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Review

Reactive mechanism and the applications of bioactive prebiotics for human health: Review

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ABSTRACT

Prebiotics plays an important role in improving the growth of gut bacteria and it majorly found in various natural food sources such as fruits and vegetables. Nowadays, the prebiotic sources are added as a supplement in various food products such as dairy products, beverages, health drinks, infant formulae, and meat products. The presence of prebiotics provides various health benefits such as improveing calcium and magnesium absorption, increases bone density, reduces cancer risk, decreases cardiovascular diseases and also improves the immune system.

1. Introduction

The Prebiotics are short-chain carbohydrates called oligosaccharides which are non-digestible by digestive enzymes that present in humans and it selectively improves the activity of specific groups of beneficial bacteria. This bacteria involves fermenting the prebiotics and produces short-chain fatty acids. Prebiotic oligosaccharides are also had drawback due to their fermentation profiles and dosages required for health effects. The pathogenic properties of harmful bacteria include liver damage, diarrhea, systemic infections, and carcinoma. In contrast to this, some of beneficial bacteria are present in gut that promotes the host's health by stimulating the immune system, inhibiting the growth of pathogenic bacteria and also improves the digestion and absorption of essential nutrients (Al-Sheraji et al., 2013; Anadón et al., 2016; Gibson and Roberfroid, 1995). Additionally, the microflora in the large intestine obtain their energy from dietary components that are not digested in the upper intestinal tract reaches the large intestine (Macfarlane et al., 1994). These dietary components contain a major amount of polysaccharides, oligosaccharides, proteins, peptides, and glycoproteins. Later these products undergo for fermentation by the gut bacteria and subsequently leads to major end products like short chain fatty acids (SCFA). The major short chain fatty is acetate, propionate, and butyrate which are produced by the gut bacteria (Al-Sheraji et al., 2013; Nagpal et al., 2018).

Large intestine that present in the GI tract is the most colonized area and contain more than one thousand bacteria per gram of waste contents with hundreds of species identified. The large intestine contains commonly strict anaerobes and they may be differentiated as bacteria that are either beneficial or harmful (Al-Sheraji et al., 2013; Canny and Mccormick, 2008).

The Probiotics are living microorganisms which when controlled in suitable amount provides various health benefits to the host (Amara and Shibl, 2015; Markowiak and Śliżewska, 2017). Lactic acid bacteria (LAB) and *Bifidobacterium* are commonly used as a probiotic source in the production of food products due to their beneficial effect towards host health and also they are considered as a safe for consumption (Gibson and Wang, 1994; Oakey et al., 1995; O'Bryan et al., 2013; Linares et al., 2017). Studies have shown that probiotics involve stimulating the immune system, decrease diarrheal incidence, decrease serum cholesterol, alleviate lactose intolerance and it control infections. It also acts as antibiotics, suppresses tumors and protects against colon/bladder cancer (Markowiak and Śliżewska, 2017; Scheinbach, 1998).

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Commercially many formulations have been developed which are ready to be incorporated into food products. Fermented dairy products, especially the *'probiotic yogurt'* are one such product containing *Lactobacilli spp* that help in maintaining a healthy colon. Prebiotics are also well known as non-digestible food ingredients that positively affect the host health by selectively stimulating the activity and/or growth of specific bacteria that present in the colon and thus increases health activity. Apart from these, a combination of nutritional supplements comprised of probiotics and prebiotics called symbiotic has been found to show promising effects in the prevention of disease and in maintaining normal health (Markowiak and Śliżewska, 2017; O'Bryan et al., 2013; Younis et al., 2015).

The present review gives information about the prebiotics, its sources, prebiotics related epidemiological studies, health benefits, and safety concerns associated with bioactive prebiotics and probiotics.

1.1. Concept of prebiotics

Considering in the last few years there has been a huge creation in both the scientific and clinical interest in the concept of *'prebiotics'*, which were first discover in 1995 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 and thus improves host health" and now the statement was redefined as a substrate that is selectively utilized by host microbes which provide various health benefits. In a recent study, it also mentioned that the prebiotic source also includes non-carbohydrate sources which also benefits to other parts of the body than GI tract (Carlson et al., 2018; Gibson et al., 1995; 2017).

The consumers regularly take a moderate levels of prebiotics available naturally from many kinds of fruits and vegetables containing chicory, leeks, onion, banana, Jerusalem artichokes, garlic, and asparagus, but the quantity of prebiotics present in these food sources are generally very low in order to exhibit any significant effect on the composition of intestinal microflora (Manning and Gibson, 2007; Markowiak and Śliżewska, 2017). Prebiotics are generally mixtures of indigestible oligosaccharides, but inulin is an exception as it is a mixture of polysaccharide and fructo-oligosaccharides which also called as carbohydrates (Gibson et al., 2000; Manning and Gibson, 2007). The most common prebiotic source are galacto-oligosaccharides, lactulose, fructans which made up of inulin, fructo-oligosaccharides, and the synthetic disaccharide.

As compared to probiotics, which can introduce exogenous bacteria into the colonic microflora, prebiotic aims at stimulating the development of one or a limited number of the potentially health-promoting indigenous microorganisms, thus modulating the structure of the natural gut environment. In other words, it can be said that prebiotics is food for probiotics.

