

Research Advances on Functional Oligosaccharides and Their Alleviation of Allergic Reactions in Organisms (Postprint)

Authors: Chang Meinan, Zhu Yaru, Zhao Yuan

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Abstract

Functional oligosaccharides are a class of prebiotics possessing dual physiological characteristics of dietary fiber and bifidogenic factors, constituting an important component of prebiotics. This article summarizes the classification and composition of functional oligosaccharides, with emphasis on their physiological functions and research progress in alleviating allergic responses, aiming to provide a reference for further development of oligosaccharide prebiotics for the prevention and treatment of allergic diseases.

Full Text

Research Progress on Functional Oligosaccharides in Alleviating Allergic Reactions and Their Mechanisms

CHANG Meinan, ZHU Yaru, ZHAO Yuan*

(Jilin Provincial Key Laboratory of Animal Nutrition and Feed Science, Key Laboratory of Animal Production, Product Quality and Security, Ministry of Education, College of Animal Science and Technology, Jilin Agricultural University, Changchun 130118, China)

Abstract: Functional oligosaccharides are a class of prebiotics with dual physiological characteristics of dietary fiber and bifidus factor, and constitute an important component of prebiotics. This review summarizes the classification and composition of functional oligosaccharides, with emphasis on their physiological functions and research progress in alleviating allergic reactions, aiming to provide a reference for further development of oligosaccharide prebiotics for preventing and treating allergic diseases.

Keywords: functional oligosaccharides; physiological function; allergic reaction; immunity; gut microbes

In recent years, food and feed allergies have become increasingly prevalent, posing a serious threat to human and animal health. Common allergens include milk, eggs, nuts, seafood [1], wheat protein [2], soy protein [3], and ovalbumin (OVA) [4]. Research indicates that after oral ingestion or contact with these allergens, both immediate-type hypersensitivity reactions mediated by specific antigens and antibodies and delayed-type hypersensitivity reactions mediated by T lymphocytes can occur. Immediate-type hypersensitivity reactions have a higher incidence rate and are primarily mediated by immunoglobulin E (IgE), leading to the release of active substances such as histamine from mast cells and basophils. This results in symptoms including skin erythema, gastrointestinal discomfort, reduced digestive capacity, vomiting, and diarrhea, which can even be life-threatening and seriously affect human health and livestock production efficiency [5].

Therefore, eliminating or mitigating allergic reactions is an urgent issue for food and feed safety. Traditional approaches have employed processing techniques to inactivate allergens in food and feed ingredients, such as heat treatment, high-pressure extrusion [6], and fermentation [7]. Additionally, using novel natural anti-allergic active substances to prevent and treat allergic reactions has emerged as an effective approach and is gradually becoming a new research focus. Current relevant studies have investigated compounds such as lipoic acid [8], herbal medicines and their extracts [9], probiotics [10], and prebiotics [11].

Functional oligosaccharides are chemical prebiotics that can alter the composition of host intestinal microbiota, promote the proliferation of *Bifidobacterium*, optimize intestinal flora, and serve as active dietary supplements. They have been applied as food and feed additives in functional health foods and animal feed. Appropriate amounts of functional oligosaccharides can enhance immune and barrier functions, although studies on their alleviation of food and feed allergies remain limited. Therefore, investigating the anti-allergic efficacy and mechanisms of functional oligosaccharides is of utmost significance for developing novel food and feed additives.

1 Classification and Composition of Functional Oligosaccharides

Functional oligosaccharides, also known as functional oligosaccharides, benefit both human and animal immune systems and intestinal health, exhibiting anti-cancer properties and regulating immune-active substances. They are widely distributed in plants, algae, bacteria, and higher fungi, and have been applied in numerous fields including nutrition, medicine, feed, cosmetics, immunostimulants, and prebiotic components [12]. Commonly used functional oligosaccharides include fructooligosaccharides (FOS), galactooligosaccharides (GOS), mannan oligosaccharides (MOS), maltooligosaccharides, isomaltooligosaccharides, soybean oligosaccharides, stachyose, raffinose, chitosan oligosaccharides, and

gracilaria oligosaccharides, as well as arabinooligosaccharides, lactosucrose, glucooligosaccharides, and gentiooligosaccharides. The chemical composition of functional oligosaccharides is presented in Table 1 .

