid metabolism

Cholesterol is a precursor in many biochemical processes of the body and plays a vital role in many functions, like as production of steroidal hormones, while extreme cholesterol in the blood can lead to arterial clogging and increases the risk of heart disease and/or stroke. Patients with hypercholesterolemia showed the risk of heart attacks three times higher, compared to patients with normal blood lipid values [51]. The scientific literature reported some probiotic strains with hypocholerolemic effects, such as: *L. bulgaricus, L. reuteri, and B. coagulans*. Also, clinical research in humans with *L. acidophilus* L1 milk, revealed a significant reduction in serum cholesterol. Further, a clinical trial on 32 hypercholesterolemic patients that consumed low-fat yogurt with *B. longum* BL1 displayed a significant decline in triglycerides, total serum and LDL cholesterol. Also, HDL cholesterol was increased with 14.5% [52]. Thirty-two hyperc-holesterolemic men and women were intake *L. acidophilus* CHO-220 and inulin, during a randomised, double-blind, placebo-controlled, and parallel-designed trial. This research study demonstrated that plasma total cholesterol and low-density lipoprotein (LDL)-cholesterol reduced by 7.84 and 9.27%, respectively, after 12 weeks [53]. Worldwide, it is known that coronary heart disease (CHD) is one of the major causes of adult's death. The main coronary arteries supplying the heart are no longer able to provide sufficient blood and oxygen to the myocardium, mainly because of the accumulation of plaques in the intimae of arteries [54]. Ranjbar et al. [54] concluded that in recent years, several foods enriched with probiotics were produced industrially. These foods have recently been subject to more research for their beneficial effects on the gut microflora and links to their systemic effects on the lowering of lipids known to be risk factors for CHD.

2.2.6 Probiotics in oral health

The human mouth harbours diverse microbiomes in the human body such as viruses, fungi, protozoa, archaea and bacteria and they cause different diseases. From a dental point of view the bacteria cause two common diseases: dental caries and the periodontal (gum) diseases. The most used probiotics for oral health are species of *Lactobacillus* and *Bifidobacterium*. In a double-blind, placebo-controlled trial the consumption of *Streptococcus salivarius* K12 decreased the occurrence of plaque and also, reduced the concentration of *Streptococcus mutans* [55]. It is known that *Streptococcus uberis* and *S. oralis* also can inhibit the periodontal pathogens [56]. Additionally, the halitosis and the volatile sulphur compounds synthesis could be prevented by probiotics consumption.

Bowen [57] declared that the evidence for periodontitis is less than dental caries, but the use of probiotics to manage the oral microflora appears tobe an effective method to control oral conditions [57]. Many more studies are needed to understand the mechanism by which these probiotics colonise and affect the oral cavity. Is needed to better understand how they improve oral health.

2.2.7 Probiotics in lactose intolerance

Daliria and Lee [58] supposed that lactose is an important nutrient in all mammalian neonates, almost all of them have the capability to metabolise lactose to glucose and galactose. It is known that in humans, lactase activity decreases during mid-childhood [58]. Medical research reports that lactose intolerance is determined

by blood glucose concentrations, and breath hydrogen test following ingestion of a lactose load [58] and symptoms include: abdominal distress like diarrhoea, bloating, abdominal pain and flatulence. The researchers noticed that treatment with probiotics (such as *Lactobacillus bulgaricus* and *Streptococcus thermophiles*) relieves symptoms of lactose intolerance. It is also observed that consumption of milk containing *Bifidobacterium longum* and *L. acidophilus* cause significantly less hydrogen production and flatulence. In researches where was used a combination of *Lactobacillus casei shirota* and *Bifidobacterium breve* Yakult has shown better effect on patients and improved the symptoms of lactose intolerance significantly [59].

