Review Article

Role of dietary prebiotics in health management of infant microbiome

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Abstract: Prebiotics are a group of nutrients that are degraded by gut microbiota. Their association with human health has been an area of growing interest in modern years. They can nourish the intestinal microbiota, and their degradation products are short-chain fatty acids (SCFAs) that are free into blood circulation, affecting gastrointestinal tracts and distant organs. Fructo-oligosaccharides and galacto-oligosaccharides are the two important groups of prebiotics with beneficial effects on human health. Any food constituent that enters the large intestine is a candidate prebiotic. However, to be effective, selectivity of the fermentation is essential. Most current attention and success have been derived using non-digestible oligosaccharides.Various data have shown that fructo-oligosaccharides (FOS) are specifically fermented by bifidobacteria.The gastrointestinal microbiota of breast-fed babies differ from classic standard formula fed infants. Different prebiotic oligosaccharides are added to infant formula are galacto-oligosaccharides, fructo-oligosaccharide, polydextrose, and blends of these. There is indication that addition of prebiotics in infant formula modifies the gastrointestinal (GI) microbiota like that of breastfed infants. They are added to infant formula because of their occurrence in breast milk. Infants on this added formula have a lower stool pH, a better stool consistency and higher concentration of bifidobacteria in their intestine compared to infants on a non-supplemented standard formula.

Keywords: *Prebiotic; Oligosaccharide; Infants; Gastrointestinal tract; Mircobiome*

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1. Introduction

Prebiotics are non-digestible food ingredients that encourage the activity and growth of bacteria in the digestive tract which are valuable to human health. Prebiotic oligosaccharides are the third most prevalent component in mother's milk, and they are essentially absent in cow's milk. Human milk prebiotic oligosaccharides found to have a complex mixture of glycan compounds. It is well recognized that the gastrointestinal (GI) microbiota develop in a different way in breastfed and standard formula fed infants.Because of its extremely low risk of serious adverse effects, ease of administration and strong potential for influencing the composition and function of the microbiota in the gut and beyond, the valuable clinical uses of prebiotics are increasing. Prebiotics preparations including galactooligosaccharides (GOS), fructooligosaccharides (FOS),2'-fucosyllactose, lacto-N-neo-tetraose are some good examples of usually used and studied products for supplementation in baby formula. Conserving a well microbiome is vital to encourage homeostasis of the gut and other organs. With more than 1,000 diverse microbial species in the gut, it is prospective more possible to modify the gut microbiota with the use of positive prebiotic mixtures rather than supplementing with a particular probiotic strain.

2. DIET AND THE GUT MICROBIOTA

Diet is progressively recognized as a key environmental factor that can modulate the composition and metabolic function of the GI microbiota. The beneficial biological effect of diet on the microbiome is attributed to its prebiotic components. In human breast milk (HBM), these components are linked to the carbohydrate fraction of the milk and referred to as Human Milk Oligosaccharides (HMOs). Presently there are more than 200 molecules of HMOs that have been characterized with the amount and composition varying significantly between lactating women and over the course of lactation (McGuire et al., 2017; Garrido et al., 2011). These advances enable supplementation of infant milk formula with the goal of promoting gut microbiota composition and function that is similar to that of a breast-fed infant (Roberfroid et.,2010; Stewart et val., 2008]. Some development like galactooligosaccharides (GOS), fructooligosaccharides (FOS), 2'-fucosyllactose, lacto-N-neo-tetraose, inulin, oligofructose and galactofructose are examples of commonly used and studied products. Some food sources of prebiotics include xylo-oligosaccharides, which are polymers of sugar xylose, produced from plant fiber, and isomalto-oligosaccharides. These are a mixture of digestion-resistant short chain carbohydrates naturally found in some foods as well as commercially manufactured products. Several chemical compounds such as polyphenols and derivatives, carotenoids and thiosulphates, which can promote gut microbiota function and are therefore being explored as a treatment for obesity and inflammatory diseases in adults are now these phytochemicals are listed a good source of prebiotics (Rastall and Gibson , 2015)**.**

Dietary modulation of the gut microbiota

One important and well-established method for modulation of the gut microbial spc composition is through the use of live microbial dietary additions, such as probiotics. A WHO/FAO working party defined probiotics as ‘‘live microorganisms that, when administered in adequate amounts, confer a health benefit on the host’’ (United Nations Food and Agriculture Organization of the United Nations 2001, 2002).Some desired features of a good probiotic are as; exerts a beneficial effect when consume, mon-pathogenic and non-toxic, comprises a large number of viable cells, ability to survive and metabolise in the gut, maintains its viability during storage and use, in food, it should have good sensory qualities (Dunne et al. 2001).