Table 1 Chemical composition of functional oligosaccharides[12-15]

Type	Monosaccharide Composition	Functional Glycosidic Bonds	Degree of Polymerization
Fructo-oligosaccharides	Sucrose, fructose	-1,2	2-10
Galacto-oligosaccharides	Mannose, glucose	-1,2, -1,4	2-10
Mannan-oligosaccharide	Mannose, glucose	-1,2, -1,3, -1,6, -1,3, -1,4	2-10
Glucose-oligosaccharides	Glucose, N-acetylglucosamine	-1,2, -1,3, -1,6	2-10
Human milk oligosaccharides	Glucose, galactose, N-acetylglucosamine	-1,2, -1,3, -1,4, -2,3, -2,6, -1,3, -1,4	3-10
Gentio-oligosaccharides	Mannose, glucose	-1,6	2-7
Malto-oligosaccharides	Galactose, fructose, glucose	-1,2, -1,4	2-10
Isomalt-oligosaccharides	Glucose	-1,6	2-10
Xylo-oligosaccharides	Xylose	-1,4	2-10
Soybean oligosaccharides	Galactose, fructose, glucose	-1,4	3-4
Stachyose	Galactose, fructose, glucose	-1,2, -1,4	4
Chitosan oligosaccharides	Glucosamine, N-acetylglucosamine	-1,6	2-10
Raffinose	Galactose, fructose, glucose	-1,4	3
Arabinooligosaccharides	Arabinose, galactose	-1,5	2-10
Arabinooligosaccharides	Arabinose, xylose	-1,4	2-10

Type	Monosaccharide Composition	Functional Glycosidic Bonds	Degree of Polymerization
Lactulose	Galactose, fructose	-1,2, -1,3, -1,4	3

2.1 Promoting Probiotic Proliferation

Functional oligosaccharides can improve the structure and composition of intestinal microbiota and selectively promote the proliferation of probiotics such as *Bifidobacterium*. *Bifidobacterium* provides excellent health benefits and is the only functional beneficial microorganism in the intestine that does not produce toxins or cause pathogenicity. Humans and animals lack the enzymes to hydrolyze functional oligosaccharides, allowing these compounds to directly enter the large intestine where they are preferentially utilized by *Bifidobacterium*, significantly promoting their proliferation [12]. When used in animal feed, functional oligosaccharides can inhibit the colonization and growth of pathogenic bacteria, increase the diversity of intestinal microbiota [16], and enhance the growth rate, production performance, and immune function of livestock and poultry [17].

2.2 Enhancing Immunity

Functional oligosaccharides can serve as immune stimulants, promoting the growth of intestinal immune cells and increasing the content of serum immunoglobulin A (IgA), immunoglobulin M (IgM), immunoglobulin G (IgG), and interleukin-2 (IL-2), thereby enhancing both humoral and cellular immune functions. After entering the intestine, oligosaccharides competitively bind to lectins on the surface of pathogenic bacteria, preventing their adhesion to intestinal epithelial cells. Simultaneously, oligosaccharides promote intestinal peristalsis, facilitating the excretion of pathogenic bacteria with feces and reducing intestinal damage [18]. Furthermore, oligosaccharides promote the massive proliferation of beneficial bacteria such as *Bifidobacterium* in the intestine, which possess immune-activating properties that enhance the phagocytic activity of macrophages and lymphocytes and induce cytokine production. These beneficial bacteria produce short-chain fatty acids (SCFAs) such as acetic acid and butyric acid in the intestine, lowering intestinal pH, acidifying the intestinal environment, and shortening the contact time between pathogenic substances and the intestinal mucosa, thereby regulating immune responses [19].

2.3 Promoting Mineral and Nutrient Absorption and Laxation

After reaching the body, functional oligosaccharides are fermented and decomposed by microorganisms, releasing mineral ions and promoting the absorption

of calcium and iron ions while increasing their solubility, which facilitates mineral absorption by the cecum and colon [20-21]. The microbial fermentation process also produces vitamins required by the body and promotes the absorption of nutrients such as lipids and proteins [22]. Additionally, after being utilized by *Bifidobacterium*, functional oligosaccharides produce large amounts of SCFAs that enhance intestinal peristalsis, thereby promoting laxation [23]. As feed additives, functional oligosaccharides function similarly to antibiotics, improving animal growth, fattening, and milk production while reducing ammonia content in feces.