2.2.8 Probiotics in cancer

Kerry et al. [50] declared that as per World Health Organisation (WHO) cancer fact sheet this is a dreadful disease affecting peoples all over the globe. Approximately 14 million new cases and 8.2 million cancer-related deaths added till 2012. The global cancer deaths are from Asian, African, and American continents (more than 70%) [60]. *In vitro* studies, probiotic strains, *Lactobacillus fermentum* NCIMB-5221 and -8829, revealed the highly potential in destroying the colorectal cancer cells and promoting normal epithelial colon cell growth by producing the SCFAs (ferulic acids). This probiotics were compared to other probiotics (*L. acidophilus* ATCC 314 and *L. rhamnosus* ATCC 51303) known with tumorigenic properties [61]. Also, *L. acidophilus* is known to prolong the induction of colon tumours. It was demonstrated that feeding milk and colostrum fermented with *L. acidophilus* resulted in 16–41% reduction in tumour proliferation [62]. Also, the other probiotic *L. bulgaricus* has also been reported to induce antitumor activity against sarcoma-180 and solid Ehrlich ascites tumours [63]. Probiotics could play a significant role in neutralising cancer but research is limited only to *in vitro* tests.

3. Prebiotics

Like probiotics, prebiotics is also being widely explored for their utility in the various field of applied science, more specifically as nutrients and supplements [50]. Food and Agriculture Organisation (FAO)/WHO defines prebiotics as a nonviable food component that confer health benefit(s) on the host associated with modulation of the microbiota [62].

Sources of prebiotics are as follows: breast milk, soybeans, inulin from diverse sources (Jerusalem artichoke, chicory roots), raw oat, wheat bran, barley bran, yacon roots, non-digestible carbohydrates (non-digestible oligosaccharides). From prebiotics, only bifidogenic, non-digestible oligosaccharides, especially inulin, and its hydrolysis products, such as oligofructose, and (trans) galactooligosaccharides (GOS), achieve all the criteria for prebiotics term [64]. Prebiotics can be obtained naturally from sources like vegetables, fruits, and grains consumed in our daily life but are also artificially prebiotic products such as: lactulose, galactooligosaccharides, fructooligosaccharides.

Kuo [65] reported that an ideal prebiotic should be:

- resistant to the actions of acids in the stomach, bile salts and other hydrolysing enzymes in the intestine;
- not be absorbed in the upper gastrointestinal tract;
- be easily fermentable by the beneficial intestinal microflora.

Prebiotics not only serve as an energy source because their presence of prebiotics in the diet may lead to numerous health benefits. Several health benefits are reported in scientific literature, such as inhibition of the development of pathogens, reducing the prevalence and duration of diarrhoea, increases the absorption of minerals, mostly of magnesium and calcium, exerting protective effects to prevent colon cancer and providing relief from inflammation and other symptoms associated with intestinal bowel disorders.

Several studies demonstrated that the colorectal carcinoma was less present at people who consume a lot of vegetables and fruits. The inulin and oligofructose from fruits and vegetables could suppress the disease [66]. When it comes to the advantages of prebiotics, it can be mention the reduction of the blood LDL (low-density lipoprotein) level, stimulation of the immunological system, increased the calcium absorbability, preservation of adequate intestinal pH value, low caloric value, and alleviation of symptoms of peptic ulcers and vaginal mycosis [67]. Other benefits of inulin and oligofructose on human health could be the prevention of carcinogenesis, as well as the support of lactose intolerance or dental caries treatment [68]. Also, prebiotics are useful in combating pathogenic microorganisms, such as *Salmonella enteritidis* and *Escherichia coli*, and reduce odour compounds and [69] confirmed a positive effect of fructooligosaccharides (FOS) on protection against *Salmonella typhimurium* and *Listeria monocytogenes* infections. Pokusaeva et al. [70] said that prebiotics are also implicated in enhancing the bioavailability and uptake of minerals, lowering of some risk factors for cardiovascular disease, and promoting satiety and weight loss.

Prebiotics have been reported to play a beneficial role in controlling the IBD. A major reduction in the number of bacteriodetes in faeces was reported in patients with chronic pouchitis treated with 24 g per day of inulin [71]. In another study, 10 Crohn's Disease patients receiving 15 g of FOS demonstrated a reduced disease activity index [72]. In another randomised study involving 103 Crohn's Disease patients who received FOS 15 g/day these showed no clinical improvement however, though no change in IL-12 was observed it was able to reduce IL-6 of lamina propria dendritic cells [1].

Kerry et al. [50] suggests that even with their enormous nutritional and medicinal benefits, research concerning screening new versatile prebiotics is quite deficient. Therefore, the research should be focused on identifying new healthy supplements, while screening novel prebiotic strains should be a major concern.