An alternative method for microflora management through diet is the practice of prebiotics, which are involved towards genus level variations in the gut microbiota composition Prebiotics were first developed in order to induce beneficial changes in the gut microbiota and to overcome some of the survivability issues that arises with probiotics. In terms of microbiota modulation, the term prebiotic was first coined in the mid-1990s (Gibson and Roberfroid 1995), and defined as non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and activity of one or a limited number of bacteria already resident in the colon. Thus, the prebiotic approach supports a management of non-viable entities. The prebiotic concept reflects that many health promoting microorganisms are already present in the human colon.

Prebiotics are now defined as selectively fermented ingredients that allow specific changes, both in the composition or activity in the gastro-intestinal(GI) microflora that confer benefits upon host wellbeing and health (Gibson et al. 2004). Any dietary constituent that is non-digestible and enters the large intestine is a candidate prebiotic. Prebiotics includes polysaccharide- type carbohydrates such as resistant starch and dietary fibre, as well as proteins and lipids. However, current prebiotics are limited to non-digestible oligosaccharides, many of which appear to confer the degree of fermentation selectivity that is required. Oligosaccharides are carbohydrates comprising of three to nine monosaccharide units. Some prebiotics found naturally in several foods such as leeks, asparagus, chicory, Jerusalem artichokes, garlic, onions, wheat and oats as well as soybeans. Fortification of more frequently eaten foodstuffs with prebiotic ingredients is an effective route for health-promotion. Prebiotics are thus group of functional food ingredients that can be added to many foods as; yoghurts, cereals, breads, biscuits, milk desserts, ice creams, spreads, drinks as well as an animal feeds and supplements. Polysaccharides are usually obtained by extraction from crops, e.g. inulin from chicory or agave. Oligosaccharides can be commercially made through the hydrolysis of polysaccharides (e.g. oligofructose (OF) from inulin), or through catabolic enzymatic reactions from lower molecular weight sugars, e.g. short-chain fructooligosaccharides (scFOS) from sucrose and trans-galactooligosaccharides (TOS) from lactose.

Prebiotics and gut microbiota

Several resident gut microbiotas are present in humans, with varied number and composition of bacterial communities throughout the gut. Variability of gut microbes is mainly due to pH, transit time, and nutrient availability in the various regions of gut. The huge number of bacteria in the human body is present in the large intestine, where the accessibility of nutrients, anaerobic conditions, slow transit time and pH are favourable for microbial growth. Gut microorganisms have sufficient opportunity to degrade the available substrates, which may be derived from either the diet or by internal secretions (Cummings and Macfarlane 1991). Key substrates accessible for colonic fermentation are starches because of various reasons; they are found to resistant against action of pancreatic amylases and can bedegraded by bacterial enzymes. Other carbohydrate sources which are accessible for fermentation include oligosaccharides and portions of nonabsorbable sugars and sugar alcohols. In addition, proteins and amino acids can utilize as effective growth substrates for colonic bacteria, although some bacterial secretions, lysis products, sloughed epithelial cells and mucins may also make a contribution. These materials are degraded by a wide range of bacterial polysaccharidases, glycosidases, proteases and aminopeptidases to smaller oligomers and their component sugars and amino acids. Intestinal bacteria are then able to ferment these intermediates to organic acids, H2, CO2 and other neutral, acidic and basic end products (Gibson and Macfarlane 1995).

