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Therapeutic applications of probiotic and prebiotic in metabolic syndrome and chronic kidney diseases

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Abstract
More than several hundreds of millions of people will be diabetic and obese over the next decades because their actual therapeutic approaches aim at treating the consequences rather than causes of the impaired metabolism. The wide analysis of the genome cannot predict more than 10–20% of the disease, whereas changes in feeding and social behaviour have certainly a major impact. Several health-related effects associated with the intake of probiotics and prebiotics, including alleviation of lactose intolerance and reducing the risk of diabetes and obesity. Probiotics are live non pathogenic bacterial components that are helpful in the prevention and treatment of metabolic syndrome or diseases. The probiotic bacteria used in commercial products today are mainly members of the genera *Lactobacillus* and *Bifidobacterium*. Additionally, oligosaccharides are the best known ―prebiotics, ―a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers health benefits to the host. The isolated carbohydrates and carbohydrate-containing foods, including galactooligosaccharides (GOS), transgalactooligosaccharides (TOS), polydextrose, wheat dextrin, acacia gum, psyllium, banana, whole grain wheat, and whole grain corn also have prebiotic effects. Overall, a number of factors influence the composition of the microflora. These include changes in physiological conditions of the host (e.g., age stress, health status), composition of the diet, and environmental circumstances (e.g., antibiotic therapy, hygiene with antiseptics, *etc*.). Recognition of the health-promoting properties of certain gut microorganisms has encouraged dietary-based modulation of the human intestinal microflora towards a more beneficial composition and metabolism. The other potential functional effects of prebiotics are on the bioavailability of minerals, and on lipid metabolism. Potential health benefits may include reduction of the risk of intestinal infectious diseases, cardiovascular disease, non-insulin-dependant diabetes, obesity, osteoporosis and cancer.

Keywords: Probiotic, prebiotic, intestinal microbiota, diabetes, obesity, metabolic diseases

Introduction
Now a days, metabolic diseases such as diabetes and obesity are becoming a social problem of utmost importance for all countries. Their impact on developing countries such as South Asia is even more dramatic since, besides being affected by the highest growing rate, the social system can certainly not afford the corresponding expenses. Therefore, the disease is poorly treated and pathological complications are blooming. Many times, a person has poor health conditions based on dietary deficiencies, such as vitamins, minerals, and other natural elements that are essential for good human health. Several health-related effects associated with the intake of probiotics and prebiotics, including alleviation of lactose intolerance and reducing the risk of diabetes and obesity. The human intestinal tract harbours a diverse and complex microbial community which plays a central role in human health. It has been estimated that our gut contains in the range of 1000 bacterial species and 100-fold more genes than are found in the human genome [35, 46]. Probiotics are live micro-organisms, which, when administered in adequate amounts, confer a health benefit to the host. Probiotics act through diverse mechanisms that affect the microbiota [56, 61]. This effect may be revealed through changes in either the populations of bacteria or bacterial metabolic activity. Probiotics have roles in epithelial cell proliferation and differentiation and the development and homeostasis of the immune system [7]. Probiotics are not an invention but existed in our traditional foods such as beverages, salty fishes, yogurt, different types of cheeses and so on since olden times [2]. The probiotic bacteria used in commercial products today are mainly members of the genera *Lactobacillus* and *Bifidobacterium* [48, 25, 28, 4]. *Lactobacillus* species from which probiotic strains have been isolated include *L. acidophilus, Lactobacilllus johnsonii, Lactobacilllus casei, Lactobacilllus rhamnosus, Lactobacilllus gasseri,* and *Lactobacilllus reuteri. Bifidobacterium* strains include *Bifidobacterium bifidum, Bifidobacterium longum,* and *Bifidobacterium infantis*.