4. Synbiotics

Due to the expansion of microbial research were discovered synbiotics as a combination of probiotics and prebiotics products which provide the survival and the implantation of the live microorganism dietary supplements in the gut [73]. The synergistic welfares are more proficiently promoted when both the probiotic and prebiotic act together in the living system. It is known that the symbiotic association between prebiotics and probiotics significantly improve the human health [50]. From the medical point of view the term of synbiotic product positively influence the host through improving the survival and implantation of live microbial dietary supplements in to the gastrointestinal tract and stimulating the growth and/or activating the metabolism of health promoting bacteria [62]. Since the word synbiotics suggests synergism, this term should be reserved for products in which the prebiotic compound(s) positively influence the probiotic organism(s) [74]. Markowiak and Śliżewska [1] suggests that when develop a synbiotic product, the most important aspect that have taken into account, is the selection of an appropriate probiotic and

prebiotic, that can act separately on the host's health. The prebiotic compounds should selectively stimulate the growth of probiotics, with beneficial effect on human health and not to be able to stimulate the other microorganisms.

Lactobacillus spp., *Bifidobacteria* spp., *S. boulardii*, *B. coagulans* are one of the probiotic strains that are used in synbiotic formulations, whereas the prebiotics used are as follows: oligosaccharides (fructooligosaccharide (FOS), GOS and xylooseoligosaccharide (XOS)), and inulin (from natural sources like chicory and yacon roots) [62]. Synbiotics consumption by humans includes the following beneficial effects:

- Increased levels of lactobacilli and bifidobacteria and balanced gut microbiota.
- Prevention of bacterial translocation and reduced incidences of nosocomial infections in surgical patients.
- Improvement of liver function in cirrhotic patients.
- Improvement of immunomodulating ability [75].

In adult subjects with non-alcoholic steatohepatisis (NASH) in a randomised study what used of a synbiotic product which contained five probiotics namely: *Lactobacillus plantarum*, *L. delbrueckii* spp. *bulgaricus*, *L. acidophilus*, *L. rhamnosus*, *Bifidobacterium bifidum* and inulin as a prebiotic has been demonstrated a significant reduction of intrahepatic triacylglycerol (IHTG) within 6 months [1]. Fifty-two adults participated for 28 weeks in a research trial based on the effects of the synbiotic product. The synbiotic comprised a mix of probiotic strains: *Lactobacillus casei, L. rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, L. acidophilus, B. longum, L. bulgaricus* and fructooligosccharides, as prebiotic. The authors stated that consumption of the synbiotic product resulted in the inhibition of nuclear factor-kB (NF-kB) and a condensed production of tumour necrosis factor α (TNF-α) [76].

Moreover, synbiotics seems to be quite attractive for improving the immune system. A significant decrease in the levels of C-reactive protein and also increase the glutathione levels was obtained through combination of *B. coagulans* with inulin, in diet for 6 weeks [77].

Recently, commercial interest in functional foods based on synbiotics has improved due to the awareness of the welfares for gut health, disease prevention and therapy. Investigates in this scientific zone is presently concentrated on designing new functional foods, as well as on screening new strains with capability to inhabit the human gut, along with their aptitude to metabolise new prebiotics [50]. Trials and investigation *in vitro* and *in vivo* demonstrated that the beneficial effects of using probiotics, prebiotics, and synbiotics in health are much more active than their unitary use known till present. Nevertheless, more investigates concerning the designing new mixtures of probiotics, prebiotics and synbiotics are imperative necessary for achieve further opportunities of improving nutritional and clinical health.

