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Prebiotics – Types, their role in Improving Health and Therapeutic Applications

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Abstract

The prebiotics are chemical ingredients associated with our normal diet and are resistant to the activity of oral and gastrointestinal digestive enzymes. They even resist the gastrointestinal absorption. The prebiotics specifically serve as nutrients to certain gut bacteria. These bacteria utilize the prebiotics and produce metabolites which maintain our gut health. The prebiotics increase the population of beneficial bacteria and control the growth of harmful bacteria. Much research is ongoing pertaining to prebiotics due to their significant therapeutic properties. Many studies had proved that prebiotics are effective in control of various diseases including some skin disorders, boosting up our immune system and overall maintenance of our health. Currently extensive research and experimental studies on humans and animals are being conducted to determine the activity of various prebiotics. In future, various prebiotic formulations may be available to maintain our health and for the treatment of diseases. In the present paper classification of different prebiotics, their mechanism of action, therapeutic applications based on clinical trials and experimental studies, dietary sources and future perspectives of prebiotics were extensively analysed and discussed.

Key words : Prebiotics, gut health, beneficial bacteria, diseases, treatment, therapeutic applications.

Globally many people are suffering from various infections due to malnutrition. On the other hand, various non-infectious diseases like diabetes, obesity, heart disorders, cancer etc., are also increasing due to imbalanced diet and unhealthy food habits[5]. All these reasons led to the increased interest on prebiotics. In 1995, Glenn Gibson and Marcel Roberfroid introduced the concept of prebiotics. They depicted prebiotic as a "non-digestible substance

when consumed, specifically enhances the growth of gut bacteria and improves the host health". In recent times prebiotics are described as only certain chemical compounds belonging to carbohydrates in particular like beta-fructans, fructo- oligosaccharides, lactulose and galacto-oligosaccharides[19]. In human, gut harbours around one thousand microbial species which constitute gut microbiota[72]. The human gut flora depending on their effects and functions can be categorized into three groups *viz.,* probiotics (beneficial microbes), pathogenic and neutral bacteria[28]. In healthy human gut, a perfect balance of all these three groups is maintained. The intestinal tract is regarded as the second brain of humans and it has a key role in maintenance of health[18,39]. If there is any disturbance in gut flora, the human health is affected and disorders like colon cancer, obesity, irritable bowel syndrome and even diabetes may occur. Hence, it is very important for the maintenance of balance of gut microflora. Especially, the population of beneficial bacteria (probiotics) must be predominantly maintained. The prebiotics (non-digestible ingredients) selectively stimulate the growth and activities of beneficial microbes of gut. The enhanced growth of probiotics and their activities can be promoted by employing prebiotics[73].

Criteria to consider a compound as a prebiotic :

A compound which can resist the activity of acidic gastric juice, host gastrointestinal digestive enzymes and it should not be assimilated (resist the gastrointestinal absorption); must be utilized by gut bacteria for fermentation; and it must be able to specifically stimulate and enhance the growth of beneficial bacteria which maintain the gut health[51].

Classification of Prebiotics :

The prebiotics can be broadly classified into two types *viz.,* Carbohydrate and Non-carbohydrate prebiotics. The carbohydrate prebiotics can be further divided into oligosaccharides, polysaccharides and disaccharides. Most of the prebiotics in use belong to carbohydrates, in particular, oligosaccharides[45].

1. Carbohydrate prebiotics :

a) Oligosaccharides, b) Polysaccharides and c) Disaccharides :

a) Oligosaccharides :

(i) *Fructo-oligosaccharides :*

The fructo-oligosaccharides are a type of fructans. They occur naturally in plants. They can be chemically prepared from chicory. A sucrose molecule is linked to a chain of three to thirty fructosyl units to form the fructo-oligosaccaride structure[15,27].

(ii) *Galactooligosaccharides :*

The galactooligosaccharides are the oligosaccharides linked to galatose. These can be regarded as extended oligosachharide products of galactose. The different galactooligosaccharides differ by length of the chain, branches and glycosyl bonds. They can be categorized into two groups *viz.,* galactooligosaccharides with adequate galactose at 3, 4 and 6 carbon positions and those prepared by enzymatic trans-glycosylation. They are resistant to the action of digestive enzymes[17].