A prebiotic, as defined by Gibson and Roberfroid, is "a non digestible food ingredient that beneficially affects the host by selectively stimulating the growth and activity of one or a limited number of bacteria in the colon that have the potential to improve host health" [17]. A number of poorly digested carbohydrates fall into the category of prebiotics, including certain fibers and resistant starches, but the most widely described prebiotics are non-digestible oligosaccharides. Prebiotics occur naturally in foods such as leeks, asparagus, chicory, Jerusalem artichokes, garlic, onions, wheat, oats, and soybeans [59]. The caloric value of non digestible oligosaccharides has been estimated between 1 and 2 kcal/g [37]. Some known prebiotics (inulin) are low digestible carbohydrates and are associated with impaired gastrointestinal tolerance, especially when consumed in large quantities [21, 36]. While other prebiotic fibers (e.g., wheat dextrin, polydextrose) exhibit high gastrointestinal tolerability (30–45 g per day) [44]. Although all prebiotics are fiber, not all fiber is prebiotic. Selectively fermented ingredient that allows specific changes, both in the composition or activity in the gastrointestinal microflora, that confer benefits. Lactobacilli and bifidobacteria are the usual target genera for prebiotics; changes in bifidobacteria are more likely to be seen compared to lactobacilli. This may be due to the fact that more bifidobacteria usually reside in the human colon than lactobacilli and they exhibit a preference for oligosaccharides. Food grade commercial prebiotics are lactulose, galactosaccharides and Fructooligosaccharides (FOS), isomalto-oligosaccharides and lacto-sucrose, gentio-oligosaccharides and xylooligosaccharides.

The term synbiotic has been proposed for such combinations. A synbiotic has been defined as "a mixture of prebiotics and probiotics that beneficially affects the host by improving the survival and implantation of live microbial dietary supplements in the gastrointestinal tract, by selectively stimulating the growth and activating the metabolism of one or a limited number of healthpromoting bacteria, and thus improving host welfare" [17].

Mechanism of action of probiotics

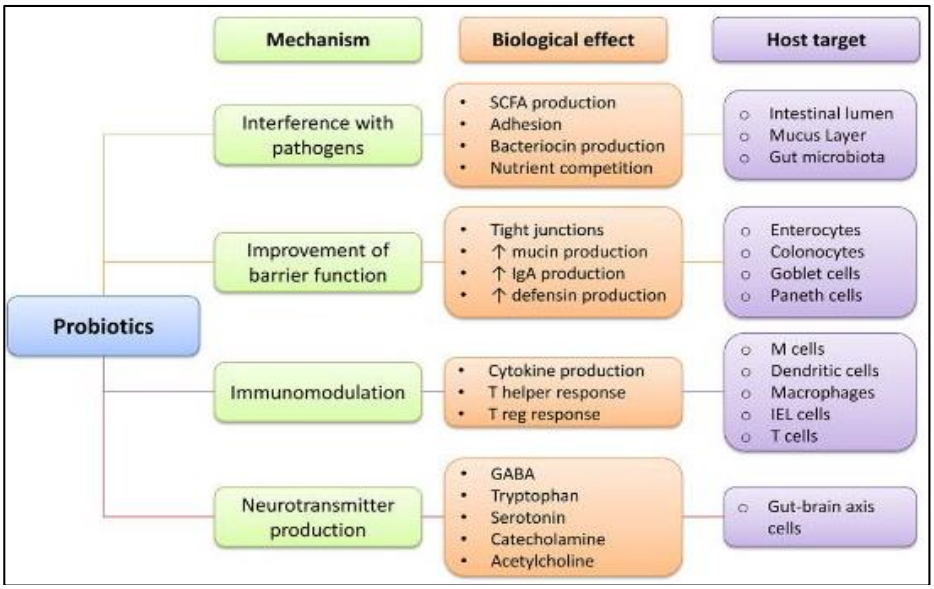

Fig 1: Diagram representing the main mechanisms of action of probiotics. Mechanisms, bio-logical processes, and host cells responsible for the interaction are shown color coded.