5. Conclusion

The use of probiotics, prebiotics, and synbiotics in health is emerging as a promising therapy which is generally safe in different disease. Probiotics, probiotics and synbiotics have systemic effects on the urogenital disease, liver disease, oral health and immune system. There are many published reports on the use of probiotics in

humans but information on prebiotics and synbiotics is quite a few. It seems that we will see and in the coming years further studies on combinations of probiotics and prebiotics, and further development of synbiotics. It is possible that future studies may explain the mechanisms of actions of those components, which may confer a beneficial effect on human health. However, the health claims made needs to be substantiated and firmly established by properly designed large scale clinical trials on human body. Therefore, current focus is on evaluating new strains of probiotics, a new prebiotics and new synbiotics products and their applicability in biomedical/clinical research, paving a new direction for exploration and exploitation of probiotics, prebiotics and synbiotics aimed at improving human health. There is a need for more randomised, placebo-controlled clinical trials with adequate statistical power. I encourage researchers to submit possible publications in peer-reviewed journals of all clinical trials, whether the outcome is positive, negative or adverse, because the scientific and medical world needs it relevant information on the dose–response effects, efficacy, and safety of probiotic, prebiotic and synbiotic products. At present, the available information on current probiotics, prebiotics and synbiotics provides convincing safety records. I believe it is highly likely that in the near future, the vast amount of research on the beneficial impact of the probiotics, prebiotics and synbiotics on human wellbeing will suppose discovery and development of innovative products derived from our microbiota. Further, these may belong to uncommon and formerly uncharacterized microorganisms with rare assets, or perhaps could be microorganisms formerly known as pathogens or pathobionts. These progresses will represent new trends but also significant challenges for scientific and medical research, for industrial exploitation and for human health and clinical nutrition.

Conflict of interest

Author declares no conflict of interest.

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References

[1] Markowiak P, Śliżewska K. Effects of probiotics, prebiotics, and synbiotics on human health. Nutrients. 2017;**9**(1021):1-30. DOI: 10.3390/nu9091021

[2] Metchnikoff E, Mitchell PC, editors. Essais Optimistes. London: Heinemann; 1907

[3] Tissier H. Tritement des infections intestinales par la methode de translormation de la flore bacterienne de lintestin. Comptes Rendus Social Biology. 1906;**60**:359-361 (in French)

[4] Havenaar R, Huis in't Veld JHJ. Probiotics: A general view. In: Wood BJB, editor. The Lactic Acid Bacteria in Health and Disease. London: Elsevier Applied Science; 1992. pp. 151-170

[5] Food and Agriculture Organization (FAO). Guidelines for the Evaluation of Probiotics in Food; Report of a Joint FAO/WHO Working Group on Drafting Guidelines for the Evaluation of Probiotics in Food. London, ON, Canada: FAO; 2002

[6] Hill C, Guarner F, Rei 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. DOI: 10.1038/nrgastro.2014.66

[7] Gibson RG, Roberfroid MB. Dietary modulation of the human colonic microbiota: Introducing the concept of prebiotics. The Journal of Nutrition. 1995;**125**:1401-1412. DOI: 10.1093/jn/125.6.1401

[8] Gibson GR, Probert HM, van Loo J, Rastall RA, Roberfroid M. Dietary modulation of the human colonic microbiota: Updating the concept of the prebiotics. Nutrition Research Reviews. 2004;**17**:259-275. DOI: 10.1079/NRR200479

[9] Food and Agriculture Organization. FAO Technical Meeting on Prebiotics: Food Quality and Standards Service (AGNS), Food and Agriculture Organization of the United Nations (FAO). Rome, Italy: FAO Technical Meeting Report; FAO; 2007. pp. 15-16

[10] Skalkam ML, Wiese M, Nielsen DS, van Zanten G. In Vitro Screening and Evaluation of Synbiotics. Copenhagen, Denmark: University of Copenhagen; 2016 (Chapter 33). pp. 477-486

[11] Cencic A, Chingwaru W. The role of functional foods, nutraceuticals, and food supplements in intestinal health. Nutrients. 2010;**2**:611-625. DOI: 10.3390/nu2060611

[12] Rioux KP, Madsen KL, Fedorak RN. The role of enteric microflora in inflammatory bowel disease: Human and animal studies with probiotics and prebiotics. Gastroenterology Clinics of North America. 2005;**34**:465-482. DOI: 10.3390/nu2060611

[13] Bengmark S. Bioecological control of the gastrointestinal tract: The role of flora and supplemented probiotics and synbiotics. Gastroenterology Clinics of North America. 2005;**34**:413-436. DOI: 10.1016/j.gtc.2005.05.002

[14] Panesar PS, Kaur G, Panesar R, Bera MB. Synbiotics: Potential Dietary Supplements in Functional Foods. Berkshire, UK: IFIS; 2009. DOI: 10.1136/gut.2005.074971