(iii) *Human milk oligosaccharides :*

The human milk oligosaccharides are

complex carbohydrates, recently identified as prebiotics. They are adequately present in breast milk. They range between 10 and 15 g/L breast milk[2]. The human milk oligosaccharide chain length varies from three to fifteen monosaccharide units. The human milk oligosaccharide contains five units (monosaccharide units) *viz.,* galactose, glucose, fructose, N-aetylneuraminic acid/ sialic acid and N-acetylglucosamine[10,16,63].

(iv) *Gluco-oligosaccharides :*

The gluco-oligosaccharides are the non-digestible compounds which have exclusively glucose monomer units in the chain. The compounds like isomalto-oligosaccharides, oligodextran, nigero-oligosaccharides, gentio-oligosaccharides and polydextrose belong to gluco-oligosaccharides group[75].

(v) *Pectic oligosaccharides :*

The pectic oligosaccharides are the derivatives of pectin. They can be prepared by partial degradation of pectin by using chemical methods or enzymes. Pectin is abundantly present in plants. It occurs in the cell wall of plant cells, orange peels, pomace of plants etc.,[37,38,67]

(vi) *Xylooligosaccharides :*

Xylooligosaccharides are the oligomers derived from xylan. The xylan is a polysaccharide present in dry mass of wood tissue (constituting about 25-35%) and lignified tissue (constitutes for about 50%) of dicot and monocot plants, respectively. The xylooligosaccharide chain is composed of 2-7 xylose units bonded by beta-1-4 glycosidic linkages. The acetyl groups, arabinose units and uronic acids linked to the main chain as branches. These non-digestible oligosaccharides exhibit various health benefits. They selectively enhance the growth of beneficial bacteria in gut, especially the growth of *Bifidobacterium* and Lactobacilli and act against the pathogenic bacteria. They even increase the rate of absorption of nutrients[47,57].

(vii) *Lactosucrose :*

It is a trisaccharide and produced chemically from the monomers, glucose, galactose and fructose. The other names of lactosucrose are galactosucrose, galactosylsucrose and lactosylfructoside[48]. It specifically enhances the growth of bifidobacterium and thus improves the health and immunity[25,62].

(b) *Polysaccharides :*

(viii) *Inulin :*

The inulin related prebiotics belong to fructans. Basically fructans are polymers formed by the polymerization of fructose monomer units. All the natural plant oligosaccharides and polysaccharides are included under fructans. The fructans group include inulin and oligofructose[14,70]. All the linear fructans with beta (2→1) fructosyl-fructose glycosidic bonds collectively comprise inulin. This type of fructans are resistant to digestive intestinal enzymes and salivary amylase due to the presence of beta bonds between fructose units in polymer chain[27,56].

(ix) *Resistant starch :*

The starch that can resist the activity of small intestine enzymes is referred to

as a resistant starch. The resistant starch was found to be useful for diabetes patients and even in reducing the concentrations triglycerides and cholesterol[23,44]. There are five types of resistant starches *viz.,* Type1 (physically inaccessible; example: whole kernel grain), Type2 (Granular starch; examples: raw potato, raw banana etc.,), Type3 (retrograded starch; example: cooked and cooled starch food items), Type4 (chemically modified starch; example: octenyl succinate starch) and Type5 (amylose lipid complex; example: stearic acid complex high amylose starch)[9].

(x) *Arabinoxylans :*

The arabinoxylans are the polysaccharides that occur in the plant cell walls. They were first discovered as viscous gum like substance in wheat flour by Hofman and Gortner (1927). The arabinoxylan is made up of pentose sugars, xylose and arabinose. Hence, arabinoxylans are referred to as pentosans. Various studies revealed the antioxidant, cholesterol decreasing and immunity boosting properties of arabinoxylans[23].

c) *Disaccharides :*

(xi) *Lactulose :*

Lactulose is a laxative of lactose which is chemically prepared from galactose and fructose. The fructose and galactose are linked by a kind of bond which is resistant to the activity of enzyme, lactase. The lactulose is fermented by gut bacteria, first to produce monosaccharides, then from monosaccharides, volatile fatty acids, hydrogen and methane gases are released. The research studies have revealed that the lactulose increased the population of beneficial bacteria like *Streptococcus, Bifidobacterium* and *Lactobacillus* in gut[72].