1.2. Characteristics of prebiotics

Prebiotics are generally non-digestible carbohydrates usually oligosaccharides and polysaccharides. Because of their backbone structure, this kind of compounds is neither hydrolyzed by the human digestive enzymes nor absorbed in the upper GI tract. Such ingredients are called as "*colonic foods*" *i.e.* foods which enter the colon and serve as substrates to the endogenous bacteria, indirectly benefiting the host by providing energy and essential micronutrients. However, not all colonic foods can be considered to have a prebiotic effect. There is a clear criterion which defines any given carbohydrate as a prebiotic ingredient (Carlson et al., 2018; Gibson et al., 2004; Roberfroid, 2007; Slavin, 2013).

1. Firstly the ingredient must be non-digestible by the human digestive enzymes.
2. It must be fermented in the gastrointestinal tract.
3. It leads selectively stimulate the growth or/and activity of beneficial bacteria in the gut [*Lactobacilli* and *Bifidobacteria*]

All the above-said properties of a prebiotic food ingredient have been demonstrated both *in-vitro* and *in-vivo* studies.

2. Types of prebiotics and its sources

Some non-digestible oligosaccharides with prebiotic activities occur naturally in human milk (Thurl et al., 1996) and plants (Campbell et al., 1997). Most of them are synthesized or isolated from plant polysaccharides such as fructooligosaccharides (FOS), galacto-oligosaccharides (GOS) or *trans*-galactooligosaccharides (TGOS), isomalto-oligosaccharides (IMO), xylo-oligosaccharides (XOS), plant cell wall-derived polysaccharides and other. It indicates at present scenario, FOS and GOS are leaders on the world market.

The prebiotic effects of FOS or inulin (a mixture of FOS and polysaccharides) have been investigated. Using animal models or volunteers fed with inulin or FOS containing product, *in vivo* experiments were conducted which supported the *Bifidogenic* effect of FOS with large variations depending on the subjects, fecal microflora composition, doses and categories of FOS and/or inulin (Carlson et al., 2018; Gibson et al., 2004; Sangeetha et al., 2005).

The following are a few non-digestible carbohydrates which exhibit the prebiotic effect.

1. Disaccharides like lactulose and lactitol.
2. Oligosaccharides such as fructooligosaccharides (FOS), Galactooligosaccharides (GOS), Xylooligosaccharides (XOS), Isomaltooligosaccharides, Soybean oligosaccharides, and Pectic oligosaccharides.
3. Polysaccharides like inulin and resistant starches.

2.1. Lactulose

The lactulose is the type of synthetic disaccharide which was used originally as a laxative (Saunders and Wiggins, 1981). The role of lactulose has also been displayed to increase *Bifidobacteria* and *Lactobacilli* and also it decreases *Bacteroides* that present in the mixed continuous fecal culture (Fadden and Owen, 1992). Recently, some of the clinical studies showed that lactulose has potential to use as a prebiotic source. The effect of dietary supplementation with lactulose (3 g/d for 2 weeks) on the fecal bacterial and fecal flora metabolism in healthy human volunteers and the intake of lactulose showed that the count of *Bifidobacteria*gets increased, whereas the number of *Bacteroidaceae* and *Clostridium perfringens* get decreased. Fecal indole, fecal P-glucuronidase, skatol and phenols, azoreductase and nitroreductase activities were also decreased significantly (Terada et al., 1992). Another study with the intake of lactulose (2×10 g/d) showed increased probiotic bacteria and decreased putrefactive bacteria and potential pathogens (Bolognani et al., 2001).

It is a disaccharide widely used as a laxative. It is derived from lactose resistant to digestion (Sanders, 1999). It is not digested by human digestive enzymes and is known to stimulate the growth of *Bifidobacteria* (Terada et al., 1993; Tomoda et al., 1991). Lactulose is sugar with greater sweetness and better solubility than lactose. It is also known to be an important constitutional factor in infant formula products (Mayer et al., 2004).

Lactulose has various types of applications in the food and pharmaceutical industries. It is one of the important medical interest used for the treatment of chronic constipation and portal-systemic encephalopathy. It is also added to commercial infant formula products as well as various milk products (Strohmaier, 1998; Zokaee et al., 2002). In addition to this, lactulose also used as a sugar substitute in confectionery products, sweetener for diabetics, a type of yogurt additive in dairy product and in various dried or liquid food preparations mainly manufactured for the elderly people (Strohmaier, 1998; Tamura et al., 1993). Thus, lactulose can be designated a prebiotic in human health (O'Bryan et al., 2013; Mizota et al., 1987; Mizota et al., 2002; Rycroft et al., 2001). Lactosucrose is a trisaccharide and is also used as a *Bifidogenic* food ingredient (Ohkusa et al., 1995).

2.2. Fructo-oligosaccharides (FOS)

The Fructo-oligosaccharides is a mixture of oligosaccharides which consists of glucose linked to fructose units by *β*-(1, 2) linkage with a degree of polymerization occurs between 1 and 5. It occurs naturally in plant sources such as Jerusalem artichokes, wheat, asparagus, and rye. Onion is a rich source of FOS which ranges from (25 to 40% of dry matter) (Jaime et al., 2001). The commercial production of FOS is based on two processing methods which can be either a batch conversion of sucrose by fungal or a fructosyltransferase or continuous process using immobilized cells in calcium alginate gel or enzyme on an insoluble carrier (Vega and Zúniga-Hansen, 2011). The FOS that present in human colon is mostly fermented to SCFA (acetate, propionate, and butyrate), lactate and gas. They are involved stimulating the *Bifidobacterial* growth and also decrease the growth of harmful species that present in the colon (Bornet et al., 2002). It also shows side effects which include a decrease in fecal *p*H, a decrease in fecal bacterial enzymatic activities, increase in fecal or colonic organic acids, and a modification in fecal neutral sterols (Bornet et al., 2002; O'Bryan et al., 2013) Fig. 1.