3 Research on Functional Oligosaccharides in Alleviating Allergic Reactions

In animal models, research on functional oligosaccharides alleviating allergic reactions remains limited, with most studies focusing on prevention rather than treatment. The most extensively studied oligosaccharides include FOS, GOS, GOS/inulin prebiotic mixtures, and MOS. These oligosaccharides primarily alleviate allergies through three mechanisms: regulating immune function, enhancing intestinal mucosal barrier function, and improving gut microbiota balance.

3.1 Regulating Immune Function

The immune and intestinal microbiota systems of early young animals are not fully developed, exhibiting complexity and diversity that make them susceptible to allergic diseases triggered by external allergens. In healthy organisms, the functions of T helper lymphocyte (Th cell) subsets Th1 and Th2 maintain a dynamic balance that preserves cellular and humoral immune functions [24]. Th1 cells primarily secrete IL-2, interferon- γ (IFN- γ), interferon- γ (IFN- γ), and tumor necrosis factor- α (TNF- α), participating in inflammatory immune responses. Th2 cells mainly secrete interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), and interleukin-10 (IL-10), stimulating B lymphocyte proliferation and generating large quantities of IgE and IgG antibodies [25]. Immediate-type hypersensitivity reactions are more common in food antigen-induced allergies in humans and animals, manifesting as Th1/Th2 immune imbalance in allergic individuals. Therefore, Th1/Th2 balance plays a crucial role in allergic reactions.

Studies have demonstrated that functional oligosaccharides can prevent and treat allergies by inducing immune-related factors and subsequently influencing immune balance. GOS/inulin prebiotic mixtures can increase IFN- γ , TGF- β , and IgA levels in perinatal and post-weaning mice, with significant elevation of IL-10, IgA, and IgG2a expression in the small intestine of mouse pups [11,26]. GOS/inulin mixtures can also increase fecal *Bifidobacterium* populations, substantially elevate serum IgG1, IgG2, and IgG3 levels, and significantly reduce the incidence of allergic diseases in infants, with long-lasting effects [27-29]. Gracilaria oligosaccharides can significantly reduce serum-specific IgE and IgG1 levels while increasing IgG2a levels in sensitized mice, inhibit Th2 cytokines [IL-

4, IL-5, interleukin-13 (IL-13)], and promote Th1 cytokine (IFN- γ) expression [30]. MOS may bind to receptors on intestinal mucosal epithelial cells to stimulate lymphocytes, promote serum IgA, IgG, and IL-10 release, and reduce serum TNF- α levels, thereby regulating immune function in livestock and poultry [31-33]. These immune responses demonstrate that functional oligosaccharides can effectively regulate immunoglobulins and certain cytokines, restoring Th1/Th2 cell balance and exhibiting preventive and therapeutic effects on allergic reactions, particularly during critical periods such as gestation, parturition, and lactation, when they exert significant immunomodulatory effects.

Functional oligosaccharides can also enhance immunity by improving mast cell degranulation. Fujitani et al. [34] found that FOS reduced the number and edema rate of duodenal mast cells in OVA-allergic mice. Vonk et al. [35] fed whey-sensitized mice with FOS and observed effective alleviation of acute allergic reactions and mast cell degranulation, prevention of specific IgE elevation, and reduced T cell responses, ultimately improving oral immune tolerance in mice. Additionally, functional oligosaccharides can affect the immune system by increasing serum galectin-9 levels [36].

3.2 Enhancing Intestinal Mucosal Barrier Function

The intestinal mucosal barrier comprises four components: mechanical, chemical, immune, and biological barriers, with damage to any component jeopardizing health [37]. The barrier function confines bacteria and endotoxins within the intestinal lumen, preventing their translocation to peripheral organs. Increased intestinal epithelial cell permeability exposes the mucosa to large quantities of antigens from food or bacteria in the lumen, stimulating immune excitation and causing intestinal inflammation that leads to various gastrointestinal diseases and allergic reactions. Research indicates that multiple gastrointestinal diseases and intestinal inflammation caused by food and feed allergies are associated with intestinal mucosal barrier damage [38]. As microecological agents, oligosaccharides promote the proliferation of beneficial intestinal bacteria, improve intestinal wall permeability, and help maintain intestinal mucosal barrier function.