[15] Lloyd-Price J, Abu-Ali G, Huttenhower C. The healthy human microbiome. Genome

Medicine. 2016;**8**:1-11. DOI: 10.1186/s13073-016-0307-y

[16] Miecznikow E. O naturze ludzkiej—Zarys Filozofii Optymistycznej (Translation F. Wermiński). Warszawa, Poland: Wydawnictwo Biblioteka Naukowa; 1907

[17] Amara AA, Shibl A. Role of probiotics in health improvement, infection control and disease treatment and management. Saudi Pharmaceutical Journal. 2015;**23**:107-114. DOI: 10.1016/j.jsps.2013.07.001

[18] O'Toole PW, Marchesi JR, Hill C. Next-generation probiotics: The spectrum from probiotics to live biotherapeutics. Nature Microbiology. 2017;**2**:1-6 (article number: 17057). DOI: 10.1038/nmicrobiol.2017.57 Available from: www.nature.com/naturemicrobiology

[19] Anadón A, Martínez-Larrańaga MR, Martínez MA. Probiotics for animal nutrition in the European Union. Regulation and safety assessment. Regulatory Toxicology and Pharmacology. 2006;**45**:91-95. DOI: 10.1016/j.yrtph.2006.02.004

[20] Gaggia F, Mattarelli P, Biavati B. Probiotics and prebiotics in animal feeding for safe food production. International Journal of Food Microbiology. 2010;**141**:S15-S28. DOI: 10.1016/j.ijfoodmicro.2010.02.031

[21] Thomas CM, Versalovic J. Probiotics-host communication: Modulationof signaling pathways in the intestine. Gut Microbes. 2010;**1**(3): 148-163. DOI: 10.4161/gmic.1.3.11712

[22] Shiou R, Yu Y, Guo Y, He SM, Andrew CHM, Hoenig J, et al. Synergistic protection of combined probiotic con-ditioned media against neonatal necrotizing enterocolitis-like intestinalinjury. PLoS One. 2013;**8**(5): e65108. DOI: 10.1371/journal.pone.0065108

[23] Cosmi L, Maggi L, Santarlasci V, Liotta F, Annunziato F. T helper cells plasticity in inflammation. Cytometry. Part A. 2014;**85**(1):36-42. DOI: 10.1002/cyto.a.22348

[24] Hardy H, Harris J, Lyon E, Beal J, Foey A. Probiotics, prebiotics and immunomodulation of gut mucosal defences: Homeostasis andimmunopathology. Nutrients. 2013;**5**:1869-1912. DOI: 10.3390/nu5061869

[25] Vandenbergh PA. Lactic acid bacteria, their metabolic products and interference with microbial growth. FEMS Microbiology Reviews. 1993;**12**:221-238. DOI: 10.1111/j.1574-6976.1993.tb00020.x

[26] Guillot JF. Probiotic feed additives. Journal of Veterinary Pharmacology and Therapeutics. 2003;**26**:52-55. DOI: 10.1046/J.1365-2885.26

[27] Isolauri E, Sutas Y, Kankaanpaa P, Arvilommi H, Salminen S. Probiotics: Effects on immunity. American Journal of Clinical Nutrition. 2001;**73**:444-450. DOI: 10.1093/ajcn/73.2.444s

[28] Brandao RL, Castro IM, Bambirra EA, Amaral SC, Fietto LG, Tropia MJM. Intracellular signal triggered by cholera toxin in *Saccharomyces boulardii* and *Saccharomyces cerevisiae*. Applied and Environmental Microbiology. 1998;**64**:564-568

[29] Schachtsiek M, Hammes WP, Hertel C. Characterization of *Lactobacillus coryniformis* DSM 20001T surface protein CPF mediating coaggregation with and aggregation among pathogens. Applied and Environmental Microbiology. 2004;**70**:7078-7085. DOI: 10.1128/AEM.70.12.7078-7085.2004

[30] Oelschlaeger A. Mechanisms of probiotic actions—A review. International Journal of Medical Microbiology. 2010;**300**:57-62. DOI: 10.1016/j.ijmm.2009.08.005

