Review Article

Clinical uses of fructooligosaccharides for gastrointestinal health in the pediatric population

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ABSTRACT

Fructooligosaccharides (FOSs) are non-digestible carbohydrates that are one of the major classes of bifidogenic oligosaccharides. Studies find that prebiotics such as FOS display health benefits pertaining to but not restricted to the gastrointestinal (GI) tract of an infant. This review article aims to discuss the therapeutic potential of FOS for different pediatric gut conditions. FOS in varying concentrations has been found to prevent constipation and soften stools; reduce the incidence and severity of diarrhea; and alleviate GI discomfort symptoms such as vomiting and regurgitation. Infants and children seem to tolerate both short- and long-chain FOS molecules well. Although FOS is beneficial for infant and child health, there is still a need for rigorous clinical trials and long-term follow-up studies to understand if FOS supplemented in infancy can confer long-term effects in adulthood.

Key words: *Bifidobacterium,* Fructooligosaccharides, Gut health, Infant, Inulin, Oligofructose, Prebiotics

An infant's gut is colonized at birth by different microbiota which is influenced by numerous environmental and host factors. Infant feeding type is a major factor influencing gut microbiota composition and good gastrointestinal (GI) function [1]. Apart from water, omega-3 lipids, protein, and micronutrients; breast milk is rich in oligosaccharides which exhibit prebiotic properties [2,3]. The International Scientific Association for Probiotics and Prebiotics defines prebiotics as a substrate that is selectively utilized by host microorganisms conferring a health benefit [4].

This unique human milk prebiotic component is practically absent in cow's milk [2,3]. Infant formulas routinely uses plant-based prebiotics such as fructooligosaccharides (FOS), galactooligosaccharides (GOS), or polydextrose to mimic the ones present in human milk [3].

This review will enlist different prebiotics, with a focus on FOS for the infant gut microbiome. It will also discuss the therapeutic potential of FOS for different pediatric conditions.

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ABOUT FOS

FOS is called by different names such as fructans and oligofructose (OF) [5]. They are non-digestible carbohydrates that are one of the major classes of bifidogenic oligosaccharides [6]. They are naturally occurring short- or medium-chain fructose units that have a terminal glucose unit linked by β-(2-1) glycosidic bonds (Fig. 1). The length of the FOS chain ranges from 2 to 60. FOS cannot be digested by small intestinal enzymes because they are specific for α-glycosidic bonds. Hence, they are identified as prebiotics because they enter the large intestine with their structure unchanged, facilitating fermentation by beneficial *Bifidobacteria*. The by-products of fermentation release short-chain fatty acids (SCFA), mainly acetate, propionate, and butyrate. They are not excreted indicating that FOS is thoroughly and fully fermented by the gut bacteria [6,7].

They are compounds of vegetable origin and a normal diet contains many of these carbohydrates. For example, inulin-type of fructans is present in large amounts in chicory root, Jerusalem artichoke, and garlic [8]. Apart from these, they are also found in smaller amounts in cereals such as wheat. Bananas and tomatoes, are also some food sources of prebiotic fructans [7].

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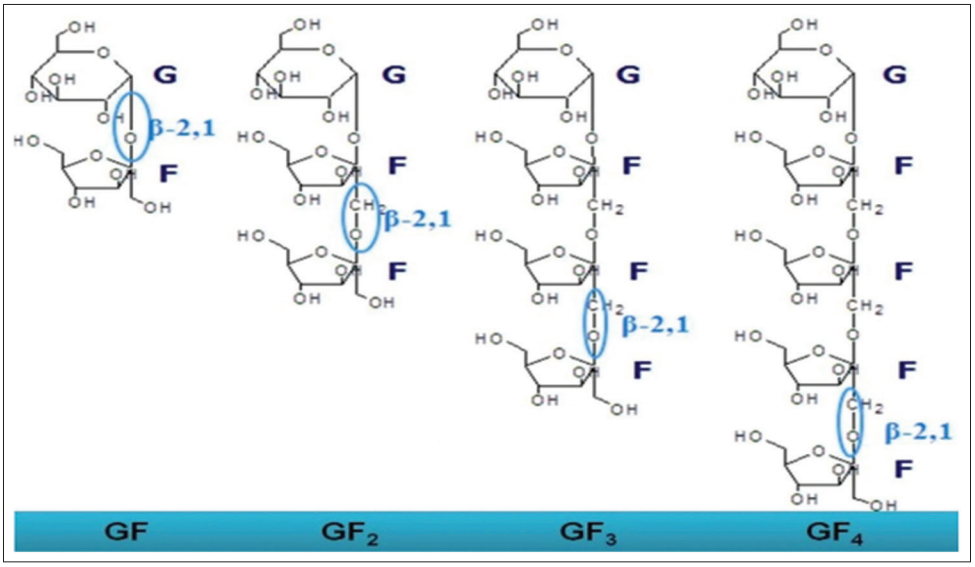