Functional oligosaccharides prevent and treat allergic reactions by enhancing intestinal mucosal barrier function through three primary aspects: intestinal mucosal morphology, mucosal permeability, and tight junction proteins. Prebiotic oligosaccharides and probiotics can influence intestinal mucosal morphology and structure in broiler chickens and piglets by improving gut microbial balance, thereby exerting protective effects on mucosal integrity in the jejunum and colon [39-40]. Plasma diamine oxidase (DAO) is an enzyme with high activity in the cytoplasm of intestinal mucosal epithelial cells of all mammals but low activity in other tissues. When the intestinal mucosal system is damaged, DAO enters peripheral blood, increasing intestinal mucosal permeability. GOS can affect intestinal mucosal permeability by influencing DAO activity. Furthermore, GOS may improve tight junctions and maintain intestinal mucosal barrier function by

regulating mRNA levels at the transcriptional stage and increasing transmembrane protein (occludins) content [41]. Functional oligosaccharides can induce intestinal epithelial cells to produce protective substances such as heat shock proteins (HSP) and epithelial mucin (MUC) through tight junction proteins and secrete SCFAs to regulate intestinal mucosal barrier function. Gourbeyre et al. [26] found that mice fed GOS/inulin prebiotic mixtures showed increased propionate content in cecal contents and elevated HSP-25, zonula occludens-1 (ZO-1), and mucin 2 (MUC-2) levels in the jejunum.

3.3 Improving Gut Microbiota Balance

The intestinal microbiota constitutes a dynamic microecosystem that prevents invasion by exogenous food antigens and pathogenic bacteria, participates in the metabolism of intestinal epithelial cells, regulates immune mechanisms, and facilitates nutrient digestion and absorption from feed. Prebiotic oligosaccharides serve as exclusive nutrients for intestinal probiotics, being selectively utilized by beneficial bacteria after entering the body to increase their population and diversity. Once beneficial bacteria become dominant, they inhibit the colonization of harmful bacteria, stabilizing the intestinal environment, protecting intestinal health, and achieving the goal of allergy prevention and treatment. Watanabe et al. [42] fed Balb/c mice a diet containing FOS, which promoted *Bifidobacterium* proliferation in the intestine and reduced contact hypersensitivity induced by 2,4-dinitrofluorobenzene. Exogenous supplementation with oligosaccharides (GOS, FOS) and beneficial bacteria (*Lactobacillus*, *Bifidobacterium*) can significantly increase microbial metabolic activity in the avian intestine and reduce colonization by harmful bacteria such as *Salmonella* [43-44]. GOS can effectively improve intestinal microbiota structure and microbial balance in piglets, regulating intestinal defense systems [40].

Microbial flora plays a crucial role in immune response regulation and intestinal barrier function. Many beneficial bacteria can interact with small intestinal epithelial cells, dendritic cells, Th1 cells, and Th2 cells to regulate immune responses by stimulating B lymphocytes to produce IgA, which then binds to antigens and inhibits their entry into epithelial cells [45]. After microbial fermentation, functional oligosaccharides form SCFAs that participate in immune responses and barrier protection, indirectly preventing allergic diseases. Studies have shown that SCFAs can reduce pro-inflammatory cytokine levels, including interleukin-10 (IL-10), IL-6, and TNF- α , while increasing the anti-inflammatory cytokine IL-10 [46-47]. SCFAs can also induce intestinal epithelial cells to secrete interleukin-18 (IL-18), MUC, and antimicrobial peptides, strengthening tight junction structures and maintaining intestinal mucosal barrier integrity [48-49]. Butyrate can serve as a regulator recognizing histone modification acetylation, improving small intestinal barrier function through tight junction proteins in intestinal epithelial cell models [50]. After infants consume formula containing oligosaccharides, fecal *Staphylococcus* and *Streptococcus* decrease while microbiota richness and diversity (particularly *Bifidobacterium*) increase, fecal acetic

acid, propionic acid, and butyric acid levels rise, and eczema incidence decreases [51].

4 Summary

In summary, allergic reactions damage intestinal structure, disrupt microbiota, and severely impair intestinal barrier systems and immune function. As a class of non-toxic prebiotics, functional oligosaccharides not only alter the richness and diversity of intestinal microbiota but also significantly enhance immune mechanisms and intestinal barrier function, thereby exerting preventive and therapeutic effects on allergic reactions. Functional oligosaccharides have broad application prospects in food and animal feed, with various types already used as food and feed additives to improve growth performance in humans and animals. However, most anti-allergy research has focused on mice and humans, with relatively few studies in livestock and poultry, indicating a need for further investigation in this area. Existing research on food allergies has primarily addressed immune enhancement, intestinal barrier function, and microbiota balance, but due to the complex mechanisms of allergic reaction onset and alleviation, current understanding remains incomplete, and allergies continue to pose a major challenge to human and animal health.

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