Bifidobacteria are Gram-positive, bifid-shaped anaerobes that constitute a major group of the human and animal gastrointestinal microbiota. Because these organisms are known to play a pivotal role in maintaining the microbial balance of a healthy intestinal tract, they are frequently applied as probiotics in health-promoting dairy products and dried food supplements [20]. These bacteria exert antimicrobial activity in the human intestine by producing lactic acid and acetic acid as a result of carbohydrate metabolism. These acids lower the intestinal pH, thereby inhibiting overgrowth of gastrointestinal pathogens. The normal balance of gastrointestinal flora can be maintained, with dietary administration of lactobacilli or bifidobacteria. Lactobacilli and bifidobacteria produce organic acids that reduce intestinal pH and thereby inhibit the growth of acid-sensitive undesirable bacteria. Lactobacilli produce lactic acid, hyrdrogen peroxide, and possibly acetic and benzoic acids. Bifidobacteria produce short chain fatty acids (SCFA) Such as acetic, propionic, and butyric acids, as well as lactic and formic acids. The most plentiful short chain fatty acid produced by bifidobacteria is acetic acid, which has a wide range of antimicrobial activities against yeasts, molds and other bacteria. Additionally, short chain fatty acids support normal gastrointestinal function by increasing colonic blood flow, stimulating pancreatic enzyme secretion, promoting sodium and water absorption, and potentiating intestinal mucosal growth. Bifidobacteria are also known to deconjugate bile salts to free bile acids, which are more inhibitory to susceptible bacteria than are the conjugated forms. Further, lactobacilli and bifidobacteria are able to produce other antimicrobial substances, Such as bacteriocins, that inhibit the growth and proliferation of harmful bacteria in the gut.

Mechanism of action of prebiotics

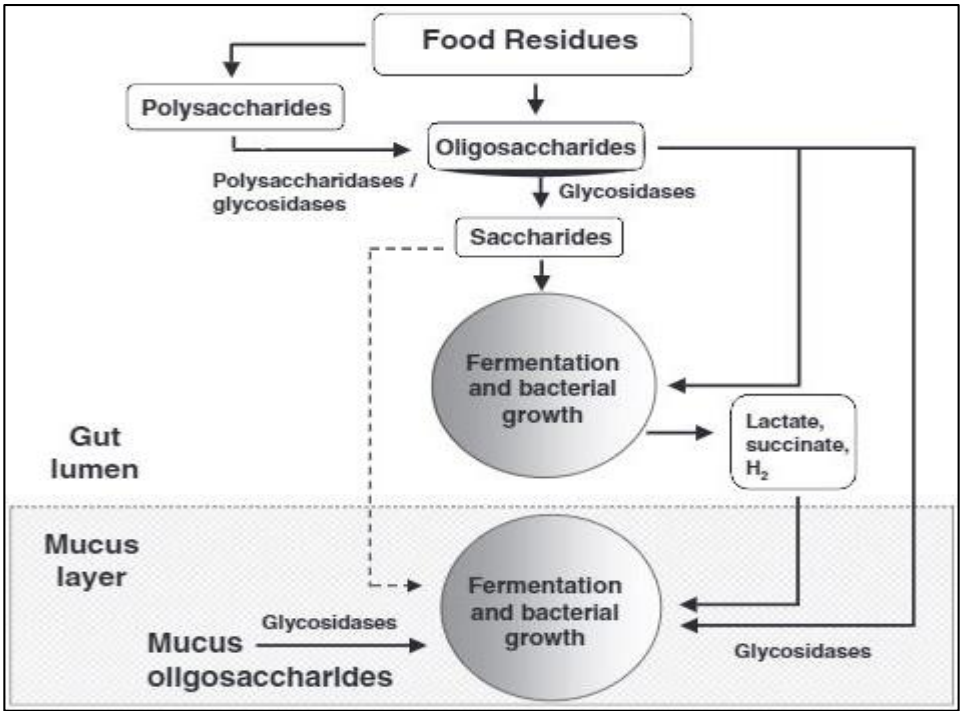

Fig 2: Mechanisms where by dietary substrates become available for mucosa-associated microbiotas in the large intestine.