Figure 1: Chemical structure of FOS with the undigestible β-(2-1) glycosidic bonds highlighted

FOS can be divided into three categories based on their structural characteristics. Inulin is a generic term that covers all β-(2-1) linear fructans. Inulin has a polymerization degree of 2–60 monomers of fructose, with an average of 12 units; OF is a fraction of oligosaccharides with a degree of polymerization lower than 20. It is produced by the enzymatic hydrolysis of inulin. Short-chain FOS (scFOS) is another class of carbohydrates which are primarily comprised of fructose molecules of <10 monomers linked through β-1,2 bonds with terminal glucose monomers [7,9].

Production of FOS

FOS was first synthesized in 1982 with the help of enzymes derived from moulds or bacteria such as *Aspergillus niger* and *Lactobacillus bulgaricus* [5,10,11].

Inulin, a type of FOS, is produced from plants such as chicory roots or Jerusalem artichoke by extraction method in hot water. The extracted inulin is refined from sugars and starches using ion exchange technology and then it is spray dried to form inulin powder which then can be used as a supplement or can be further used for enzymatic FOS production [5,10].

sc-FOS, the other type of FOS, is naturally present in several plants and vegetables, but at a lower concentration. This makes their extraction from these sources time-consuming and difficult. Hence, sc-FOS is produced by the hydrolysis of inulin using endoinulinase enzyme [9]. Since FOS is widely found in foodstuff, humans have been traditionally ingesting FOS as a safe food ingredient. Hence, when acute and subacute toxicity tests of synthetically produced FOS were conducted on animals, they were found to be safe for consumption [10].

Metabolism of FOS by the Gut Microbiota

The human gut houses over 10 trillion bacteria belonging to the family *Bacteroidetes, Firmicutes, Proteobacteria,* and *Actinobacteria* among others [1]. Hence, the gut microbiota can be rightly called a "metabolic organ." It has a metabolic potential which could be similar to that of the liver. Fermentable carbohydrates such as FOS provide energy to these bacteria in a way that also modulates the composition and function of these microorganisms [11,12].

Fig. 2 shows the anaerobic fermentation of FOS which releases SCFA such as acetic, propionic, and n-butyric acids; gases such as carbon dioxide, hydrogen, methane, and biofactors such as amino acids and vitamins [10,12]. These SCFAs released from fermentation are immediately absorbed and converted to energy in the large intestine. Hydrogen released during the fermentation process is excreted through expiration [10].

MECHANISM OF ACTION OF FOS IN PROMOTING HEALTH

Diet is being recognized as an important indicator that has been shown to modulate the function and numbers of gut microbiota. Numerous studies find that prebiotics not only benefits the GI tract but also show far-reaching health benefits on the cardiovascular system, mental health, and bone [13].

The beneficial effects of the microbiota seem to be orchestrated by gut microbial activity. FOS once ingested passes the small intestine as it is and enters the cecum. It is here that it undergoes bacterial hydrolysis. The gut bacteria produce glycolytic enzymes which cleave the FOS into mono- or disaccharides. These are then transported to the interior of the cell where they are metabolized to SCFAs such as acetate, butyrate, propionate, L-lactate, carbon dioxide, and hydrogen [8]. After repeated ingestion of FOS, a large amount of SCFAs acidify the gut lumen to a pH lower than 7. This decrease in the pH suppresses the growth of pathogenic strains of bacteria whereas the beneficial strains, namely, *Lactobacilli* and *Bifidobacteria* flourish (Fig. 3) [10].