2.3. Galactooligosaccharides

The Galactooligosaccharide (GOS) is a group of carbohydrates which is made up of oligo-galactose along with glucose and lactose. They are commercially produced from lactose by *β*-galactosidase (Macfarlane et al., 2006). Oligosaccharides that naturally occur in human milk resembles GOS, which may be one of the important substances that protects the breast fed infants from gastrointestinal pathogenic bacteria (Fanaro et al., 2005). Animal studies have shown that the intake of GOS stimulates the growth of *Bifido-bacteria* (Djouzi and Andrieux, 1997; Morishita et al., 2002; Rowland & Tanaka, 1993). The effect of consumption of GOS with or without *Bifidobacterium breve* was studied by using rats as a model that colonized with a human fecal microflora. The test was carried out for four weeks and it was observed that there were increases in the fecal concentration of total anaerobic bacteria such as *Bifido-bacteria* and *lactobacilli* and decreases in numbers of entero-bacteria (Rowland & Tanaka, 1993).

The GOS and TGOS fermentations are also well documented in the literature. TGOS are GOS derived from lactose by an enzymatic process. Depending on the reaction conditions they consist of oligosaccharides from tri- to penta-saccharide with β (1–6), β (1–3) and β (1–4) linkages (Crittenden and Playne, 1996).

The effect of galacto-oligosaccharide mixture (B-GOS) on gut bacteria of elderly persons have been studied and it was observed that the consumption of B-GOS mixtures showed an increase in the bifidobacteria, Bacteroides in the gut (Vulevic et al., 2015).

2.4. Xylooligosaccharides

Xylooligosaccharides (XOS) are chains of xylose molecules linked by β1–4 bonds which are produced enzymatically by hydrolysis of xylan from oats, birch wood or corn cobs (Moure et al., 2006; Vazquez et al., 2000). The *in vitro* batch culture system proven by very selective for *Bifidobacteria*, and it also proved as a prebiotic source (Campbell et al., 1997; Hsu et al., 2004; Rycroft et al., 2001; Santos et al., 2006; Zampa et al., 2004). Lecerf et al. performed a parallel, placebo-controlled, double-blind study of XOS in healthy humans and found that the