Prebiotics were first defined as-non digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, thus improving host health [17]. An important mechanism of action for prebiotics is fermentation in the colon and changes in gut microflora. The human large intestine is one of the most diversely colonized and metabolically active organs in the human body [18]. The colonic environment is favourable for bacterial growth due to its slow transit time, readily available nutrients, and favourable pH [10]. The intestinal flora salvages energy through fermentation of carbohydrates not digested in the upper gut. The main substrates are endogenous (e.g., mucus) and dietary carbohydrates that escape digestion in the upper GI tract. These include resistant starch, non-starch polysaccharides (e.g., cellulose, hemicellulose, pectin, and gum), non-digestible oligosaccharides, and sugar alcohols. The main fermentation pathway generates pyruvate from hexoses in the undigested carbohydrate. Colonic bacteria use a range of carbohydrate hydrolyzing enzymes to produce hydrogen, methane, carbon dioxide, SCFAs (mainly acetate, propionate and butyrate), and lactate. Certain colonic bacteria generate energy from these fermentation products. At both the colonic and systemic levels, fermentation and especially SCFA production play an integral role. Colonic epithelial cells preferentially use butyrate as an energy source. Butyrate is considered a key nutrient determining the metabolic activity and growth of colonocytes and may function as a primary protective factor against colonic disorders, although data on this topic are conflicting [39]. SCFAs are water-soluble and are absorbed into the blood stream. The brain, muscles, and tissues metabolize acetate systemically whereas propionate is cleared by the liver and may lower the hepatic production of cholesterol by interfering with its synthesis. Transport to and further metabolism of SCFAs in the liver, muscle, or other peripheral tissues is thought to contribute about 7%–8% of host daily energy requirements [10]. Fermentation and SCFA production also inhibit the growth of pathogenic organisms by reducing luminal and fecal pH. Low pH reduces peptide degradation and the resultant formation of toxic compounds such as ammonia, amines, and phenolic compounds, and decreases the activity of undesirable bacterial enzymes.

Overall, a number of factors influence the composition of the microflora. These include changes in physiological conditions of the host (e.g., age stress, health status), composition of the diet, and environmental circumstances (e.g., antibiotic therapy, hygiene with antiseptics, *etc.*) [12]. Recognition of the health-promoting properties of certain gut microorganisms has encouraged dietary-based modulation of the human intestinal microflora towards a more beneficial composition and metabolism.

Criteria for Classification of a food ingredient as a prebiotic requires:

- Resistance to upper gut tract
- Fermentation by intestional microbiota
- Beneficial to the host health
- Selective stimulation of probiotics
- Stability of food processing treatments

Therapeutic applications and health benefits of probiotics and prebiotics

Potential health benefits of probiotic and prebiotic may include reduction of the risk of intestinal infectious diseases, cardiovascular disease, non-insulin-dependant diabetes, obesity, osteoporosis and cancer [49, 52].