SCFAs, the byproducts of FOS fermentation, have been shown to have many health benefits. When produced in the colon, SCFAs act as an energy source for the gut epithelial cells. In addition, they

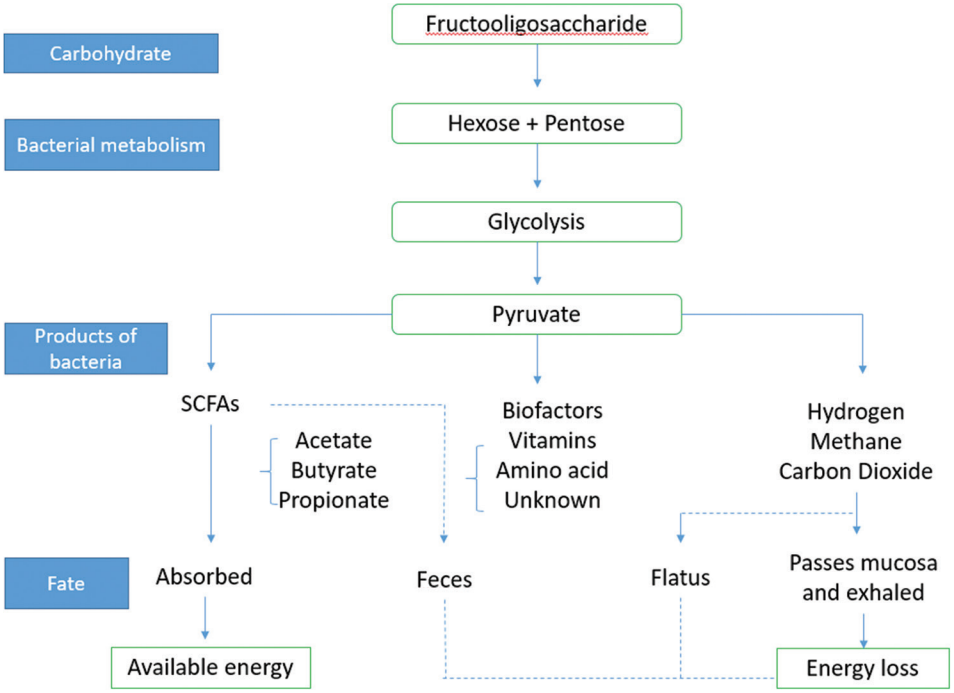

Figure 2: A flowchart depicting the metabolism by-products of FOS by gut microbiota

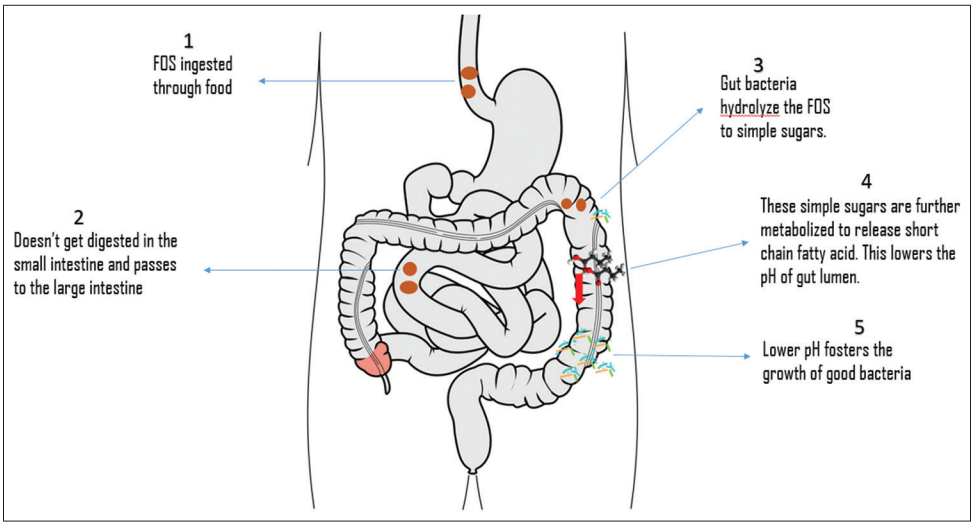

Figure 3: Diagrammatic representation of the mechanism of FOS for health

diffuse into the bloodstream wherein they have systemic benefits. In addition to these, SCFA has shown immunomodulatory properties such as influencing toll-like receptor-4 signaling and the production of pro-inflammatory cytokines [7]. This combined with the specific advantage of stimulating the growth of selective beneficial bacteria helps promote the health of the host [8].

MECHANISM BY WHICH FOS HELPS FOSTER SUBTLE INDICATORS OF GOOD GUT HEALTH

Several *in-vitro* studies have found that FOS such as inulin has been shown to increase the counts of *Bifidobacteria* and thus exert health benefits.

An abundance of *Bifidobacteria* in the infant's gut is considered a marker of good infant health. This marker is significantly different for adults and infants. For example, in adults, a less diverse gut bacteria denote a disease state whereas richness of microbial diversity would mean good health [1].