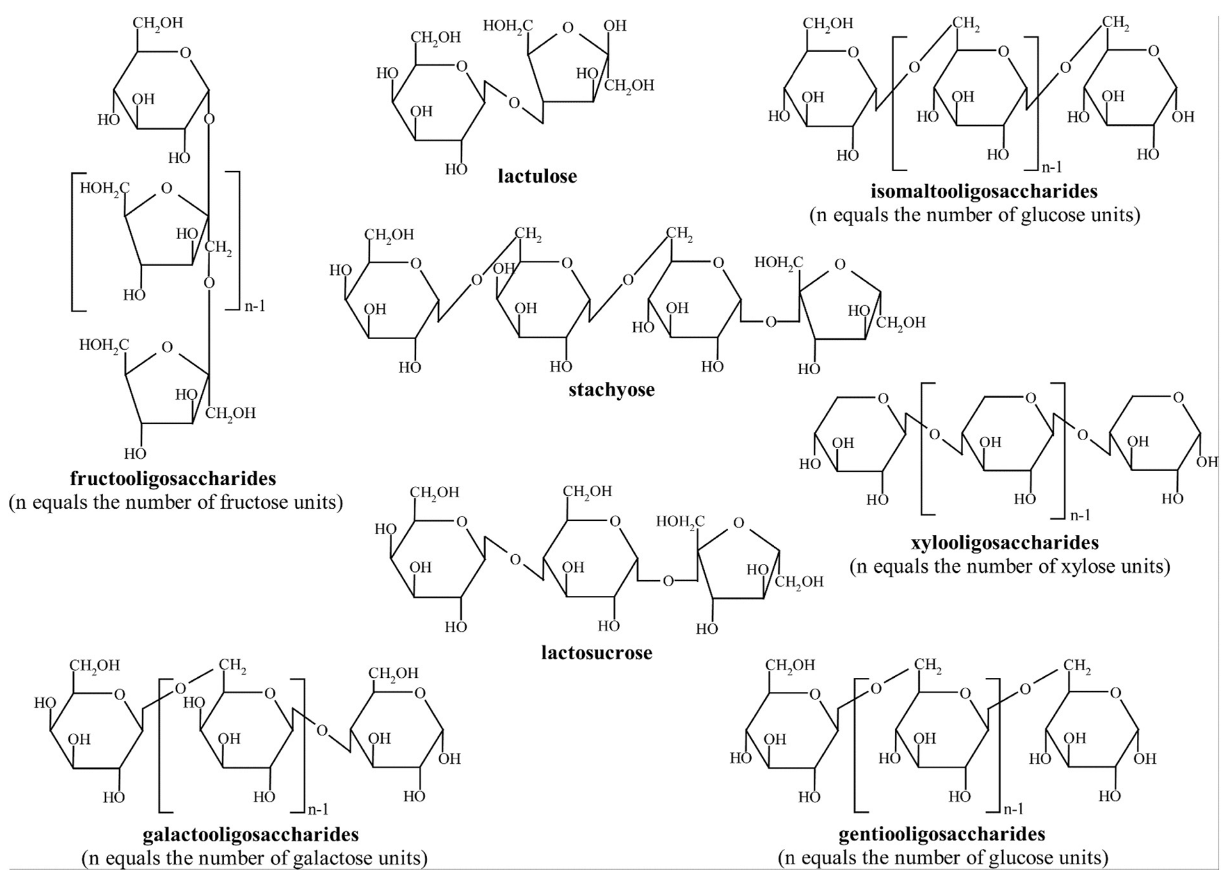

Fig. 1. Chemical structures of various types of probiotics oligosaccharides (Fernández Fernández et al., 2015; Joshi et al., 2018; Murphy, 2001).

presence of XOS increased the *Bifidobacterium* and butyrate and also increased the activities of β-glucuronidase and α-glucosidase while there was decreasing in the concentrations of *p*-cresol and acetate. Thus it showed a good prebiotic effect (Lecerf et al., 2012).

The *in vitro* studies showed no significant demonstration of bacterial growth stimulation. There is no scientific evidence so far to prove their selective fermentability (Crittenden and Playne, 1996; Okazaki et al., 1990). But XOS are categorized as prebiotics based on studies on human volunteers. Xylooligosaccharides have many potential applications due to its various health benefits. These include their non-cariogenic nature, anti-freezing activity, non-digestibility, high water activity and also their positive effects on intestinal flora, and their use in pharmaceuticals (Okazaki et al., 1990).

2.5. Isomaltooligosaccharides

They are manufactured from starch by enzymatic hydrolysis and are known to be *Bifidogenic* in human volunteers (De Boever et al., 2000; Hayakawa et al., 1990; Kohmoto et al., 1991) and are hence regarded as potential prebiotics food ingredients.

2.6. Soybean oligosaccharides

They are isolated from soybeans. They are not digestible and reach the colon intact, thereby acting as prebiotics. They are also *Bifidogenic*and are found to have similar effects as that of GOS (Hayakawa et al., 1990; Joshi et al., 2018; Rycroft et al., 2001).

In addition, recent literature has detailed numerous other oligosaccharides like gluco-oligosaccharides and oligosaccharides from melibiose, mannan oligosaccharides, oligodextrans and gentio-oligosaccharides with prebiotic activities (Barreteau et al., 2006; Olano-Martin et al., 2002; Palframan et al., 2003; Raman et al., 2016; Singh et al., 2017)

Several other materials are being investigated to identify them as potential prebiotics. *Aloe Vera* is one such example. It has been found to facilitate digestion and promote the growth of some bacteria in the colon. However clinical evidence is awaited.

2.7. Pectic oligosaccharides

The pectin is a complex in nature made up of galacturonic acid with rich polysaccharide. It occurs naturally in the cell walls of higher plants and the cellulosic components of the plant cell wall. The main polysaccharides forming pectin includes rhamnogalacturonan-I (RG-I), rhamnogalacturonan-II (RG-II) and homogalacturonan (HGA) which are linked together by a covalent bond (Ridley et al., 2001). The physical or enzymatic method can be used to produce pectic oligosaccharides. In the enzymatic method, the hydrolysis of apple and citrus pectin in membrane reactors gives oligosaccharides with a molecular weight of 3–4 kDa (Olano-Martin et al., 2001). Nitric acid hydrolysis of citrus peel produces arabinose-based oligosaccharides with a low molecular weight (Fishman et al., 2000). This type of oligosaccharides from two different materials have been analyzed for prebiotic effect in fecal batch cultures and concluded that it promotes the growth of probiotic bacteria such as *Bifidobacteria* (Fishman et al., 2000; Olano-Martin et al., 2001). Pectin and pectic oligosaccharide are involved in promoting the anti-inflammatory commensal microorganism in the human colon (Chung et al., 2017).

2.8. Inulin

Inulin is a naturally occurring storage carbohydrate mostly found in Jerusalem artichoke, garlic, wheat, asparagus, onions, leeks, and chicory (Carpita et al., 1989; Jackson et al., 1999). Nowadays inulin is commercially produced from chicory and Jerusalem artichokes (Kaur and Gupta, 2002). The effect of inulin or placebo on human health were studied over a period of 8 weeks by providing 10 g inulin on daily basis with noted fasting glucose, blood lipid, and insulin levels in healthy normal women and men with moderately raised in their triacylglycerol levels and total plasma cholesterol(Jackson et al., 1999). The fasting blood samples were collected before the intake of inulin and at fourth and eighth week with a follow up at in the twelve weeks. The results were compared with the baseline value and it was observed that concentration of insulin was significantly lower at four weeks in the inulin group and there was a trend for triacylglycerol values to be lower in the inulin group at a period of eight weeks returning to baseline concentrations in the twelve weeks (Jackson et al., 1999). Nair et al. reviewed the literature search on functional aspects of inulin and reported that several animal and human studies have displayed inulin having many kinds of application like positively influence lipid metabolism, promote optimal digestive health, decrease the risk of osteoporosis by increasing the absorption of calcium, as well as reduce the high risk of colon cancer, breast cancer and tumor growth (Kalyani Nair et al., 2010).