[31] Olveira G, González-Moleroa I. An update on probiotics, prebiotics and symbiotics in clinical nutrition. Endocrinología y Nutrición. 2016;**63**(9):482-494. DOI: 10.1016/j.endoen.2016.10.011

[32] Floch MH, Walker WA, Sanders ME, Nieuwdorp M, Kim AS, Brenner DA, et al. Recommendations for probiotic use-2015update: Proceedings and consensus opinion. Journal of Clinical Gastroenterology. 2015;**49**(Suppl. 1):S69-S73. DOI: 10.1016/j.iccn.2010.07.001

[33] McFarland LV. Probiotics for the primary and secondary preven-tion of *C. difficile* infections: A meta-analysis and systematic review. Antibiotics. 2015;**4**:160-178. DOI: 10.3390/antibiotics4020160

[34] Dang Y, Reinhardt JD, Zhou X, Zhang G. The effect of probioticssupplementation on *Helicobacter pylori* eradication rates andside effects during eradication therapy: A meta-analysis. PLoS One. 2014;**9**:e111030. DOI: 10.1371/journal.pone.0111030

[35] Parvez S, Malik KA, Ah Kang S, Kim HY. Probiotics and their fermented food products are beneficial for health. Journal of Applied Microbiology. 2006;**100**:1171-1185. DOI: 10.1111/j.1365-2672.2006.02963.x

[36] Domingo JJS. Review of the role of probiotics in gastrointestinal diseases in adults. Gastroenterología y Hepatología. 2017;**40**(6):417-429. DOI: 10.1016/j.gastre.2016.12.001

[37] Guslandi M. Role of probiotics in Crohn's disease and in pouch-itis. Journal of Clinical Gastroenterology. 2015;**49**(1):S46-S59. DOI: 10.1097/MCG.0000000000000351

[38] Chibbar R, Dieleman LA. Probiotics in the management of ulcerative colitis. Journal of Clinical Gastroenterology. 2015;**49**(1):S50-S55. DOI: 10.1097/MCG.0000000000000368

[39] Tong JL, Ran ZH, Shen J, Zhang CX, Xiao SD. Meta-analysis: The effect of supplementation with probiotics on eradication rates and adverse events during *Helicobacter pylori* eradication therapy. Alimentary Pharmacology & Therapeutics. 2007;**25**:155-168. DOI: 10.1111/j.1365-2036.2006.03179.x

[40] Zhang MM, Qian W, Qin YY, He J, Zhou YH. Probiotics in *Helicobacter pylori* eradication therapy: A systematic review and meta-analysis. World Journal of Gastroenterology. 2015;**21**:4345-4357. DOI: 10.3748/wjg.v21.i14.4345

[41] Chávez-Tapia NC, González-Rodríguez L, Jeong MS, López-Ramírez Y, Barbero-Becerra V, Juárez-Hernández E, et al. Current evidence on the use of probiotics in liver diseases. Journal of Functional Foods. 2015;**17**:137-151. DOI: 10.1016/j.jff.2015.05.009

[42] Xu RY, Wan YP, Fang QY, Lu W, Cai W. Supplementation with probiotics modifies gut flora and attenuates liver fat accumulation in rat nonalcoholic fatty liver disease model. Journal of Clinical Biochemistry and Nutrition. 2012;**50**(1):72-77. DOI: 10.3164/jcbn.11-38

[43] Lee DK, Kang JY, Shin HS, Park IH, Ha NJ. Antiviral activity of Bifidobacterium adolescentis SPM0212 against hepatitis B virus. Archives of Pharmacal Research. 2013;**36**(12):1525-1532. DOI: 10.1007/s12272-013-0141-3

[44] Zhang W, Gu Y, Chen Y, Deng H, Chen L, Che S, et al. Intestinal flora

imbalance results in altered bacterial translocation and liver function in rats with experimental cirrhosis. European Journal of Gastroenterology & Hepatology. 2010;**22**(12):1481-1486. DOI: 10.1097/MEG.0b013e32833eb8b0

[45] Rayes N, Seehofer D, Hansen S, Boucsein K, Müller AR, Serk S, et al. Early enteral supply of lactobacillus and fiber versus selective bowel decontamination: A controlled trial in liver transplant recipients. Transplantation. 2002;**74**(1):123-128 12134110

