Chapter 15

Exploring the Impact of Prebiotics on Gut Microbiota in the context of Atopic Diseases

Kainat Sarwar[1*], Sidra Altaf[2], Zahwa Arshad Rana[3], Khadija Saif[4], Tuba Sahar[5] and Tasawar Iqbal[6]

[1]Department of Epidemiology and Public Health, University of Agriculture, Faisalabad, Pakistan
[2]Department of Pharmacy, University of Agriculture, Faisalabad, Pakistan
[3]Department of Epidemiology and Public Health, University of Agriculture, Faisalabad, Pakistan
[4]National Institute of Food Science and Technology, University of Agriculture, Faisalabad, Pakistan
[5]National Institute of Food Science and Technology, University of Agriculture, Faisalabad, Pakistan
[6]Institute of Physiology and Pharmacology, University of Agriculture, Faisalabad, Pakistan
*Corresponding author: dietetian.upgrade.01@gmail.com

ABSTRACT

The gut microbiota, consisting of hundreds of defined bacterial species, plays a crucial role in modulating the immune system and maintaining gut health. However, alterations in the gut microbiota, known as this dysbiosis, increases susceptibility to allergic reactions and have a link with atopic diseases. Prebiotics which would promote the growth or activity of the beneficial bacteria in the gut have been studied for their role in modulating gut microbiota and reducing their risk of atopic diseases. Prebiotics can be obtained from various dietary sources and added as supplements to infant formulas and dietary products. Evidence suggests that prebiotic supplementation in infants and adults may positively influence the gut microbiota composition and activity, potentially reducing the risks of allergic disorders. However, further research is needed to establish definitive conclusions regarding the long-term benefits of prebiotics in reducing the incidence of atopic diseases. This aims to explore the relationship between gut microbiota, dysbiosis and atopic diseases, highlighting the potential role of prebiotic in preventing and managing these conditions. By understanding the complex interplay between the gut microbiota and the immune system, we can develop targeted interventions to restore gut microbiota balance and alleviate the burden of atopic diseases.

KEYWORDS	Received: 21-May-2024	A Publication of
Prebiotics; Gut Microbiota; Dysbiosis; Atopic Diseases; Atopic Dermatitis	Revised: 12-Jul-2024 Accepted: 04-Aug-2024	Unique Scientific Publishers

Cite this Article as: Sarwar K, Altaf S, Rana ZA, Saif K, Sahar T and Iqbal T, 2024. Exploring the impact of prebiotics on gut microbiota in the context of atopic diseases. In: Liu P (ed), Gut Heath, Microbiota and Animal Diseases. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 119-126. https://doi.org/10.47278/book.CAM/2024.253

INTRODUCTION

Atopic Disease

"Atopy" is from Greek word 'Atopia' means 'out of place'. Atopic disease refers to a hereditary tendency to bring forth immunoglobulin E (IgE) antibodies in result to small amounts of environmental protein e.g. pollen, house dust mite and food allergens. Atopic diseases are prevalent worldwide, affecting individuals of all ages and ethnic backgrounds and reached an epidemic proportions during past industrializing era (Thomsen, 2015). At least 171 million individual were affected with atopic dermatitis (Faye et al., 2023). The prevalence varies across regions and is influenced by genetic, environment, climate, exposure to allergens and lifestyle factors. In 2019, 418 million cases were reported per year (Logoń et al., 2023).

The atopic diseases like atopic dermatitis often begin in infancy and early childhood. Asthma and allergic rhinitis may manifest at any age, with different patterns observed in childhood, adolescence and adulthood (Gray et al., 2017). Family history, genetic predisposition, environment, obesity, stress, allergic sensitization, paracetamol use, tobacco smoke, cesarean section, respiratory virus infection, occupational exposures, diet, obesity, air pollution and breastfeeding and mental health are risk factors of atopic diseases. Factors during pregnancy, modes of birth and early childhood, such as maternal age, maternal smoking, exposure to tobacco smoke, and early introduction of certain foods, may progress towards atopic diseases (Lin et al., 2022). Limited exposure to microbes and infections during early childhood, often associated with increased hygiene and reduced family size, may contribute to a higher risk of atopic diseases (Faye et al., 2023).

Gut Microbiota

The gut microbiota, consisting of hundreds of defined bacterial species, plays a crucial role in modulating the immune system and maintaining gut health. However, alterations in the gut microbiota, known as this dysbiosis, increases susceptibility to allergic reactions and have a link with atopic diseases.