2.9. Resistant starch

The resistant starch is the fraction of starch that usually a starch that gets diverted from digestion that occurs in the upper GI tract and reaches the colon which later gets fermented by the colonic microbiota (Topping et al., 2003). Several studies were carried out on animals to understand the prebiotic properties of resistant starch and it showed increase in the growth of probiotic bacteria *Bifidobacteria* and SCFA in rats (Dongowski et al., 2005; Jacobasch et al., 2006; Le Blay et al., 1999), human-flora-associated rats (Silvi et al., 1999), and pigs (Brown et al., 1997). Le blay et al. studied the effect of prolonged feeding of resistant potato starch on butyrate production in rats and it was identified that butyrate production was promoted by long-term ingestion from the cecum towards the distal colon, suggesting a slow adaptive process within the digestive tract in response to a chronic load of indigestible carbohydrates. One more rat study displays the resistant starch increased the rate of fermentation accompanied by a decrease of *p*H in colon, cecum, and feces. Bile acids became bound to the resistant starch and thus were not reabsorbed, resulting in a higher turnover through the large bowel (Le Blay et al., 1999). The effect of resistant starch on human gut microflora along with associated parameters in human flora-associated (HFA) rats, colonized with microflora populations from Italian or UK was studied. In both case, the UK and Italian flora-associated rats, numbers of *Bifido-bacteria* and *Lactobacilli* were increased from 10 to 100 folds and also there was a decrease in enterobacteria (Murphy, 2001; O'Bryan et al., 2013; Silvi et al., 1999; Keenan et al., 2015). The sources of prebiotics are given in the Table 1 (Al-Sheraji et al., 2013; Joshi et al., 2018).

3. Prebiotics as functional ingredients

Nondigestible oligosaccharides are proved to improve mineral absorption and many experimental studies have claimed that consumption of these carbohydrates lowers cholesterol and triglyceride levels in blood and hence prevents CVD. All these kind of properties of prebiotics allow them to be used as functional food ingredients in a variety of foods. Prebiotics are being extensively used in a wide range of products including dairy, beverages and health drinks, infant formulae, meat products, animal feeds and as supplements. The prebiotic oligosaccharides are being widely explored and used as food ingredients especially in the European countries and Japan. Oligosaccharides have excellent functional properties and have obtained FOSHU [Foods of Specific Health Use] under Japanese legislation. They are being added along with probiotics in yogurt and other drinks to produce symbiotic products (Al-Sheraji et al., 2013; Gibson et al., 1995; Younis et al., 2015).

Table 1
Sources of prebiotics.

Type of prebiotic	Sources
Lactulose	Lactose (milk)
Maltooligosaccharides	Starch
Fructooligosaccharides	Sugar beet, asparagus, garlic, onion, chicory, wheat, barley, rye, tomato, banana, honey, Jerusalem artichoke
Isomaltooligosaccharides	Sugarcane juice and honey
Xylooligosaccharides	Fruits, vegetables, bamboo shoots, milk, wheat bran, and honey
Raffinose oligosaccharides	Seeds of legume, peas, lentils, and beans
Arabinoxyloligosaccharides	Wheat Bran
Soybean oligosaccharides	Soybean
Galactooligosaccharides	Human's milk and cow's milk
Isomaltulose	Sucrose
Cyclodextrins	Water-soluble glucans
Lactosucrose	Lactose
Palatinose	Sucrose
Enzyme-resistant dextrin	Potato starch

4. Nutritional benefits of prebiotics

The major nutritional effect of prebiotics is a direct function of the physiological effects they induce in the host. The main mode of action is the development of short chain fatty acids namely butyrate, acetate and propionate (Cummings et al., 2001).

4.1. Physiological effects of prebiotics

A variety of benefits have been attributed to prebiotics intake (Gibson et al., 2000; Parvez et al., 2006; Sanders, 1999).

4.1.1. Relief from constipation

This is a well-documented effect and many prebiotics are carbohydrates, which get fermented mainly in the large intestine region. The release of fermentation gases results in increases the volume and reduce the transit time of the digested food in the intestine. Therefore, the slow intestinal passage (slow transit time) results in constipation. Reducing the transit time thus leads against constipation and carbohydrates that present reaches the large intestine and have a laxative effect on bowel habit (Cummings, 1994).

In addition to context, many carbohydrates also increase the water content of the intestine and the acids produced increase intestinal motility (Den Hond et al., 2000). These two major effects also decrease transit time. A possible effect of prebiotics consumption is the reduced incidence of traveler's diarrhea (TD). According to a clinical study by Cummings et al. involving two groups of subjects, one placebo and the other on FOS diet; it was found that there was the lesser occurrence of TD in the FOS diet group. However, this cannot be conclusive as TD may not be only due to infection. It can even be caused due to exposure to rarely encountered food, anxiety or excess alcohol consumption. Moreover, the infectious agents that cause TD like Yersinia, *E* coli affect the small intestine mainly and prebiotics are known for their effects in the large intestine (Cummings et al., 2001).

4.1.2. Increased mineral absorption

In recent years, the intake of minerals is increased due to its various health benefits in particular calcium absorption through the consumption of naturally present prebiotics. Although the small intestine is the major region of calcium absorption in humans, significant amounts may be absorbed throughout the gut. The present research on animal studies have identified that prebiotics like inulin and oligo-fructose increased the absorption of calcium from the colon, leads to major increased bone density (Coudray et al., 2003; Delzenne et al., 1995; Ohta et al., 2002; Scholz Ahrens et al., 2002). The studies also indicated that, Magnesium absorption in post-menopausal women, increased due to consumption of oligo fructose (Tahiri et al., 2001).