In infants, this is just the opposite. Low diversity of gut microbiota in addition to ample numbers of *Bifidobacteria* is associated with good health for infants. Higher diversity of other microbiota and low numbers of *Bifidobacteria* was seen in infants that showed colic, atopic dermatitis, and an increased risk of necrotizing enterocolitis development, obesity, celiac disease, and autoimmune diseases [1]. Studies find that the microbiota of breastfed infants is dominated by *Bifidobacteria* [14].

Bifidobacteria have been described to have saccharolytic features which means they can hydrolyze sugars. This quality helps these bacteria to make an important metabolic contribution to the host's health. They are effective in the degradation of

diet-derived glycans and host-provided carbohydrates. In addition to their metabolic activity, *Bifidobacteria* interact with the host immune system to elicit a pro-inflammatory response. This especially helps the immature neonatal immune system by aiding to development of immunological programming [1].

ROLE OF FOS IN DIFFERENT PAEDIATRIC CONDITIONS

Events in the early life of an infant help shape their gut microbiota and with it, their overall health and physiology. As outlined earlier, an abundance of Bifidobacteria in infants is associated with good health and FOS helps foster the growth of these bacteria beneficial for infant health. The health benefits of FOS for different pediatric conditions and their mechanisms are discussed.

FOS IN PREVENTING CONSTIPATION AND IMPROVING STOOL CHARACTERISTICS

Constipation is a frequent occurrence in children, accounting for 25% of visits to pediatric gastroenterology OPD. Constipation usually manifests when the child is transitioning to solid foods. Breastfeeding protects infants against constipation due to the presence of human milk oligosaccharides [15].

As per the 2011 European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) report, prebiotic supplementation of infant formula has the potential to decrease stool pH, increase stool frequency, soften stools, and increase stool colony counts of *Bifidobacteria* and *Lactobacilli* [16]. This effect was amply illustrated in the study that administrated 0.4 g inulin per 100 mL of formula meant for infants aged 3–5 months [17].

Souza *et al.* enrolled infants aged 6–24 months reporting constipation and assigned them to receive either FOS or a placebo in their formula for 4 weeks. The study group had a higher frequency of softer stools and fewer episodes of straining to pass stools. The counts of *Bifidobacterium* were also higher when compared to the placebo group [15].

Moore *et al.* enrolled infants aged 16.2–46.2 weeks with a mean age range of 32.5 weeks and supplemented them with 0.75–3 g of OF daily based on their age. They found that an average daily consumption of 0.75 g OF helped in softening the stools of infants [18]. Preschool children aged 3–6 years when given a dose of 6 g/d of inulin-type fructan showed softer stools along with increased counts of *Bifidobacterium* and *Lactobacillus* when compared to the placebo group given maltodextrin [19].

Studies have found that inulin-type fructans, added to infant and follow-on formula, promoted a bifidogenic effect, and softened stools [19,20]. The SCFAs produced in the colon and the resultant acidic environment were shown to increase the peristaltic movement facilitating defecation and also making the infant stool soft [10,14]. Repeated FOS intake was shown to accelerate defecation by increasing stool volume and frequency, increasing the counts of *Bifidobacteria* thus making stools softer, and reducing stool putrescence which in turn makes passing motions easier (Fig. 4) [10]. Thus, FOS helped promote a gut microbiome and stool characteristics that are closer to those of breastfed infants [19,20].

FOS IN REDUCING THE DURATION OF INFANTILE DIARRHOEA

Diarrhea if not treated can lead to mortality in children. Clinical studies examining the role of FOS seem to be favorable in alleviating diarrhea. When children in an urban slum in Bangladesh were given an isotonic solution containing 2 g of FOS daily for 6 months, it showed a reduction in the duration of diarrhea [10]. An Indonesian randomized and control trial study found FOS supplementation to shorten the duration of diarrhea. In the study, researchers supplemented 2.5–5 g/day FOS daily to 95 children aged 1–14 years and compared the effect to the placebo group. The children who consumed FOS reported these three major findings – shorter duration of diarrhea, a decrease in the production of putrefactive substances in the gut and a significantly reduced pH of the stools. These show that an increase in *Bifidobacteria* growth in the gut reduces putrefactive changes [21].

In another double-blinded, randomized, and controlled study, 0.55 g of OF per 15 g of infant cereals was given to healthy infants, aged 4–24 months, attending daycare. The study found that the addition of OF reduced the incidence of diarrhea, the severity of a diarrheal episode, and a general decrease in GI discomfort such as vomiting and regurgitation. OF was also better tolerated without any reported flatulence [22].