2. *Non-carbohydrate prebiotics*

(a) *Polyunsaturated fatty acids :*

The polyunsaturated fatty acids are considered as candidate prebiotics by International Scientific Association for Probiotics and Prebiotics in its final statement due non-availability of proper scientific proof. Still some research studies proved that dietary polyunsaturated fatty acids can serve as efficient prebiotics[54]. Especially, dietary omega-3 polyunsaturated fatty acids had shown extensive health benefits. They are effective against certain chronic degenerative diseases[65]. In a research study conducted by Kobyliak *et al.,*[33] (2020) they used omega-3 polyunsaturated fatty acids in combination with mixture of probiotics on fifty four patients suffering from diabetes 2. There was a remarkable reduction in insulin resistance and improvement in obesity related issues in the type 2 diabetes patients.

(b) *Polyphenols :*

The polyphenols are the secondary metabolites produced in plants. A polyphenol is a compound containing aromatic ring and with minimum one hydroxyl group. The polyphenols are categorized into different classes based on the phenol rings number and type of structures linking these rings. They are broadly divided into two major classes *viz.,* Flavanoids and Non-flavanoids. The flavnoids are further divided into six sub-classes which include flavones, isoflavones, flavanols, flavanones, antho-

cyanidins and flavan-3-ols[8]. The major sub-classes of non-flavanoids are Stilbenes, lignans and Phenolic acids. The polyphenols selectively enhance the growth of beneficial gut bacteria (probiotics) such as bacteria belonging to the families of Lactobacillaceae and Bifidobacteriaceae. In addition, they control the infectious agents like *Helicobacter pylori,* pathogenic *Escherichia coli* and *Clostridium perfringens*[52].

(c) *Sorbitol :*

The sorbitol is a polyol. It is a natural sugar alcohol compound and employed as sweetener in many food industries. In addition, it also serves as a texturing agent and humectant. It is preferably utilized by gut *Bifidobacterium* species and even some *Lactobacillus* species. Hence, some researchers regarded sorbitol as a prebiotic[58].

IV. *Mechanism of action of prebiotics :*

The prebiotics are the non-digestible ingredients which reach the digestive system via dietary components. They are not digested by small intestine enzymes and not assimilated into the body. They are selectively fermented by the bacteria in colon. The beneficial bacteria utilize the prebiotics to produce short chain fatty acids like butyric acid, propionic acid and acetic acid. The short chain fatty acids serve as energy sources for intestinal epithelial cells. They maintain the intestinal homeostasis. The prebiotics modulate the metabolism and host immunity[71].

V. *Therapeutic applications of Prebiotics:*

1. *Treatment of rectal colon cancer :*

Globally, the colorectal cancer constitutes the third most common tumor malignancy. Recent data reveals that the cases are increasing enormously in developing countries due to irregular and bad food habits, alcohol consumption, decreased physical activities and present life style. The research studies on animals revealed that the prebiotics can control the colorectal cancer. In a recent study, the $APC^{Min/+}$ mice (animal model with multiple intestinal neoplasia) administered with the prebiotic compounds, triterpenoid saponins and probiotic bacterium, *Bifido-bacterium animalis* showed significant decrease in the number of polyps in the colon. The triterpenoid saponins and *Biofidobacterium animalis* had exhibited a synergistic effect. In another experimental study, jujube polysaccharide (polysaccharide derived from Chinese jujube fruit) had exhibited protection against colon cancer caused by azoxymethane/deztran sodium sulfate in C57BL/6 mice[42]. The prevention of colorectal cancer through initiating and enhancing apoptosis is attributed to the fermentation products like butyric acid released by bacteria from prebiotics[13,20,41].

2. *Treatment of Crohn's disease :*

The Crohn's disease is a type of inflammatory bowel syndrome. It is chronic and relapsing and any organ of the gastrointestinal system may be affected. The Crohn's disease occurs due to decrease in the population of certain beneficial bacteria like *Bifidobacteria,* Bacteroides, Firmicutes and *Faecalibacterium prausnitzii*[68,69]. In an experiment conducted by Paineau *et al.,*[49] (2008) on fifty four volunteers revealed that consumption of 5g/day short-chain fructo-oligosaccharides for a

period of six weeks decreased the symptoms of inflammatory bowel syndrome. In another study, Silk *et al.,*[61] (2009) reported that by consuming 3.5 g/day galacto-oligosaccharides for twelve weeks there was an improvement in health condition of individuals suffering from inflammatory bowel syndrome.

