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for dairy nutrition and health

Publication on the health effects of 2'-FL

Human breast milk is known to be associated with a number of health benefits¹⁻⁴, with recent evidence suggesting that many of these benefits are likely to be associated with human milk oligosaccharides (HMOs).⁵

Studies indicate that HMOs may play an important role in maintenance of health and prevention of disease.⁵ One important and abundant HMO, 2'-fucosyllactose (2'-FL), has been investigated in a number of studies, with recent studies in human infants showing supplemental 2'-FL to be well tolerated with promising signs of efficacy.^{6,7}

The composition of HMO (types and quantity of various oligosaccharides) in human milk is influenced by maternal genetics, environmental factors and lactation stage.^{8,9}

The concentration of major HMOs in human milk, except 3-FL, decreases during lactation.^{10,11} A study in Chinese women found that 2'-FL levels decreased from 2.5 g/L to 1.2 g/L during the first 6 months of lactation;¹⁰ another study followed HMO levels in breast milk of Malaysian women up to 1 year of lactation, and found the level of 2'-FL drops from 2.2 g/L at the start to 0.8 g/L after 1 year of lactation.¹¹

Table 1: Concentrations of major HMO in human milk¹²⁻¹⁵

Categories of HMO	Categories of HMO (% total)	Mean oligosaccharides	Mean concentration (range), g/l
Neutral	Fucosylated (35-50%)	2'FL	2.7 (1.88-4.9)
		3'FL	0.5 (0.25-0.86)
		LNFP I	0.122 (0.106-0.145)
		LNFP II + III	0.156 (0.120-0.161)
		Nonfucosylated (42-55%)	LNnT
Acidic	Sialylated (12-14%)	3'SL 6'SL	0.2 (0.1-0.3)

2'-FL, 2'-fucosyllactose; 3-FL, 3-fucosyllactose; 3'-SL, 3'-sialyllactose; 6'-SL, 6'-sialyllactose; HMO, human milk oligosaccharides; LNFP, lacto-N-fucopentaose; LNnT, lacto-N-neotetraose.

Health benefits of 2'-FL

Effects on gut microbiota and infections

Studies suggest that 2'-fucosylated oligosaccharides, among which 2'-FL, drive colonization of the infant gut with bifidobacteria.¹⁵⁻¹⁸

(Figure 1) *In vitro* studies have shown that 2'-FL can be used as a substrate by bifidobacteria in the gut, thereby stimulating their growth.¹⁶⁻¹⁷ In addition, clinical association studies indicate that infants receiving breast milk lacking 2'-FL show delayed establishment of bifidobacteria in the gut.¹⁵⁻¹⁸ These data suggest that 2'-FL plays an important role in shaping a healthy gut microbiota composition early in life.

Stimulating growth of bifidobacteria

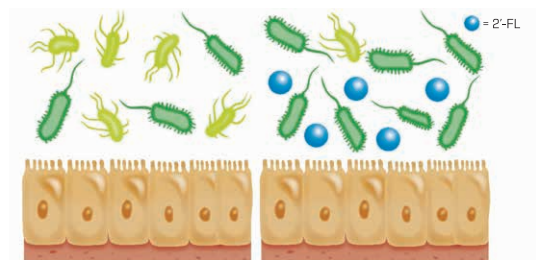


FIGURE 1. By serving as a substrate, 2'-FL gives bifidobacteria a competitive advantage for growth in the gut.^{15,16}

In vitro studies showed that 2'-FL can inhibit enteric (e.g. norovirus, EPEC, *Campylobacter*, *Salmonella*) and respiratory pathogens (*Pseudomonas aeruginosa*) from adhering to human epithelial cell lines.¹⁹ Another study showed 2'-FL reduced the infectivity of human rotaviruses, an effect that was attributed to interaction directly between the oligosaccharide and the virus.²⁰ **(Figure 2)**

Reducing risk of infections (anti-microbial and anti-viral activity)

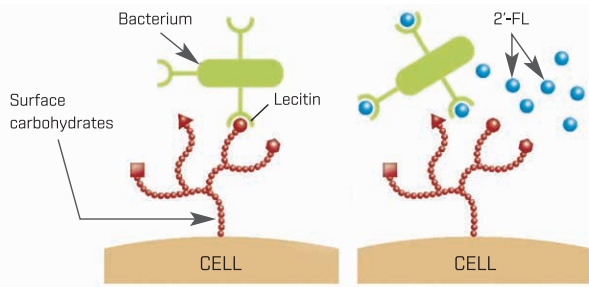


FIGURE 2. By serving as a decoy receptor, 2'-FL can inhibit binding and infectivity of pathogens.

High levels of 2'-FL in breast milk have been shown to be protective against diarrhoea associated with specific pathogens.¹² More specifically, rates of *C. jejuni* diarrhoea during breastfeeding were shown to be inversely associated with 2'-FL as a percentage of milk oligosaccharides. Compared with infants fed milk with medium and high levels of 2'-FL, infants receiving milk with low levels of 2'-FL had significantly higher rates of *Campylobacter* diarrhoea during breastfeeding. Overall, a significant inverse association was found between total 2-linked fucosylated oligosaccharides as a percentage of HMO and rates of all moderate-to-severe diarrhoea during breastfeeding.