Prebiotics which would promote the growth or activity of the beneficial bacteria in the gut have been studied for their role in modulating gut microbiota and reducing their risk of atopic diseases. Prebiotics can be obtained from various dietary sources and added as supplements to infant formulas and dietary products. Evidence suggests that prebiotic supplementation in infants and adults may positively influence the gut microbiota composition and activity, potentially reducing the risks of allergic disorders. However, further research is needed to establish definitive conclusions regarding the long-term benefits of prebiotics in reducing the incidence of atopic diseases.

This aims to explore the relationship between gut microbiota, dysbiosis and atopic diseases, highlighting the potential role of prebiotic in preventing and managing these conditions. By understanding the complex interplay between the gut microbiota and the immune system, we can develop targeted interventions to restore gut microbiota balance and alleviate the burden of atopic diseases.

Beneficial Effects of Prebiotics

Atopic diseases are complex conditions characterized by immune dysfunction and inflammation. Recent studies have shed light on the significant influence of the gut microbiota on the pathogenesis and severity of atopic diseases, including atopic dermatitis, asthma, and allergic diseases (Muir et al., 2016). The gut microbiota plays a key role in grooming and modulating the immune system, and exposure to a diverse range of microbes during early life contributes to the development of immune tolerance (Kunst et al., 2023). Dysbiosis, or the dis-regulation of the microbiome, potentially leads to an increased susceptibility to various health problems (Dahiya and Nigam, 2023). Inadequate microbial stimulus causes an imbalance in the gut microbiota, resulting in a persistent Th2-dominant immune response and atopy (Rø et al., 2017). Dysbiosis has been observed in individuals with atopic dermatitis, and may influence the development of respiratory allergies and asthma through complex interactions with the immune system (Pantazi et al., 2023). Atopic dermatitis in infants progresses due to a lack of immune system modulation in the gut microbiota (Cukrowska, 2018). Patients with atopic disease have reduced gut microbiota diversity (Candela et al., 2012). The intestinal microbiota of atopic children has increased Clostridium and reduced Bifidobacterium compared to non-atopic children (Kalliomäki et al., 2001). An appropriate gut microbiome and its intestinal metabolites act as a protective factor for patients (Stec et al., 2023). Understanding the interplay between atopic diseases and gut microbiota is crucial for developing targeted therapeutic interventions (Donald and Finlay, 2023).

Prebiotics

Prebiotics promote the growth of beneficial gut microbiota by improving gut barrier function, enhancing immune response, regulating host metabolism, and reducing the risk of allergies (Markowiak-Kopeć and Śliżewska, 2020). They are abundant in human milk, superior meal for good species, and prevent the adhesiveness of pathogens. Long-term use of prebiotics improves immune function, lowers inflammatory cytokines, improves digestion, and produces SCFAs (Alderete et al., 2015). By boosting the growth of beneficial bacteria, prebiotics can create an environment difficult for the maturation of pathogenic bacteria, lowering the risk of infections and imbalances in the gut (Zhou et al., 2024). Diet plays an important role in shaping gut microbiota, and a lack of essential nutrients and diet diversity leads to dysbiosis and other health issues (Piccioni et al., 2023). Diet can modify intestinal microbial diversity and improve its function (Li et al., 2014). Diet supplemented with prebiotics can be used to balance gut microbiota (Scott et al., 2013). Prebiotics can be obtained from dietary sources as shown in table 1 (Khan et al., 2023).

Table 1: Prebiotics Dietary sources

Fruits	Mango, orange, green banana (resistant starch), strawberries, blue berries and raspberries, papaya pulp, apples (pectin), kiwi
Vegetables	Garlic (inulin), onions (inulin, FOS), asparagus (inulin), leeks, bamboo shoots, gourd (5 families), leafy green vegetables, mushrooms
Whole grains	Oatmeal, whole oats (beta-glucan), barley (beta-glucans and soluble fiber), whole wheat bread and whole wheat pasta, quinoa (fiber), corn
Legumes	Chick peas (fiber, resistant startch), lentils green beans (soluble fiber), kidney beans (red), lima beans, cow beans, soy beans,
Nuts and seeds	Flaxseeds (soluble fiber, alpha-linolenic acid), chia seeds (soluble fiber) , fenogreek seeds, almonds (soluble and insoluble fiber), walnuts , cashew apple, chest nut and defatted coconut residues
Root vegetables	Sweet potatoes (fiber, resistant starch), carrots (soluble fiber), chicory roots.
Miscellaneous	Jerusalem artichokes (inulin), dandelion greens (inulin), seaweed like nori and kombu (prebiotic fibers), olive oil,
Dairy Food	Yogurt (inulin), kefir,
Spices	Cinnamon, cayenne pepper, black pepper, turmeric, rosemary, editerranean oregano
Honey	Oligosaccharides