The activity and compositional status of the microbiota has a distinct impact on health and disease conditions through its involvement in pathogenesis and immune function of the host (Gibson and Roberfroid 1995). In terms of end products, several metabolites produce but some predominant are the short-chain fatty acids (SCFA) such as acetate, propionate and butyrate (Cummings 1995). Colonic bacteria can be characterized as beneficial or potentially harmful on the basis of their metabolic activities and fermented end products. An active health-promoting characteristics of the microflora may include immunostimulation, improved digestion and absorption, synthesis of vitamins, inhibition of the growth of potential pathogens, cholesterol reduction and lowering of gas distension.The equilibrium between species of resident bacteria influences the gastrointestinal (GI) health (Guarner and Malagelada 2003). Bifidobacteria and lactobacilli are considered to be best examples of health-promoting components of the microflora. Lactobacilli may aid digestion of lactose in lactose-intolerant individuals, reduce constipation and infantile diarrhoea, help resist infections caused by salmonellae, prevent traveller’s diarrhoea and help in irritable bowel syndrome (IBS; Salminen et al. 1998). Bifidobacteria are found to stimulate the immune system, yield B-vitamins, inhibit pathogen growth, reduce blood ammonia and blood cholesterol levels and also support to restore the normal flora after antibiotic therapy (Gibson and Roberfroid 1995; Guarner 2006).

Prebiotics

Human breast milk (HBM) is a complex fluid exclusively suited to nourish infants. Its composition is specifically adapted to the digestive system and suitable for nutritional and growth essentials of infants. HBM contain essential nutrients, as well as immense array of non-nutritional bioactive components and microbiota that deliberate benefits to the health of infants in the short and long terms. Mother colostrum is composed of oligosaccharide concentrations (15–23 g/L), whereas mature Human breast milk (HBM) contents range from 1 to 10 g/L. Most of these oligosaccharides are non-absorbable and reach the colon, and responsible for different functions. They compete with pathogenic bacteria and viruses for membrane receptors in intestinal epithelium. They contribute to acidification during fermentation in colon in presence of colon bacteria and inhibit the growth of bacteroides, clostridia, and coliforms. In this way they promote lactobacilli and bifidobacteria growth and stimulate the development of infant's immune system. Fermentation of prebiotics constituents by gut bacteria produces short-chain fatty acids (SCFA). SCFA apply a direct anti-inflammatory effect and stimulate intestinal barrier integrity by encouraging the proliferation and differentiation of gut mucosal cells.

3. MECHANISM OF ACTION OF PREBIOTICS

The mechanism of action of prebiotics is suggested to be largely due to secondary effects. This components action as a fuel source for selective fermentation by resident health-promoting microorganisms of the GI tract. These microorganisms are mainly involved in protecting against pathogens, to improve intestinal barrier function, boost immune pathways and influence brain function (Parnell and Reimer, 2012)**.** Short chain fatty acids (SCFAs) are the key end products of selective fermentation (Wasilewski et al., 2015).They help the direct effects of the prebiotics by providing an energy source to the gut epithelium. Short chain fatty acids (SCFAs) play an important part in local gene expression by improving availability to transcription factors, improving intestinal barrier by regulating the assembly of tight junction proteins, improving gut motility, metabolite absorption, sugar and lipid homeostasis and immune function (Fig.1). Prebiotics, such as GOS, can exert a direct antimicrobial effect by adhering to the binding sites of bacteria on the enterocyte surface and thus, block the adhesion of pathogenic bacteria to intestinal epithelial cells (Gibson et al., 2005; Shoaf and Mulvey, 2006).