4.1.3. Reduction in intestinal pH

This kind of effect is considered due to a change in metabolism from protein fermentation as the release of ammonia leads to high *p*H to more carbohydrate fermentation as the release of acid. In meanwhile, some of the intestinal related diseases, such as IBS (irritable bowel syndrome) and Crohn's disease, are characterized by a high level of *p*H. Reducing the *p*H thus reduces the symptoms of these diseases, which is helpful to the patient. A low intestinal *p*H involves increasing bowel movement and also protect against pathogenic bacteria. The most useful effects are obtained by rapidly fermenting carbohydrate mixtures. It is considered on a change in metabolism and not on the stimulation of specific bacteria (Hemarajata and Versalovic, 2013; Markowiak and Śliżewska, 2017).

4.1.4. Restore of intestinal bacterial balance

Prebiotic can able to restore the intestinal balance even after the disturbance caused due to diarrhea, antibiotics, stress and other drugs. It can be possible by either selectively stimulating a particular group of bacteria and the balance can be restored. This may be possible for many different bacterial groups. This can be carried out by direct stimulation in which the selected bacteria grow on the prebiotic or by indirect stimulation in which the bacteria create a favorable environment for other bacteria. The type of stimulation and changes in the metabolism plays an important role in the restoration of bacterial balance in the intestine (Hemarajata and Versalovic, 2013; Markowiak and Śliżewska, 2017).

4.1.5. Effect on lipid metabolism

In the food industry, the recent trend is to develop the functional foods by using prebiotics in order to modulate blood lipids such as triglycerides and cholesterol. But, the studies on lipid metabolism showed that there was no successful outcome and the study record shows that there was no effect on lipid metabolism, while some studies indicated a decrease in total cholesterol (TC) and LDL-cholesterol (LDL-C) and in a few other studies, a decrease in fasting triglyceride levels were observed due to the consumption of prebiotics (Jackson et al., 1999; Ooi and Liong, 2010; Sharma and Puri, 2015). According to Van Loo, these contradictory results could be to the complexity in the lipid metabolism. There is evidence that FOS decreases the *de novo* synthesis of triglycerides in the liver. The reduction in triglycerides (TG), TC and LDL-C can reduce the risks of cardiovascular diseases (CVD) (Van Loo, 2004; Delzenne and Kok, 1999).

4.1.6. Anticarcinogenic effects

This one is well known that several species of bacteria commonly found in the colon produce carcinogens and tumor promoters from the metabolism of food components. Prebiotics showed the anti-carcinogenic effect against the animal models. For example, inulin showed inhibition against the formation of aberrant crypt foci (ACF), a biomarker for colon cancer, particularly in rats (Reddy et al., 1997). Bolognani et al. have shown that there is a reduction in the ACF with inulin and *L. acidophilus* ingestion. A pronounced reduction of ACF in the distal parts of the colon was demonstrated clearly (Bolognani et al., 2001; Van Loo, 2004). Only a very few human studies have been conducted in out. FOS and GOS have been investigated in this regard. There are two mechanisms that explain the effect of prebiotics on cancer development (i) production of short chain fatty acids [SCFAs] like butyrate which involves stimulating apoptosis in colonic cancer cell lines and it also acts as a fuel for healthy bacteria in the colon (ii) Shift of colonic metabolism away from protein and lipid metabolism to saccharolysis (Manning and Gibson, 2004; Prasad, 1980). Prebiotics may also indirectly affects the activities of enzymes produced by the lactic acid bacteria that are involved in carcinogenesis (Al-Sheraji et al., 2013; Reddy, 1998).

4.1.7. Effects on immune system

Prebiotics directly showed no harmful effect on the human immune system. But indirectly it gets affected due to change in intestinal microflora, the immune system may get influenced (Schley and Field, 2002). This stimulation may be beneficial or non-beneficial to the host. If it showed beneficial effect then it resulted in a stronger immune system that gets activated against pathogens and if prebiotics is non-beneficial it shows the allergic reactions towards the host. In recent studies, showed that the prebiotic showed no beneficial effect on human immune system.

Another promising health benefit is the possible prevention or delay in the onset of diabetes mellitus. A fasting blood sugar level under 100 mg/dL is considered as a normal. If this range is between 100 and 125 mg/dL, it is said to be the prediabetes condition. Prediabetes is also called impaired fasting glucose [IFG] and progresses to type II diabetes if left untreated. Hence prebiotics serves as effective foods in the prevention of diabetes (Yao et al., 2017).

5. Health benefits of probiotics

The literature display the probiotics produce the following health benefits (Nomoto, 2005; Parvez et al., 2006; Sanders, 1999).

a) Effects of Lactobacilli

This bacteria are normal inhabitants of human colon and have potential health-promoting effects like refining intestinal tract health, enhances the bioavailability of nutrients, enhances the immune system and decreases the symptoms of lactose intolerance, the risk of certain cancers and also decreasing the prevalence of allergy (Nomoto, 2005).

b) Effects of Bifido-bacteria

The *Bifido-bacteria* have shown to possess several health promoting effects such as production of SCFAs like acetate and lactate and also excretion of metabolic end products inhibitory to Gram-positive and negative bacteria, reduction in the blood ammonia levels, reduction in the blood cholesterol levels, immunomodulation *i.e.* promoting attack on malignant cells production of B-vitamins (Gibson and Roberfroid, 1995; Rivière et al., 2016).