3. *Treatment of Necrotizing Enterocolitis :*

Necrotizing enterocolitis is a dreadful gastrointestinal disorder which occurs majorly in premature newly born babies. It is a condition where necrosis occurs in some parts of the bowel[50]. It was assumed that certain prebiotics, especially, fructo-oligosaccharides and galacto-oligosaccharides, enhance the growth of beneficial intestinal bacteria like *Bifidobacteria* and decrease the number of infectious agents in premature infants[11,29,32]. Still clinical trials have to be conducted to determine the effectiveness of prebiotics in controlling Necrotizing enterocolitis.

4. *Prebiotics for enhancing immunity:*

The intake of prebiotics enhances the immune functions by selectively increasing the number of beneficial and protective bacterial population (indirect effect). Studies had revealed that administration of prebiotics on to animals and humans increased the population of *Lactobacillus* species and Bifidobacteria, which in turn had controlled the population of pathogenic bacteria[22,31,40]. The prebiotics enhance the immunity by interacting with both innate and acquired immune components (direct effect on immunity). The prebiotics exert their influence on gut epithelial cells and immune cells via Toll-like receptors. The combined effect maintains the epithelial cells barrier strength and enhances innate immunity by secreting cytokines (pro and anti-inflammatory) which induces the macrophages functioning and polarization. Further migration of neutrophils, differentiation of dendritic and regulatory T-cells occur[53]. Vulevic *et al.,*[66] conducted clinical trials to study the effect of galacto-oligosaccharides on immune system functioning in old age volunteers. They selected the volunteers between the age 65 and 80 years. The volunteers were administered with galacto-oligosaccharides 5.5 g/day for a period of ten weeks with a wash out period of four weeks in between. The prebiotics administered into the volunteers enhanced the concentration of interleukin-10, Interleukin-8 and natural killer cells activity. Interestingly, there was a decreased secretion of interleukin-1 beta. Thus the studies of Vulevic *et al.,* (2008) revealed that the administration of galacto-oligosaccharides reduced the manifestations of chronic inflammation accompanied with age due to the increased secretion of interleukin-10 and reduced secretion of interleukin-1beta.

5. *Prebiotics in treatment of Autism :*

Majority of the autism individuals (about 70%) are suffering from various gastrointestinal complications like severe constipation and its related issues, abdominal pain accompanied with diarrhea, bloating, inflammation of esophagus and stomach etc.,[12]. The normal gut microbial population will change in persons suffering from autism complications. Certain research studies have revealed that in the feces of autism patients, the population of beneficial bacteria like *Bifidobacterium* was decreased and the population of *Clostridium* increased. The gut

metabolic products of autism children are different from healthy ones. The concentration of short chain fatty acids is less in the gut of autism children in comparison with healthy children[1,21]. The prebiotics present in the wheat fiber decrease the population of deleterious bacteria like *Clostridium* and increase the population of Bifidobacterium in the gut[36]. Grimaldi *et al.,*[24] (2018) performed clinical trials for six weeks on thirty children exhibiting autism by using the prebiotic compound, Bimuno galacto-oligosaccharide. The gastrointestinal disorders were reduced in the children who were administered with Bimuno galacto-oligosaccharide and the population of *Faecalibacterium prausnitzii* and Bacteriodes species was increased in the gut. Even in the children the anti-social behavior was decreased and a significant improvement was observed. There was a remarkable change in the metabolic products of urine and fecal matter of children volunteers. Still much scientific evidence is needed to consider prebiotics for the treatment of autism.