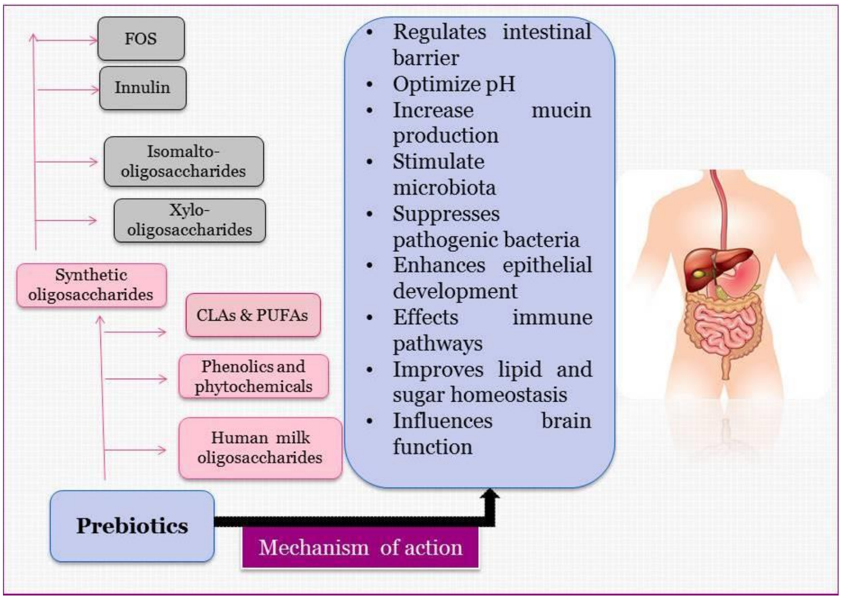

Fig 1 Mechanism of action and potential health benefits of prebiotics.

2. PREBIOTIC USE IN INFANTS

At the time of birth, the gastrointestinal (GI) tract is basically germ-free, with early microbial colonisation happening during birth or just later. The GI tract of new-borns baby is predominantly inoculated by organisms originating from the maternal microbial flora of the genital tract and colon, and also from the environment (Mountzouris et al.2002). The bacterial colony populations in infants grow during the first few days of life (Collins and Gibson 1999). An intestinal microflora rises as an effect of the intestinal physiology and diet pattern. The major differences in the composition and structure of the gut microflora have also been identified in response to infant feeding managements. The microflora of specifically breast-fed infants is ruled by populations of bifidobacteria in comparison to their formula-fed counterparts (Harmsen et al. 2000). Formula-fed infants have a more complex microbiota and predominant in bifidobacteria, bacteroides, lactobacilli, clostridia and streptococci (Harmsen et al. 2000). It is thought that the occurrence of certain glycoproteins and soluble oligosaccharides in human breast milk is responsible for stimulatory action for bifidobacteria and consider human breast milk is considering a classical prebiotic (Petschow and Talbott 1991). One key approach to strengthen the microbiological part of formula feeds has been to use prebiotics as stimulants for bifidobacteria and thereby purpose to improve the gut microbiota composition. Table 1 summarises some specific aspects of prebiotic use.

3. MODULATION OF THE GUT MICROBIOTA BY DIET

Number of current studies have emphasized the links between diet and distinct microbial profiles and, in turn, overall gut health (Turnbaugh et al., 2008). Having an understanding of how diet influences microbial communities will be of critical importance with respect to using food to positively modify the gut microbiota. The composition of the three chief dietary components, i.e. protein, carbohydrates and fat, has a intense impact on the gut microbiota. Short-chain fatty acids (SCFAs), primarily butyrate, propionate and acetate, are the common end products generate from the microbial degradation of protein and carbohydrates in the

Table 1. Studies of specific aspects of prebiotic in infants

S.No	Oligosaccharides used in experiments	Dose	Evidence of prebiotic efficacy	Reference
1.	Trans-galactooligosaccharides (TOS) and long chain fructooligosaccharides (FOS) (inulin)	4 g/L prebiotic/ formula or standard formula (no prebiotic)	Significant decrease in clostridia (FISH), trend of increased bifidobacteria and Escherichia coli,	Costalos et al. 2008