5.1. Intestinal effects

Probiotic microorganisms promote recovery from diarrhea, produce lactase and alleviate symptoms of lactose intolerance. They also relieve constipation Traveler's diarrhea is a very serious problem that the residents of advanced countries faced after traveling to subtropical and tropical zones. Oral consumption of *Lactobacillus* GG strain is reported to extensively decrease the incidence of diarrhea in travelers (Sanders, 1999; Nomoto, 2005; de Vrese and Marteau, 2007; Oak and Jha, 2018).

5.2. Immune system effects

The probiotics have been shown to improve specific and nonspecific immune response, which inhibits pathogen growth and translocation. It stimulates gastrointestinal immunity and also reduces the chance of infection from common pathogens like Salmonella. The Other effects which includes reduce risk of certain cancers such as colon and bladder, detoxification of carcinogens, suppression of tumors, lowering serum cholesterol concentrations, treating food allergies, synthesis of nutrients like folic acid, niacin, riboflavin, vitamins B_6 and B_{12}, increased nutrient bioavailability, improved urogenital health (Sanders, 1999; Markowiak and Śliżewska, 2017; Suvarna and Boby, 2005).

6. Applications

The use of prebiotics in recent years is more significant because we can avoid the drawbacks of using probiotic bacteria such as maintaining viability. By incorporating Prebiotics into a wider range of products and stable to heat treatment. Prebiotics and probiotics are now being used in combination, this being termed a '*symbiotic*' (Gibson et al., 2000).

Symbiotic can improve the survival of the probiotic organism by providing the specific substrate to the probiotic organism for its fermentation. The prebiotic oligosaccharides, they may enhance the colonic absorption of calcium and magnesium in food.

6.1. Food applications

Prebiotics can be extensively used in various types of food products including dairy, beverages and health drinks, infant formulae, meat products, animal feeds and as supplements. The prebiotic oligosaccharides are being widely explored and used as food ingredients especially in the European countries and Japan. Oligosaccharides have excellent functional properties and have obtained FOSHU [Foods of Specific Health Use] under Japanese legislation. They are being added along with probiotics in yogurt and other drinks to produce symbiotic products. Oligofructose is a sweet product obtained from inulin and it contains 30–60% sweet as sugar. In the market it is available as an oligosaccharide as because it contains most of fructose units with some glucose-terminated chains and is also available as a mixture form along with inulin in order to reduce the amount of non-glucose terminated chains. The unbound fructose chains have prebiotic properties and are mostly fermented by a variety of probiotic bacteria. Therefore, desirable in foods which require low sweetness in order to enhance the effect of other flavors. Also, because they are not digestible they can be used in foods consumed by diabetic people. They are hence being used in desserts, confections, and jams as low calorie, non-cariogenic sugar substitutes. In addition this, the bioactive prebiotics showed various applications which includes health benefits, stimulation of the viability of probiotics, epidemiological studies. (Crittenden and Playne, 1996; Sridevi et al., 2014; Younis et al., 2015; Carlson et al., 2018).

The oligosaccharides are strong inhibitors of starch retrogradation, which has made them useful to the dairy and baking industry. They are also used in toffee preparation, ice cream, jelly sweets, cereal-based foods, fiber-milk and infant food. Oligofructose in the food material has the ability to form a brown layer during baking which is an additional value to the product. Oligofructose produced from inulin by enzymatic hydrolysis using inulinase is used as a fat replacer. It has excellent mouth feel and sensory properties similar to vegetable oils and fats. Oligofructose as a functional food ingredient added in dairy products as well as bread which improves the growth of beneficial gut bacteria (Nakakuki, 1993; Franck, 2002; Nobre et al., 2015).

Inulin is generally used in various food products due to its texture and taste. They are used to improve mouth feel of a wide variety of foodstuffs, used as a sugar substitute, for stabilizing foam includes desserts, fermented dairy products, bakery products, and infant formulas. Inulin has glucose terminals and it mainly involves in stimulating the growth of *Bifidobacterium* in the large intestine. Due to its longer chain structure, inulin takes longer fermentation times that are required in the colon system. Inulinare absorbed better in large intestine than they would have been in the small intestine and this kind of activity showed beneficial in the prevention of osteopenia and osteoporosis (Younis et al., 2015).

7. Available products in the world market

A rapid growth of food industries across the globe is exploring the commercial opportunities for foodstuffs containing probiotics and prebiotics, either individually or in combination as symbiotic. The production of these food products has centered on health propositions such as lowering blood cholesterol, improving gut health and improving the body's natural defenses.

The use of probiotics and prebiotics are known to be in dairy products such as yogurt and other fermented products. However, the prebiotics application in baked products such as bread is also gaining popularity. Many companies, especially in the western world and the European countries have been producing and supplying prebiotics for the preparation of healthy foods. Some examples of prebiotics suppliers are Orafti [Belgium], Beghin-Say [France] and Cosucra (Markowiak and Śliżewska, 2017; Younis et al., 2015)

The following are the commercially available prebiotics are

RAFTILINE: It is a branded prebiotics produced by the Belgian company Orafti. Chemically it is inulin powder extracted mainly from chicory roots.

RAFTILOSE: This is also a product of Orafti. It is oligofructose used in various food applications.