6. *Prebiotics in improving memory, concentration and learning abilities :*

The studies on various types of prebiotics have revealed that the certain prebiotic compounds increase memory power in middle-aged group of adults[6,7]. The prebiotics are effective in retaining the learning and recall. Schmidt *et al.,*[59] (2015) conducted an experimental study (randomized, placebo-controlled and double blind) on adult volunteers for a period of three weeks to study the effect of fructo-oligosaccharides and galacto-oligosaccharides on amount of salivary cortiscol production. The fructo-oligosaccharides had not shown any effect on salivary cortiscol production, where as the consumption of galacto-oligosaccharide 5.5 g/day enhanced the production of cortisol in saliva and thus the concentration was improved in the adult volunteers. A clinical trial on middle aged adult group volunteers revealed that consumption of non-starchy polysaccharides 3.6 g/day for a period of 12 weeks improved the memory power in the middle aged volunteers[6,7].

7. *Prebiotics for the treatment of skin disorders (Atopic dermatitis) :*

The balanced microbiota of skin maintains the skin health. Sometimes, due to host's compromised immunity, some commensals turning out into pathogens on skin and other reasons can cause itching, inflammation etc., If any imbalance occurs in the microbiota of skin, the clinical symptoms arise. The reasons for the imbalance of skin microbiota include personal hygiene, skin hair, sebum secretion, cosmetics, pH of the skin and lifestyle[3]. The atopic dermatitis is such a type of very common inflammatory skin disorder. Its clinical manifestations include dry skin, erythema, crusting, eczematous lesions and erosions. The prominent characteristic feature of atopic dermatitis is severe itching sensation. The patient with severe atopic dermatitis exhibit hyperpigmentation on neck[35]. Hong *et al.,*[26] (2015) performed experiments to study the effect of galacto-oligosaccharides on the hairless mice which were exposed to ultraviolet radiation. The hairless mice were administered with galacto-oligosaccharide for a period of 12 weeks. The mice exhibited enhanced water retention capacity and did not develop any erythema. Further the galacto-oligosaccharides

can enhance the skin barrier strength by increasing the production of adhesion and matrix related compounds[30]. Feeding newly born infant with galacto-olilgosaccharides 0.8 g/day for a period of six months decreased the complications of atopic dermatitis[34].

VI. *Food sources of prebiotics :*

Table-1. The dietary sources of various prebiotics

Sl.No.	Prebiotic substance	Food source
1	Inulin	Chicory, Jerusalem artichoke and dahlia[60]
2	Galacto-oligosaccharides	Milk, cheese whey, leguminous plant seeds[46]
3	Pectic oligosaccharides	Sugar beet, apple, olive and citrus[4]
4	Resistant starch	Whole kernel grains, raw potato and raw banana starch[26]
5	Arabinoxylan	Wheat, barley, corn, rice, rye and oat[74]
6	Xylooligosaccharides	Sugarcane bagasse, corn cob, bamboo shoot shell, wheat straw[64] etc.,
7	Lactulose	Heated cow's milk
8	Polyunsaturated fatty acids	Almond, cashew nut, olive oil, mustard, peanut[55] etc.,
9	Polyphenols	Blackberry, blueberry, strawberry, kiwi, cherry[43]
10	Sorbitol	Apples, dates, peaches, figs apricots etc.,

The prebiotics are the ingredients present in various foods and upon reaching the gastrointestinal tract they are not digested and selectively metabolized by gut bacteria. The gut bacteria ferment the prebiotics and produce the vital products which maintain the gut health. The prebiotics selectively enhance the growth of beneficial bacteria like *Bifidobacterium* and *Lactobacillus* and control the growth of harmful bacteria. The prebiotics maintain the balance of microbiota in gut region. The prebiotics are useful in the treatment of various common human disorders. The clinical trial studies on humans and animals revealed that the prebiotics were able to effectively control obesity, inflammation due to age, psychological disorders, skin diseases (atopic deramatitis) etc., Further the prebiotics enhance the immunity of humans. The studies had proved that they modulated the migration of neutrophils and differentiation dendritic cells and increased secretion of specific interleukins. Most of the studies revealed that oligosaccharide prebiotics are more effective when compared to other types. Much research is still ongoing and presently various clinical trials are being conducted on humans using different prebiotics to determine and identify the actual mechanism of action of prebiotics. In future, many other prebiotics may be identified. The prebiotics may

emerge as useful food ingredients to maintain our health and protect ourselves from various diseases. The formulations of different prebiotics may be available for the treatment of diseases.

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