			higher stool frequency softer stools with respect to control group.	
2.	trans-galactooligosaccharides (TOS) and fructooligosaccharides (FOS) (inulin)	10 g/L prebiotic/ formula or standard formula	Significant reduction in gastrointestinal transit time and stool frequency, well tolerated.	Mihatsch et al. 2006
		8 g/L prebiotic/ formula (90% TOS), formula and simethicone (6 mg/kg)	Significant reduction in crying episodes after 7 and 14 days when compared with standard formula	Savino et al. 2006
		4.5 g/day prebiotic in weaning food or weaning food (no prebiotic)	Significant increase in bifidobacteria % (FISH) with prebiotic significantly different to control.	Scholtens et al. 2006
		8 g/L prebiotic/ formula (90% TOS); breast-fed control group	Real-time PCR analysis, similar flora composition between formula- and breastfed infan	Haarman and Knol 2006
3.	trans-galactooligosaccharides (TOS) and fructooligosaccharides (FOS)	8 g/L prebiotic/ formula; maltodextrin control	Significantly higher bifidobacteria with prebiotic when compared with control.	Moro et al. 2005
4.	trans-galactooligosaccharides (TOS) and polydextrose, lactulose	4 or 8 g/L prebiotic/ formula	Normal growth and stool characteristics similar to breast-fed infants.	Ziegler et al. 2007
5.	trans-galactooligosaccharides (TOS) and fructooligosaccharides FOS; Bifidobacterium animalis	6 g/L prebiotic/ formula; 6 — 1010 viable B. animalis/L formula; standard formula	Similar metabolic activity of the flora in TOS/FOS group as breast-fed, B. animalis group similar to standard formula	Bakker Zierikzee et al. 2005
6.	trans-galactooligosaccharides (TOS)	2.4 g/L prebiotic/ formula; formula; mixed (breast-fed and prebiotic formula)	Significant increases in bifidobacteria, lactobacilli and stool frequency in prebiotic and mixed groups but not the standard formula group	Ben et al. 2004
7**.**	Native inulin	0.25 g/kg/day native inulin	Inulin significantly increased lactobacilli and bifidobacteria, stool frequency was not affected.	Kim et al. 2007

FOS, fructooligosaccharides; FISH, fluorescent in situ hybridisation; TOS, trans-galactooligosaccharides

gut portion. SCFAs have a different physiological effects on the host to provide energy to mucosal cells. An exceptional publication related to the benefits of SCFAs on the host has been published by Macfarlane & Macfarlane (2012). The majority of microbial protein degradation occurs in the distal part of colon where the level of pH is found to neutral and this condition are very favourable for the growth of proteolytic bacteria such as Bacteroides spp., Clostridium perfringens and Propionibacterium spp.(Macfarlane et al., 1986). The main pathway of protein degradation is deamination of amino acids to the above-mentioned SCFAs and ammonia (Cummings, J. and Macfarlane 1991). The range of end products generated by protein digestion also includes branched-chain amino acids, phenols, indoles and amines. The major studies are focussed on the effect of dietary protein on the gut microbiota. They also addressed finding of altered fermentation products in the cecum and faeces. In one study indicated that there is a significantly higher count of bifidobacteria and lactobacilli in the faeces of rats if diets comprised of cheese whey protein isolate or casein supplemented with either amino acid threonine or cysteine. Use of whey protein isolate (WPI) has also been found to modify the composition of the gut microbiota of mice in a dose-dependent manner (McAllan, L. et al., 2014).

In presence of high fat diet it was found to significantly better proportions of Lactobacillaceae and significantly reduced proportions of Clostridiaceae compared to high-fat fed controls. Some constituents of the normal human carbohydrates diet cannot digested directly by the host and work as the major energy source from diet for microorganisms in the gut layer. This portion mainly comprised of resistant starches and non-starch polysaccharides which is degraded by microbial fermentation to a mixture of gasses and SCFAs. Many such types of carbohydrates are also categorised to as prebiotics. Prebiotics have most frequently used for stimulating the growth of either lactobacilli or bifidobacteria, with many studies focussing on inulin (Ramnani et al., 2010), oligofructose (Lewis et al., 2005) or fructooligosaccharides (Respondek et al., 2008). In one recent study, it was reported that if murine diet supplemented with SCFAs or fructooligosaccharides causes a shift in microbiota composition which correlated with valuable alterations in body weight, adiposity and glucose control. These physiological changes were brought about via butyrate- and propionate-mediated activation of intestinal gluconeogenesis (Gabert, L. et al.,2011). The majority of dietary fat is absorbed in the human small intestine and some amount also recovered in faeces.