[46] Waigankar SS, Patel V. Role of probiotics in urogenital healthcare. Journal of Midlife Health. 2011;**2**:5-10. DOI: 10.4103/0976-7800.83253

[47] Petricevic L, Domig K, Nierscher F, Sandhofer M, Fidesser M, Krondorfer I, et al. Characterisation of the vaginal *Lactobacillus* microbiota associated with preterm delivery. Scientific Reports. 2014;**4**:1-6 (article number: 5136). DOI: 10.1038/srep05136

[48] Commane D, Hughes R, Shortt C, Rowland I. The potential mechanisms involved in the anti-carcinogenic action of probiotics. Mutation Research. 2005;**591**:276-289. DOI: 10.1016/j.mrfmmm.2005.02.027

[49] Reid G, Bruce A. Probiotics to prevent urinary tract infections: The rationale and evidence. World Journal of Urology. 2006;**24**:28-32. DOI: 10.1007/s00345-005-0043-1

[50] Kerry GR, Patra JK, Gouda S, Park Y, Shin HS, Das G. Benefaction of probiotics for human health: A review. Journal of Food and Drug Analysis. 2018;**26**(3):927-939. DOI: 10.1016/j.jfda.2018.01.002

[51] Ghosh AR. Appraisal of probiotics and prebiotics in gastrointestinal infections. Webmed Central Gastroenterology. 2012;**3**(10):WMC003796. DOI: 10.9754/journal.wmc.2012.003796

[52] Homayouni A, Payahoo L, Azizi A. Effects of probiotics on lipid profile: A review. American Journal of Food Technology. 2012;**7**(5):251-265. DOI: 10.3923/ajft.2012.251.265

[53] Ooi LG, Liong MT. Cholesterol-lowering effects of probiotics andprebiotics: A review of *in vivo* and *in vitro* findings. International Journal of Molecular Sciences. 2010;**11**:2499-2522. DOI: 10.3390/ijms11062499

[54] Ranjbar F, Akbarzadeh F, Homayouni A. Probiotics usage in heart disease and psychiatry, chapter 61, in book: Probiotics, Prebiotics, and Synbiotics Bioactive Foods in Health Promotion: Probiotics and Prebiotics, Edited by R. Ross Watson and V. R. Preedy. Elsevier Inc., Academic Press, London, UK, 2016, pp.807-811

[55] Burton J, Drummond B, Chilcott C, Tagg J, Thomson W, Hale J, et al. Influence of the probiotic *Streptococcus salivarius* strain M18 on indices of dental health in children: A randomized double-blind,placebo-controlled trial. Journal of Medical Microbiology. 2013;**62**:875-884. DOI: 10.1099/jmm.0.056663-0

[56] Hillma J, McDonell E, Hillman C, Zahradnik R, Soni M. Safety assessment of ProBiora3, a probiotic mouthwash: Subchronic toxicity study in rats. International Journal of Toxicology. 2009;**28**:357-367. DOI: 10.1177/1091581809340705

[57] Bowen DM. Probiotics and oral health. Journal of Dental Hygiene. 2013;**87**:5-9

[58] Daliria EBM, Lee BH. New perspectives on probiotics in health and disease. Food Science and Human Wellness. 2015;**4**(2):56-65. DOI: 10.1016/j.fshw.2015.06.002

[59] Vonk RJ, Reckman GA, Harmsen HJ, Priebe MG. Probiotics and lactose intolerance. In: Rigobelo EC, editor. Probiotics. Rijeka, Crotatia: InTech; 2012. DOI: 10.5772/51424

[60] Vidya S, Thiruneelakandan G. Probiotic potentials of lactobacillus and its anti-cancer activity. International Journal of Current Research. 2015;**7**:20680-20684

[61] Kahouli I, Malhotra M, Alaoui-Jamali MA, Prakash S. *In-vitro* characterization of the anti-cancer activity of the probiotic bacterium *Lactobacillus fermentum* NCIMB 5221 and potential against colorectal cancer cells. Journal of Cancer Science and Therapy. 2015;**7**:224-235. DOI: 10.4172/1948-5956.1000354