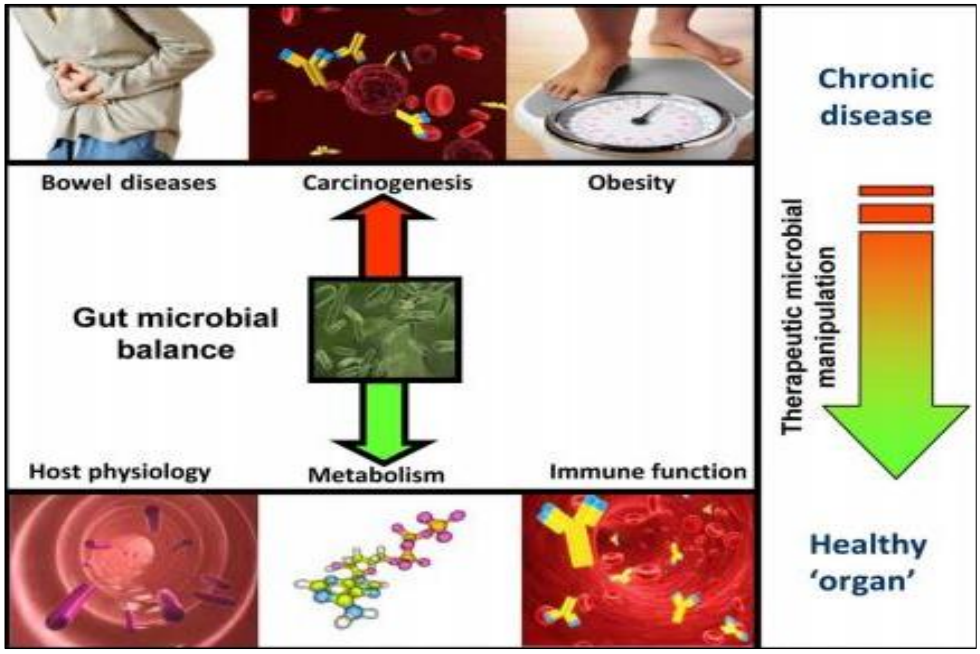

Fig 3: The gut microbiota in health and intestinal disease. The gastrointestinal microbiota play a role in host physiology, metabolism and nutrition. An alteration in the gut microbial community is linked to a number of intestinal conditions, including cancer, obesity and a variety of bowel disorders. The contribution of beneficial components of the gut microbiome to host physiology, metabolism and immune function has become the focus of ever more attention, and will undoubtedly lead to new therapeutic approaches [22].

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a gastrointestinal tract dysfunction with a complicated etiology [23]. Irritable bowel syndrome (IBS) is a common disorder affecting millions of people worldwide. Besides the interference with daily life of patients and caregivers, socioeconomic costs of IBS have increased, as the majority of IBS patients are young (20-39 years). Genetic background, environmental factors, history of inflammatory bowel disease in a family member and psychological factors are involved in the pathogenesis of IBS. However, due to lack of favourable efficacy and associated adverse events with pharmacologic treatments, some IBS patients look for alternative treatments such as herbal medications and Chinese acupuncture. Probiotics may influence the IBS symptoms including abdominal pain, bloating, distension, flatulence, altered bowel movements, and gut microbiota [11]. The nature of probiotics explains their beneficial role in intestinal function as they can protect against pathogenic bacteria via their antimicrobial properties [16]. Probiotics also amplify the intestinal tight junctions and stabilize the permeability. Moreover, probiotics stimulate goblet cells to produce mucus to enhance the intestinal barrier function, normalize bowel movements, and reduce visceral hypersensitivity [16] in pediatric and adult patients [32, 14]. Several probiotic strains showed beneficial outcomes in IBS patients [43, 60].

Prebiotics are dietary materials which escape absorption in the small bowel and enter the colon where they provide nutrients for particular bacteria. Lactulose is probably one of the best known and has been successful as a treatment for constipation. Unfortunately, it tends to produce substantial amounts of gas and abdominal pain and may actually aggravate symptoms of IBS. Fructose, sorbitol and a range of polyhydric alcohols are also poorly absorbed and enter the colon where they can act as substrates for bacteria. Oligofructoses, inulin and galactose oligosaccharides produce a modest increase in stool weight, but often produce increasing flatulence and bloating in healthy volunteers, an undesirable feature in a treatment for IBS [40]. Whether they would have a better effect when combined with bacteria, which ferment the prebiotic. Soluble dietary fiber such as fructo-oligosaccharides and inulin, that provide the typical advantages of dietary fiber and additionally are low in calories, does not affect blood glucose or insulin levels, further including beneficial/ friendly bacteria which favor the growth of other beneficial bacteria in the gastrointestinal tract while at the same time inhibiting the growth of potentially pathogenic or harmful microorganisms would be a significant advancement in the art.

Obesity and type 2 diabetes

Obesity, type 2 diabetes and related metabolic disorders, have become increasingly common in recent decades. Obesity is a complex syndrome that develops from a prolonged imbalance of energy intake and energy expenditure. Although lifestyle factors, diet and exercise contribute largely to the modern epidemic, it has also been indicated by an ever-increasing body of work that the microbial communities within the human intestine play an important role in obesity [33, 34, 57, 58]. Although it has been suggested that increased energy harvest due to the presence of specific microbial populations contributes to obesity [34, 58]. and indeed, it is becoming increasingly apparent that there can be very many other ways in which the microbiota can influence weight gain and host metabolism [9]. Obesity was associated with phylum-level changes in the microbiota, reduced bacterial diversity, and altered representation of genes and metabolic pathways.