The undigested slice passes through the colon where it can have a significant effect on the intestinal microbiota. Recently published study showed that life-long calorie restriction significantly altered the gut microbiota in mice fed on both high-fat and low-fat diets. This study suggests that fat content of the diet and number of calories consumed has the possible to influence the bacterial colonies present in the GI tract.There are many studies reviews the effect of dietary fat on the intestinal microbiota. This specific combination of dietary constituents can vary according to geographic location, food availability, cultural practices and age and can have an intense impact on the conditions within the gut and the requirements of the microbiota (Table 2) Specifically, a diet rich in protein and animal fat was associated with higher proportions of Bacteroides while Prevotella were more abundant when the diet was enriched with plant-derived carbohydrates. Some recent study indicate to the effect of diets composed entirely of animal or plants products on the gut microbiota. It discovered that an animal-based diet improved the numbers of bile-tolerant microorganisms present and reduced the numbers of plant polysaccharide degrading Firmicutes. Remarkably, the respective diets carried about a transcriptional response among the gut microbiota that was consistent with previously reported differences in gene abundances between herbivorous and carnivorous animals. These groups of bacteria are well-known for their capability to transform dietary fibre to SCFAs.

Table 2. Some examples of studies assessing the influence of diet on the microbiota and health of the host.

Diet	**Effect on host**	**Effect on microbiota**	**References**
Plant-derived polysaccharides (Rich source)	Faster gut transit time in comparison to high protein and animal fat diet	Increases the level of Bacteroidetes, decreases the level of Firmicutes.	De Filippo, C. et al. (2010) Wu, G.D. et al.

		Associated with Prevotella-rich enterotype	(2011)
High-fat and simple carbohydrate	Diet-induced obesity. Subsequent transplantation of obese microbiota to germ free mice increased adiposity	Increases the Firmicutes, decreases the Bacteroidetes	Turnbaugh et al., 2008
Low carbohydrate intake	Literature not available	Reduces Bifidobacterium, Roseburia spp. and Eubacterium rectale	Duncan et al., 2007
Animal product-based (high protein and animal fat)	Decreases the weight independent of calories consumed	Increases b-diversity and bile-tolerant bacteria (Bacteroides) Decreases Firmicutes Associated with Bacteroides-rich enterotype	Wu, G.D. et al. (2011)
Low level of fruit, vegetables and fish	Increases insulin resistance, fasting serum triglyceride levels, LDL cholesterol and inflammation	Reduces microbial gene richness	Cotillard, A. et al. (2013)
Limited variety due to long-stay care	Increases Bacteroidetes and reduced overall diversity	Increases frailty and poorer general health	Claesson, M.J. et al. (2012)
Shift from a vegetarian diet to an animal-based diet	Literature not available	Decreases Prevotella, increases Bacteroides	Wu, G.D. et al. (2011)

4. PREBIOTIC FORTIFIED INFANT FORMULAS AND MICROBIOTA DYNAMICS IN EARLY LIFE

Many environmental factors may affect GI microbiota composition as well as development during early life. The exposures during early life and linked GI microbiota perturbations have been linked with alterations in immune development prominent to possibly serious and lifetime health effects. Some earlier studies advocated that infants nourished formula were at higher risk of nutritional deficiencies, atopy, obesity, metabolic syndrome, coeliac disease, diabetes and other diseases, as compared to breastfed infants (Le Huerou-Luron et al., 2010). Some of the early life exposures cannot be avoided; however, the use of formula feeding is, at least in some cases, a choice made by the parents9. Over the last century, when formula feeding became more popular worldwide10, intensive research led to developing infant formulas that are increasingly similar to human milk with regard to nutrient composition and function. However, they are certainly not identical.

Human milk contains a wide range of compounds that modulate the infant intestinal microbiota. One of the prevalent and important groups of components are the human milk oligosaccharides (HMOs) that have unique nutritional and functional properties (Barile et al., 2013). The prebiotic function of breastmilk as source of growth factors for the “bifdus fora” was recognized more than a hundred years ago (Kunz and Egge,2016). Various studies confrmed that the GI microbiota of breastfed infants is dominated by bifdobacteria, as compared to formula fed infants, because of presence of HMOs in the human milk, and their absence in infant formulas (Kunz and Rudlof ,1993).