Effects on allergy

An animal study on food allergy revealed that 2 HMOs—neutral 2'-FL and acidic 6'-sialyllactose—led to significant attenuation of intestinal allergy.²¹ Additional evidence for a role of HMOs in allergy comes from an association study conducted in infants at elevated risk of allergic disease, with results showing that eczema was more likely at age 2, but not at age 5, among those born by C-section who received milk lacking in 2'-FL.²² It needs to be noted, however, that a recent study did not find such an association between 2'-FL level in human milk and cow's milk allergy risk in infants.²³

Anti-inflammatory effects of 2'-FL

Evidence also suggests that HMOs, especially 2'-FL, may have anti-inflammatory effects.²⁴ A study on necrotizing enterocolitis (NEC) showed that rats receiving HMOs with their formula had an average pathology score that did not differ from disease-free rats, and was significantly lower than the standard formula-fed NEC controls.²⁴ Addition of 2'-FL alone to formula was also associated with significantly lower pathology scores than those in the formula-fed rats, but pathology scores remained higher than those in the disease-free rats and in the HMO group. Although these results look promising, it has to be noted that another recent animal study did not show an effect of 2'-FL on NEC development. In a preterm piglet model, 2'-FL supplementation had no effect on intestinal structure and digestive function, and no effect on NEC incidence.²⁵ A recent

association study showed that the DSLNT (disialyl-lacto-N-tetraose) content in human milk is associated with a reduced risk of NEC development in preterms, not the 2'-FL content.²⁶ These results suggest that other HMOs may play a more important role in NEC prevention.

Effects on cognition

Preclinical studies have also demonstrated that 2'-FL is able to enhance memory and learning;^{27,28} rats fed 2'-FL had increased long-term potentiation at the hippocampus. Moreover, there was evidence in these animals of enhanced memory consolidation, spatial learning and associative learning.

Clinical studies show 2'-FL safe, well-tolerated

While much of the evidence for the health benefits of 2'-FL comes from *in vitro* and *in vivo* studies, there is also a number of clinical studies involving children and adults that showed the first evidence of both good tolerability and potential efficacy of 2'-FL supplementation.^{5,7,29,30}

In a study involving 420 infants, 2'-FL supplementation (0.2 or 1.0 g/L) was found to be well-tolerated.⁷ Post-hoc analysis on this study revealed that infants receiving 0.2 g/L 2'-FL had a significantly reduced incidence of respiratory infections as compared to the control group.⁷ This effect was not seen in the group receiving 1.0 g/L 2'-FL.³¹ In a further analysis of the same study, the effect of 2'-FL on plasma inflammatory markers was examined. Compared with infants who received the control formula, those who received 2'-FL-containing formula had significantly lower plasma inflammatory cytokines, which resembled closely the levels found in breastfed infants.²⁹ In another multi-center, randomized, double-blind trial, 2 parallel groups of formula-fed infants received control formula or formula supplemented with 2'-FL and lacto-N-neotetraose (LNnT).⁶ 2'-FL and LNnT were shown to be safe, well-tolerated and to support age-appropriate growth. Moreover, secondary outcome findings of lower morbidity (particularly bronchitis) and medication use (antipyretics and antibiotics) were reported in infants fed supplemented formula. Also, this study showed that the addition of 2'-FL and LNnT to infant formula shifted the stool microbiota towards that observed in breastfed infants, both in composition and function.³²

Recently, 2 short tolerance trials with formula containing 2'-FL were reported in infants.^{31,33} Both of the 1 month-studies showed that a formula supplemented with 2'-FL was safe and well tolerated. In addition to these studies in infants, a randomized, double-blind, placebo-controlled study examined the effect of HMO supplementation in healthy adults (2'-FL, LNnT or their combination). When given at daily doses of up to 20 g for 2 weeks, 2'-FL and LNnT were safe and well tolerated. Furthermore, HMO supplementation led to modifications in gut microbiota: in this study, 2'-FL increased actinobacteria and *Bifidobacterium*, and more specifically increased *Bifidobacterium adolescentis*.³⁰

To conclude, current clinical evidence on the benefits of 2'-FL looks promising. It is expected that additional studies will be performed in the near future to try and confirm the beneficial effects of 2'-FL on

microbiota composition, infection and inflammation, cognition and allergy prevention that were observed in preclinical studies.

Key points

- Early clinical trials indicate that 2'-FL is safe and well tolerated.^{6,7,29,30,31,33}
- Preclinical and human association studies suggest that 2'-FL may contribute to:
 - Reduction of infections^{12,19,20}
 - Stimulation of healthy gut microbiota (prebiotic effect)¹⁵⁻¹⁸
 - Reduction of the risk of developing allergy^{21,22}
- Currently, there is limited evidence available from clinical studies in infants on the health benefits of 2'-FL:
 - 1 g/L 2'-FL (in combination with LNnT) may reduce lower respiratory tract infections and medication use⁶
 - 1 g/L 2'-FL (in combination with LNnT) may stimulate a healthy gut microbiota^{6,32}
 - 0.2 g/L 2'-FL may reduce respiratory infections, whereas 1.0 g/L 2'-FL may not^{7,31}

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Important note

Breastfeeding is the best nutrition for healthy growth and development of babies. Exclusive breastfeeding for six months is the optimal way of feeding infants. Thereafter infants should receive complementary foods with continued breastfeeding up to two years or beyond. Mothers should receive guidance on proper maternal nutrition in order to help sustain an adequate supply and quality of breast milk. Unnecessary introduction of bottle-feeding, partially or fully, or of other complementary foods and drinks may have a negative impact on breastfeeding, which may be irreversible. Mothers should consult their doctor and consider the social and financial implications before deciding to use breast milk substitutes or if they have difficulty breastfeeding. Usage, preparation and storage instructions of breast milk substitutes or of other complementary foods and drinks should be followed carefully as improper or unnecessary use may pose a health hazard.

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