Dietary intervention is one of the main therapies proposed in the case of type 2 diabetes patients, and hence non-digestible dietary fibers and polysaccharides are gaining importance for the treatment of diabetic subjects [38]. FOS, inulin, isomalto-oligosaccharides (IMO), polydextrose, lactulose and resistant starch are considered as the main prebiotic components through their fermentation in the colon to yield SCFAs [6]. The latter products are referred to as prebiotics, improving the health state of humans [53]. Fructooligosaccharides (FOS) are widely used in functional foods throughout the world. FOS are used as a food ingredient in various food items and

consumed regularly in appreciable amounts in typical Western diets [59]. The physiological effects of FOS, which are indigestible carbohydrates, especially mixtures of different sugar length such as 1-kestose, nystose and fructofuranosyl-nystose in which, they are safe for diabetic and improve the intestinal flora [1, 29]. It has also been suggested that SCFAs may directly prevent the low-grade inflammatory response, a condition closely associated with type 2 diabetes, through maintaining intestinal integrity.

Cardiovascular Disease

Cardiovascular diseases (CVD) are one of the most significant diet related health problems, representing a major cause of premature death in western countries. CVD comprise most or all of the following: overweight or obesity with atherogenic triglyceride rich lipoproteins, dyslipidemia, hypertriglyceridemia, hypertension, insulin resistance and glucose intolerance [41]. Administration of probiotics and prebiotics are effective in improving lipid profiles such as the reduction of serum total cholesterol, triglycerides, and low-density lipoprotein-cholesterol. Fibers added to diets, including fermentable carbohydrates such as inulin have an effect on lowering cholesterol and triglycerides [62]. One reason for this lowering effect is the viscous nature of fiber that binds the dietary or biliary cholesterol in the intestinal lumen increasing fecal excretion of the bile acids [50]. The regular consumption of fructans has benefits reduction or prevention of cardiovascular disease [13]. The rats were fed a 10% oligosaccharide diet showed a reduction of glycemia and insulinemia by 17% and 26% respectively [8]. Moreover, FOS affected delaying gastric emptying, and/or shortening their transit time through the GI tract [31]. Lactobacilli with probiotic characteristics isolated from traditionally homemade koumiss, Lactobacillus strains were able to lower cholesterol *in vitro*. Research found that FOS consumption increased the number of bifidobacteria and lactobacilli in associated with FOS fermentation may provide digestive benefits and improve gut health [24].

Colorectal cancer

Colorectal cancer (CRC) is the third most prevalent form of cancer in men and women, with a 5-year survival rate of 63%, decreasing to 10% in patients with metastatic disease [19]. Mortality and incidence of CRC is the third only to that of prostate and lung cancer in men, breast and lung cancer in women and has shown little sign of decreasing in the last 20-30 years. Diet makes an important contribution to CRC risk [47], implying that the risks of CRC are potentially reducible. The colonic microflora are involved in the etiology of CRC [47] and has led to an intense interest in factors that can modulate the gut microflora and their metabolism, such as probiotics and prebiotics. Some epidemiological studies have indicated that consumption of large quantities of fermented milk products containing lactobacillus or bifidobacteria are associated with a lower incidence of colon cancer [54] although, other studies have suggested that consumption of fermented dairy products imparts little, or no, protection [30]. The mechanisms by which probiotics may inhibit colon cancer are not yet fully characterized. However, there is evidence for: Alteration of the metabolic activities of intestinal microflora, alteration of physicochemical conditions in the colon, binding of potential carcinogens, short chain fatty acid production, production of anti-tumorigenic or anti-mutagenic compounds, elevating the hosts' immune response and altering the hosts' physiology. The production of SCFAs, such as butyrate, is one key mechanism by which probiotics and prebiotics may impart beneficial effects. Butyrate has been shown to inhibit cancer cell proliferation and promote apoptosis *in vitro* [23]. The bacterial strain Butyrivibrio fibrisolvens MDT-1 has been investigated in the context of CRC treatment as it produces high amounts of butyrate [42]. Prebiotics may be potential chemopreventative agents based on the observation that health-promoting bacteria such as bifidobacteria do not produce carcinogenic or genotoxic compounds, but instead produce SCFAs, which might be protective. Prebiotics have also been linked to the reduction of CRC. Friedenreich *et al.* [15] concluded in a meta-analysis that the consumption of over 27 g of fiber per day Fotiadis CI *et al.* Synbiotics in chemoprevention for colorectal cancer 6455 www.wjgnet.com resulted in a 50% reduction in CRC compared to consumption of less than 11 g. Inulin-type fructans present in foods such as garlic, onion, artichoke and asparagus have been demonstrated to elevate the levels of bifidobacteria and to increase SCFA concentrations in the intestinal lumen. Inulin and oligofructose have been demonstrated to reduce the severity of 1,2-dimethylhydrazine induced colon cancer in rats [27].