[62] Pandey KR, Naik SR, Vakil BV. Probiotics, prebiotics and synbiotics—A review. Journal of Food Science and Technology. 2015;**52**(12):7577-7587. DOI: 10.1007/s13197-015-1921-1

[63] Lee JH, Nam SH, Seo WT, Yun HD, Hong SY, Kim MK, et al. The production of surfactin during the fermentation of *cheonggukjang* by potential probiotic B*acillus subtilis* CSY191 and the resultant growth suppression of MCF-7 human breast cancer cells. Food Chemistry. 2012;**131**(4):1347-1354. DOI: 10.1016/j.foodchem.2011.09.133

[64] Pokusaeva K, Fitzgerald GF, van Sinderen D. Carbohydrate metabolism in Bifidobacteria. Genesis Nutrition. 2011;**6**(3):285-306. DOI: 10.1007/s12263-010-0206-6

[65] Kuo SM. The interplay between fiber and the intestinal microbiome in the inflammatory response. Advances in Nutrition: Journal of Internal Medicine. 2013;**4**(1):16-28. DOI: 10.3945/an.112.003046

[66] Mojka K. Probiotyki, prebiotyki i synbiotyki—Charakterystyka i funkcje. Problemy Higieny i Epidemiologii. 2014;**95**:541-549

[67] Socha P, Stolarczyk M, Socha J. Wpływ probiotyków i prebiotyków na gospodarke˛ lipidowa˛. Pediatria Współczesna Gastroenterologia Hepatologia I Żywienie Dziecka. 2002;**4**:85-88

[68] Jakubczyk E, Kosikowska M. Nowa generacja mlecznych produktów fermentowanych z udziałem probiotyków i prebiotyków, produkty synbiotyczne. Przegląd Mleczarski. 2000;**12**:397-400

[69] Buddington KK, Danohoo JB, Buddington RK. Dietary oligofructose and inulin protect mice from enteric and systemic pathogens and tumour inducers. The Journal of Nutrition. 2002;**132**:472-477. DOI: 10.1093/jn/132.3.472

[70] Pokusaeva K, Fitzgerald GF, Sinderen D. Carbohydrate metabolism in bifidobacteria. Genes & Nutrition. 2011;**6**:285-306. DOI: 10.1007/s12263-010-0206-6

[71] Langen LV, Mirjam AC, Dieleman LA. Prebiotics in chronic intestinal inflammation. Inflammatory Bowel Diseases. 2009;**15**(3):454-462. DOI: 10.1002/ibd.20737

[72] Lindsay JO, Whelan K, Stagg AJ, Gobin P, HO A-H, Rayment N, et al. Clinical, microbiological, and immunological effects of fructo-oligosaccharide in patients with Crohn's disease. Gut. 2006;**55**(3):348-355. DOI: 10.1136/gut.2005.074971

[73] Tufarelli V, Laudadio V. An overview on the functional food concept: Prospectives and applied researches in probiotics, prebiotics and synbiotics. Journal of Experimental Biology and Agricultural Sciences. 2016;**4**:274-278. DOI: 10.18006/2016.4(3S).273.278

[74] Cencic A, Chingwaru W. The role of functional foods, nutraceuticals, and food supplements in intestinal health. Nutrients. 2010;**2**(6):611-625. DOI: 10.3390/nu2060611

[75] Zhang MM, Cheng JQ, Lu YR, Yi ZH, Yang P, Wu XT. Use of pre-, pro-and synbiotics in patients with acute pancreatitis: A metaanalysis. World Journal of Gastroenterology. 2010;**16**(31):3970. DOI: 10.3748/wjg.v16.i31.3970

[76] Eslamparast T, Poustchi H, Zamani F, Sharafkhah M, Malekzadeh R, Hetmatdoost A. Synbiotic supplementation in nonalcoholic fatty liver disease: A randomized, double-blind, placebo-controlled pilot study. The American Journal of Clinical Nutrition. 2014;**99**:535-542. DOI: 10.3945/ajcn.113.068890

[77] Panda AK, Rao SVR, Raju MV, Sharma SR. Dietary supplementation of Lactobacillus sporogenes on performance and serum biochemico-lipid profile of broiler chickens. The Journal of Poultry Science. 2006;**43**(3):235-240