The wide usage of infant formulas and the increasing evidence for the importance of GI microbiota for health throughout life, it became very clear that the functional prebiotic properties of infant formulas needed to be considered seriously. In European countries the prebiotics contain commonly short chain galacto-oligosaccharides (GOS) only or mixed with a chicory root derived inulin having long chain fructo-oligosaccharides (FOS) (Efsa ,2014). Prebiotics mimic the bifdogenic effect of HMOs in human milk and have been associated with improved immunity, bowel function and other health benefting efects in infants. Though, the precise efect of these useful alternatives on the GI tract microbial biome, most importantly with respect to the dynamics of bacterial colonisation in early life, are not yet well understood and should be investigated.

Infant formulae supplemented with prebiotics

The European Scientific Committee on Food approved prebiotic supplementation in infant and follow-on formulate up to a maximum of 0.8 g/100 ml to a GOS: FOS ratio of 9:1. By contrast, a systematic review on the safety and health effects of prebiotic-supplemented infant formulae conducted by ESPGHAN Committee on Nutrition (Braegger et al., 2011) did not provide conclusive evidence due to variability in the type and dose of the prebiotic used and period of intervention. Potential Benefits in N 2′-flucosyllactose, a HBM oligosaccharide were recently synthesized and have been incorporated to some infant formula (Donovan et al., 2016). Safety Formulae fortified with prebiotics do not raise safety concerns with regard to growth and adverse effects (Braegger et al., 2011). Infant formulae containing HBM oligosaccharides have proven to be safe and well tolerated, and synthetic oligosaccharides have demonstrated to have similar effects to those of HBM oligosaccharides (Reverri et al., 2018). 2′-flucosyllactose, a HBM oligosaccharide, was recently synthesized and has been incorporated to some infant formula (Reverri et al., 2018).

5. ADVANCES IN FOOD PROCESSING WITH ADDED PREBIOTICS

The addition of prebiotics in commercial foods has become a viable and healthy alternative, since there is a great request of consumers for functional foods that can help in maintaining health. The food industry has advantages by the use of prebiotics in food products, such as enhancement of sensory characteristics, better nutritional composition and extended shelf life. In general, prebiotics are added to bakery products, breakfast cereals, beverages (e.g., fruit juices, coffee, cocoa, and tea), dairy products, table spreads, butter-based products, and desserts (ice cream, puddings, jellies, and chocolates) (Al-Sheraji SH et al., 2013; de Sousa et al., 2012). Several prebiotics also reported to have gelling properties (e.g., inulin), which maintain the emulsion stability, provide spreadable texture and water retention (e.g., inulin and FOS) in food matrix and , allowing the formulation of processed foods with low fat content, with pleasant taste and texture (Al-Sheraji SH et al., 2013).

In some important characteristics of the manufacturing process (pH, high temperatures, and conditions favoring the Maillard reaction) the selection of the prebiotic is always useful in order to avoid the formation of anti-nutritional compounds, hindrance of sensory quality of the final product and consumer health. Among prebiotics commonly used in the food industry, GOS are more stable at high temperatures and low pH. GOS have beta bonds in their structure, which offer more hydrolysis stability compared to FOS and inulin (Charalampopoulos and Rastall,2012).

6. EXPERIMENTAL EVIDENCES OF USE PREBIOTICS IN GROWTH

Growth parameters are important parameters for evaluation of prebiotic supplemented formulas. In comparison of prebiotic enriched to standard infant formula, there were no group differences found in growth rate between 14 to 120 d of age (Ashley et al.,2008).Discontinuation rates were not significantly different among study groups(Ashley et al.,2008). Tolerance of a formula enriched with FOS/GOS oligosaccharides was exceptional and there was no alteration in growth parameters was detected after 6 and 12 weeks (Costalos et al., 2008).A temporary increase in body weight was detected in children on use of prebiotics compared to controls during the first 6 months of follow up (Bruzzese et al., 2009)-.Prebiotics in formula increases the weight but had no influence on length or head circumference (Mugambi et al., 2012, Holscher et al., 2012. Application with a GOS/FOS mixture the growth parameters was normal and very similar to a standard infant formula (Arslanoglu et al., 2008). In the study of a multicentre, randomized, double-blind, placebo-controlled trial comprising 1130 well term infants indicated a similar mean weight, length and head circumference, skin fold thicknesses and arm circumference evolution in all infants. The skin thicknesses in the breastfeeding group at 8 weeks were amazingly higher than those in formula fed infants, whereas the opposite is true at 52 weeks (Piemontese 2011).Some systematic review and publications estimated the influence of prebiotics on growth during the first year of life and concluded that none of these trials showed a significant difference in growth parameters (Rao et al., 2009). Infants fed the added formula had a little better weight gain (Rao et al., 2009).