Chronic kidney diseases

Diet has a major role in shaping the gut microbial flora. Strict dietary restrictions intended to prevent severe hyperkalemia and oxalate overload in patients with advanced CKD severely limit consumption of fruits, vegetables, and high-fiber products, which are rich in potassium and oxalate. These products normally contain most of the indigestible dietary complex carbohydrates that serve as the primary source of nutrients for the gut microbiota. Therefore, these dietary restrictions could affect the makeup and/or metabolism of the gut flora [51]. Patients with advanced CKD are invariably instructed to take large quantities of phosphate-binding agents (calcium acetate, calcium carbonate, aluminum hydroxide, and anion-exchange resins) with each meal, to control hyperphosphatemia by limiting phosphate absorption. Long-term consumption of these agents can modify the luminal milieu of the gut and affect the resident microbial flora [26].

Probiotics, being administered in adequate amounts, provide a health benefit to the host in CKD. Administration of Bifidobacterium longum in enteric capsules to patients with CKD had minimal effects on the progression of the disease in patients with CKD [3]. The generation of uraemic toxins could be reduced by selectively increasing saccharolyticbacteria (which digest dietary fibre) and decreasing proteolytic bacteria (protein and amino acid fermenters) in the colon. The main regulator of metabolism of colon bacteria is the availability of nutrients and specifically the rate of fermentable carbohydrates vs. nitrogen. Prebiotics are non-digestible food components which, through selective fermentation, allow for specific changes in the composition or activity in gastrointestinal microflora, which are beneficial to the health and well-being of the host. Prebiotics stimulate the growth or activity of one or a limited number of bacteria in the colon; they may increase carbohydrate fermentables vs. nitrogen; they include inulin, fructooligosaccharides, galactooligosaccharides, etc. Inulin enriched with oligofructose reduces the generation of PCS and the serum concentrations in hemodialysis patients. Resistant starch reduces IS levels in hemodialysis patients and reduces PCS but not significantly [54].

Conclusion

In this review, probiotic and prebiotics have been widely assessed for their effects on various chronic diseases such as obesity, diabetes, cardiovascular diseases, cancer and irritable bowel diseases, in context of cardiovascular diseases, it affects lipid profiles such as total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides. In order to justify the varying cholesterol-lowering effect exhibited by various strains of probiotics or types of prebiotics, researchers have endeavored to reveal the mechanisms of probiotics and/or prebiotics on hypocholesterolemic effect through *in vitro* and *in vivo* studies. The hypocholesterolemic effect of prebiotics has been mainly attributed to SCFAs. The other potential functional effects of prebiotics are on the bioavailability of minerals, and on lipid metabolism. Potential health benefits of probiotic and prebiotic are reduction of the risk of intestinal infectious diseases, cardiovascular disease, non-insulin-dependant diabetes, obesity, osteoporosis and cancer. Therefore, probiotic and prebiotic should be used as a dietary supplement, because it existed in our traditional foods and have several health-related effects, including alleviation of lactose intolerance and reducing the risk of diabetes and obesity.

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