ACTILIGHT: It is the commercial prebiotic manufactured by the French company Beghin-Say.

BENEO™ OLIGOFRUCTOSE: It is a product of Orafti. It is available in liquid or powder form and consists of oligofructose along with natural sugars like glucose, fructose, and sucrose in varying proportions.

BENEO™ SYNERGY1: This product of orafti is a unique combination of oligofructose and inulin mainly targeted to improve bone health.

BENEO™ INULIN: It is a mixture of oligo- and polysaccharides which are composed of fructose units connected by β-(2–1) links.

Commercially available products containing prebiotics.

Jour après jour: it is skimmed milk produced by the French company Lactel, containing the commercial prebiotic *Actilight*. It is known to improve gut health.

Low sugar sorbet: it is the product of the Thiriet Company, France. It contains the added prebiotic FOS and is found to improve gut health.

Bifielcontains GOS and is a product of Yakult, Japan (Kan et al., 1989).

Kelloggs launched a prebiotic cereal ***Rice CrispiesMultigrain***containing inulin, for children. It provides necessary nutrition, improves gut health and facilitates calcium absorption in children.

Warburtons' Healthy Inside is wholemeal bread added with the prebiotic inulin.

Ryvita goodness bar is a healthy cereal bar with rice crispies, pumpkin seeds, wholegrain rye, and dried fruits.

Fruit bowl prebiotic fruit 10ergy bar contains the natural prebiotic oligo-fructose and helps by stimulating the growth of beneficial bacteria in the gut, like *Bifido-bacteria*.

Biocare FOS is a powder formulation of FOS used along with yogurt, breakfast cereal or fruit juices. It is known to benefit health by suppressing the growth of harmful bacteria.

Newtree Purplaisir*chocolate spread* contains the commercial prebiotic *Beneo inulin* from chicory roots which boosts the growth of friendly bacteria in the gut and also stimulates calcium assimilation.

Several health drinks and athletic beverages have been incorporated with oligosaccharides. Korduner et al. have patented a general-purpose sports beverage containing oligosaccharides at the concentration of 20 g/L (Korduner et al., 1982). An international patent (Newsholme et al., 1988) for an instant beverage mix for athletes containing 0–750 g oligosaccharides per liter is held by a company called Pripps Bryggerier. The Wrigley Company of the United States has manufactured wax-free chewing gum incorporating oligosaccharides like FOS, isomaltose, and oligo-fructose which function as binders (Yatka et al., 1994). The British company Tata and Lyle has patented (Beyts, 1989) the use of gluco-oligosaccharides in a synergistic mixture of sweeteners used in dietetic foods, beverages, and confections. Hayashibara has patented the use of FOS in frozen desserts, sweetened condensed milk, ice creams, and other dairy products (Hayashibara, 1974).

Inulin is a soluble dietary fiber compound which is extracted from the chichory roots and incorporated in the meat products to study its effects and the results showed the positive effect on physiochemical properties and also improves the viability of gut microorganism (Ozturk and Serdaroglu, 2016).

The development of non-bovine milk-based dairy products have been introduced which is mainly a goat milk that acts as a probiotic carrier (Ranadheera et al., 2018)

8. Safety concerns

It is important to understand the nature of prebiotics and its role in the human body. The consumers should be aware of the dosage and selection of the prebiotic sources. The important criteria's that prebiotic based product should possess are, the product should get approval from government as generally recognized as safe for consumption (GRAS). The safe level of consumption should be established. The product should not contain any contaminants or impurities that affect human health (Anadón et al., 2016).

9. Conclusions

Prebiotics and probiotics are the highly acclaimed food ingredient/additive that gaining more importance in the field of preventive medicine and improve the life span of a human being. In human gastrointestinal tract, approximately about 10^{14} bacterial cells are present. The replacement of this bacterial community into probiotic bacteria through prebiotics leads to the improvement in human health.

In this review article, the preliminary results displayed on prebiotic effects are promising and some of the health claims that are mentioned about prebiotics are need to be verified by human trials (Simmering and Blaut, 2001). Most of the fruits and vegetables contain dietary fiber which is a source of prebiotics that promotes the gut bacteria which results in good health effect but a majority of people depend on processed foods. Knowing that the prebiotic oligosaccharides confer functional properties to processed foods, efforts should be made to increase fiber and non-digestible oligosaccharide content of popular foods to assist consumers in obtaining the recommended levels of prebiotics in the diet. In recent years, consumer awareness towards the health benefits of prebiotics and the demand in the market also increased. Active research is likely to create interest in the development of novel prebiotics in other countries all over the world. Further developments in the carbohydrate materials themselves are in progress and it is likely that more novel ingredients demonstrating new physiological effects will emerge over the next few years. At present, one of the largest emerging product in the market is symbiotic products containing probiotic *Bifidobacteria* and prebiotic oligosaccharides (Al-Sheraji et al., 2013; Anadón et al., 2016; O'Bryan et al., 2013; Simmering and Blaut, 2001). Prebiotic sources influence the growth of gut probiotic bacteria which clinically showed positive results on various diseases such as diarrhea, IBS and food allergies. The future study involves to know the effect of probiotic bacteria on the autoimmune diseases or to correct dysbiosis that might influence metaboloic disorders. In food industries, various prebiotic based non dairy products have to develop to improve human health.

Conflict of interest

The authors declare no conflict of interest.

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