Notably, another study from Indonesia experimented with 3.2 or 4% of FOS among 6-month-old children and found fewer episodes of diarrhea and a reduction in the diarrheal episodes lasting <2 days [23]. Researchers tested the efficacy of adding 0.3 g of FOS to 1 liter of oral rehydrating solution (ORS) along with xylooligosaccharide in the same proportion and 1 mmol of zinc. This formulation of ORS seemed to reduce the duration of diarrhea without the need for any additional drugs. Researchers of these studies suggested that SCFAs such as butyrate in the colon have the same osmotic effect in the gut as that of glucose [23,24]. Toddlers in day-care given 2 g per day of OF for 3 weeks reported fewer episodes of diarrhea and emesis, less flatulence, and fewer infectious diseases that required antibiotic treatment [25].

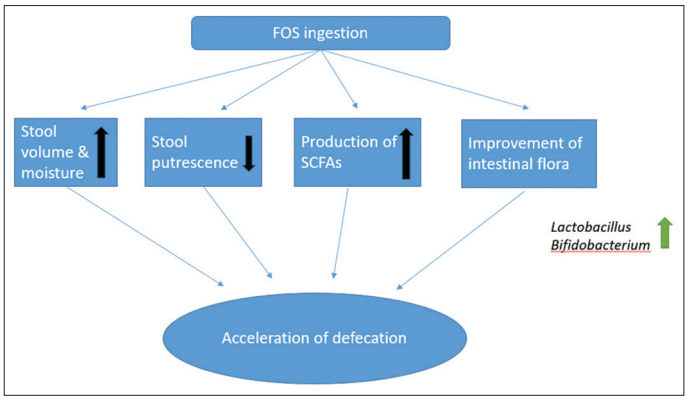

Figure 4: How FOS ingestion helps elimination

FOS seems to mediate these effects by improving the gut and the fecal microflora which in turn has been shown to improve the intestinal environment. This fosters the growth of beneficial microbiota such as *Bifidobacterium* and *Lactobacillus* (Fig. 5), also noted in numerous studies [10,21-25].

FOS IN PREVENTING OR REDUCING ANTIBIOTIC-ASSOCIATED DIARRHEA (AAD)

Studies have found that the intestinal microbiota is quantitatively and qualitatively altered by the use of anti-inflammatory nonsteroidal anti-inflammatory drugs, laxatives, and antibiotics. When given to infants for a long period of time, opportunistic pathogens such as *Klebsiella*, *Enterobacter*, *Pseudomonas*, *Candida*, and some species of *Clostridium* seem to grow in numbers. These pathogens then lead to the development of antibiotic-associated diarrhea [26].

In a study conducted by Brunser *et al.*, 140 children aged 1–2 years were getting treated with amoxicillin for acute bronchitis. The children in the experimentation group received 500 mL per day of a formula with OF or inulin for 3 weeks. The fecal sample is taken after antibiotic administration showed an increase in the counts of *Escherichia coli*. On supplementation, the prebiotics significantly increased the counts of *Bifidobacteria* and *Lactobacteria*. The children in the supplementation group did not show any GI symptoms [26]. However, an ESPGHAN study conducted among infants and children aged 6 months–11 years who were given antibiotics with 5 g per day of FOS and inulin failed to show any significant effect on AAD when compared to the placebo group. There is a need for further large-scale systematic studies to clearly elucidate the role of FOS in preventing AAD in infants and children [27].

Prebiotics such as FOS seem to mediate these benefits by increasing the counts of beneficial bacteria, exerting regulatory effects on functions of the colon, and increasing fecal bulk and water retention by increasing bacterial mass as they are a suitable substrate for fermentation [26].

FOS IN ACUTE INFECTIOUS GASTROENTERITIS (AGE)

AGE is defined as loose or watery diarrhea that consists of three or more bowel movements in a day. It can be accompanied by other symptoms such as nausea, vomiting, fever, or abdominal pain. These symptoms usually last for less than a week, most often improving after 1–3 days [28]. Among patients with severe AGE, a significant reduction in the microbial diversity of gut microbiota has been observed. Studies have found an abundance of coliforms, *Streptococcaceae, Enterobacteriaceae*, and *Pasteurellaceae* and a reduction in the numbers of *Bifidobacteriaceae, Clostridiaceae*, and *Lactobacillaceae* in the fecal analysis [29-31].