7. PREBIOTICS AND INFANT DISORDERS

There is evidence that infant formula comprising prebiotics is linked with less-consistent faces and a higher frequency of defecation (Vandenplas et al., 2014) . However, unpredictable indication has been also obtained on the association between prebiotics and the frequency of defecations (Mugambi et al., 2012). The usage of prebiotic-fortified formulae has been linked with a lower risk for intestinal and respiratory infections (Arslonoglu et al., 2008; Bruzzese et al., 2009). It was also found that prebiotic use increase the faecal secretory IgA levels (Scholtens et al., 2008). In general terms, there is no convincing evidence indicate that prebiotics_supplemented infant formulae applies any defensive effects against infections, colic, irritability, regurgitation and vomiting (Braegger et al., 2011). Fortification with prebiotic formula constituent 2′-flucosyllactose does seem to improve infant immunity, as it has been reported to be related to a lower incidence of infections, especially respiratory infections (Reverri et al., 2018).

GOS: FOS mixtures support the growth of *Bifidobacteria* and *Lactobacilli* in the faeces of infants using fortified formulae. However, an inadequate influence on the drop of pathogenic bacteria ((Vandenpla et al., 2014). However, some studies recommend that use of prebiotics diminish pathogenic micro-organism levels, if infant is getting a formula supplemented with oligosaccharides (Knol et al., 2005). A number of studies (Mugambi et al., 2012; Veereman-Wauters et al., 2011) have not able to explain that *bifidobacteria, lactobacilli,* or pathogen count decreases with prebiotics. Other studies have shown similarities between the bifidogenic effect of prebiotic-fortified formulae and HBM, as compared to non-fortified formulae (Sierra et al., 2015; Borewicz et al., 2019). Indeed, prebiotics have been reported to have special effects on some bifidobacteria species such as Bifidobacterium breve. Thus, faecal *Bifidobacterium breve* Levels in infants fed with a fortified formula have been known to be comparable to those found in breastfed infants. In some reports it was found that prebiotic-supplemented formulae can prevent eczema in infants at high risk of developing allergies (Arslonoglu et al., 2008; Moro et al., 2006), there is little evidence on the role that prebiotics play in the prevention of food hypersensitivity (Osborn and Sinn, 2007; Bozensky et al., 2015). A partially hydrolysed formula comprising specific prebiotics has been reported to generate a gut microbiota similar to that of breastfed infants.

8. CONCLUSION

Prebiotics are now recognized as a favourable therapeutic tool in the prevention and management for numerous diseases in children and for encouraging overall health. The significance of the intake of prebiotics is conclusive and they should be part of healthy diet. Prebiotics exert several scientific functions in food and many health benefits not only associated to the modulation of the intestinal microbiota but also to other valuable physiological actions. Prebiotics are developing as an immunoactive constituent that may possess the possibility of exerting long-lasting effects. This concept will further grow to cover future novel health possibilities applicable to any microbial community to achieve advantageous effects beyond the food and pharmaceutical domains. As technology advances, the development of curated prebiotic molecules with specific functional properties is an attractive and potential future achievement. In this sense, the development of foods added due to prebiotics by the industry can be advantageous due to the demand and profitability of this market, as well as for consumers who will have healthy foods available that can be readily consumed for the prevention or treatment of diseases, thus reducing public health costs. Both in vivo and in vitro models have helped advances of researches aimed at evaluating the prebiotic potential of foods through the composition and metabolism of the intestinal microbiota and their interactions. The advance in prebiotics was an addition of the probiotic idea for the management of gut microbiota. It has resemblances with dietary fibre functionality in that microbial fermentation of carbohydrate occurs

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