As mentioned earlier, prebiotics have been effective in preventing or treating diarrhea [16]. Modulation of the gut microbiota has been shown to modulate the severity of AGE. *In vitro* and *in vivo* studies have found good bacteria such as *Bifidobacterium* and *Lactobacillus* to produce antimicrobial substances such as bacteriocins, lactic acid, and nitric oxide; stimulate the production of antimicrobial peptides, mucin, and cytokines; and also activate the local adaptive and innate immunity [7-11,22-25,32].

FOS FOR IMPROVING MINERAL ABSORPTION

Childhood is an important period of time, characterized by rapid growth and development. Of the many beneficial physiological roles attributed to FOS, its influence on mineral absorption is of interest both in childhood and adulthood. Animal studies have found some stimulatory effects on the absorption of iron, zinc, calcium, magnesium, copper, and phosphorus [33].

Although a majority of the studies on the effect of FOS on mineral absorption were conducted in adolescents, there were two studies that included children. Castro *et al*. investigated the effect of 30 g of inulin with Vitamins A and C and minerals such as iron, zinc, and copper among 2–5-year-old children. At the end of the study, values for z-scores for weight and height, erythrocytes, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, and ferritin were significantly higher after intervention [34]. In another study, children with celiac disease were given OF-supplemented inulin at 10 g per day. By the end of the study, Vitamin D and E levels were significantly high, with Vitamin D reaching an optimal of 46% among supplemented children [35].

The authors opine that the presence of fermentable prebiotics such as FOS stimulates the growth of good gut bacteria that

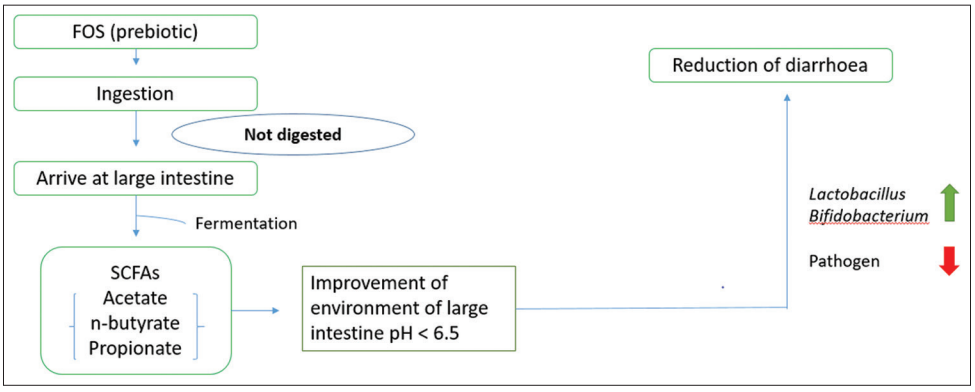

Figure 5: Mechanism by which FOS causes a reduction in the duration of diarrhea

facilitate the absorption of divalent cations. Gut bacteria also produce SCFA along with vitamins such as B3, B5, B6, B12, biotin, tetrahydrofolate, and Vitamin K. All of these together can help promote mineral absorption [36]. When it comes to calcium, FOS increases calcium absorption independently of intake because the acidification of the gut milieu makes calcium more soluble and more easily absorbable [26].

CONCLUSION

An infant's gut is colonized at birth with various microbiota by many factors playing a role. The abundance of certain bacterial taxa denotes good gut and overall infant health. FOS is one of the preferred prebiotics as it has been shown to promote the growth of two of the most beneficial gut bacteria, namely, *Bifidobacteria* and *Lactobacillus* in the infant.

The growth of these probiotic bacteria and their metabolites, namely, SCFAs have been identified as the main drivers of conferring protection against various gut-related conditions. Previously, reviewed studies have consistently found FOS to reduce the incidence and severity of diarrhea; alleviate GI discomfort symptoms such as vomiting and regurgitation; prevent constipation and soften stools. When it comes to tolerance, both short- and long-chain FOS molecules seemed to be well-tolerated by infants and children without displaying adverse GI problems, as also noted by the ESPGHAN committee.

However, there are some limitations – most of the studies had different age groups and different dosages of FOS used. Most of the studies included in the review only identified the changes in the fecal microbiota during the period of supplementation. Long-term follow-up of the participants was not carried out.

The reviewed literature showed that FOS helps foster good gut bacteria development thus alleviating common gut-related conditions in the infant. However, there is a need for rigorous clinical trials and long-term follow-up studies to understand if FOS supplemented in infancy can confer long-term effects in adulthood.

CONTRIBUTION DETAILS

All authors contributed to the content of the manuscript. All authors read and approved the final manuscript.

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