Prebiotics Impact on Gut Microbiota Modulation

Prebiotics and certain dietary interventions may have prophylactic or therapeutic effect (Logoń et al., 2023). Prebiotics helps in manufacturing of short-chain fatty acids, lowering pH in colon, stimulation of mucus production, selective growth of beneficial bacteria, enhancing nutrient absorption, anti-inflammatory effects and modulation of immune responses (Roberfroid et al., 2010). The gut microbiota assists in the development of immune tolerance, healthy bacteria maintain gut health, immunity, integrity and homeostasis (Mishra et al., 2023) allowing immune system to differentiate between a-toxic substances and possible threats. This is crucial for preventing unnecessary allergic for autoimmune responses. Gut bacteria produces different metabolites, such as short-chain fatty acids (SCFAs), that have anti-inflammatory attributes (Maslowski et al., 2009). These metabolites can modulate immune cell activity and contribute to a balanced immune response. The SCFAs anti-inflammatory effects and maintain epithelial function (Maslowski and Mackay, 2011).

Prebiotics helps stimulating in microflora activity, gut microbiota diversity and maintaining normal gut health (Shirsath and Zawar, 2024). Prebiotics promotes beneficial bacteria by selective fermentation, microbial fermentation and produce SCFAs that act as nutrient source for beneficial bacteria. They selectively enhance development of certain probiotic bacteria in colon, esp. *Bifidobacteria* species (Liu et al., 2024).

Inulin helps in promoting the growth of gut bacteria, improves digestion, reduce inflammation, reduce blood cholesterol level, and increases blood sugar level (Slavin, 2013). The FOS improves gut health, reduces risk of colon cancer, improves mineral absorption and enhances immunity (Sabater-Molina et al., 2009), beta-Glucan Improve gut health (Davani-Davari et al., 2019), Pectin Improve digestion, reduce inflammation (Jackson et al., 2007), and XOS reduce inflammation, improve mineral absorption, enhance immune function (Aachary et al., 2015).

Once in the colon, prebiotics like inulin and oligosaccharides are fermented by the enzymes of gut bacteria, specifically by healthful bacteria like *Bifidobacteria* and *Lactobacilli*. The fermentation process of prebiotics produces short-chain fatty acids such as acetate, propionate and butyrate along with gases like hydrogen, methane and carbon dioxide. They help to maintain a somewhat acidic environment of colon, which suppress the growth of noxious bacteria and pathogens while promoting the growth and activity of beneficial bacteria (Zhou et al., 2024).

The SCFAs improves nutrient absorption and are energy sources for colonocytes in particular butyrate (Mishra et al., 2023), serves as a favored energy source for colonocytes (colonic epithelial cells), promoting their health, integrity and enhance the production of mucins (the proteins that make the protective mucus layer in the gut) (Song et al., 2023). The mucins play crucial role in keeping the integrity of mucosal barrier, providing protection against pathogens and prevent inflammation. This strengthen the gut barrier function, permeability reduction and prevents the translocation of harmful substances from the gut into the bloodstream (Ney et al., 2023). Prebiotics in the colon promotes the proliferation of beneficial bacteria, which can have various positive effects on health, including enhanced nutrient absorption, improved gut barrier function, immune system modulation, and potential reduction in inflammation (Peredo-Lovillo et al., 2020).

Upon prebiotics fermentation by gut bacteria produces short-chain fatty acids including butyrate, propionate and acetate. The SCFAs have immunomodulatory effects and maintains immune system balance (Kim, 2023).

Evidence of Prebiotics Supporting in Atopic Disease

Prebiotics and certain dietary interventions may have a prophylactic or therapeutic effect (Logoń et al., 2023). Prebiotics help manufacture short-chain fatty acids, lower pH in the colon, stimulate mucus production, selectively grow beneficial bacteria, enhance nutrient absorption, and have anti-inflammatory effects and modulate immune responses (Roberfroid et al., 2010). The gut microbiota assists in the development of immune tolerance, and healthy bacteria maintain gut health, immunity, integrity, and homeostasis (Mishra et al., 2023), allowing the immune system to differentiate between harmless substances and possible threats.

Gut bacteria produce different metabolites, such as short-chain fatty acids (SCFAs), which have anti-inflammatory attributes (Maslowski et al., 2009). These metabolites can modulate immune cell activity and contribute to a balanced immune response. SCFAs have anti-inflammatory effects and maintain epithelial function (Maslowski and Mackay, 2011).

Prebiotics stimulate microflora activity, gut microbiota diversity, and maintain normal gut health (Shirsath and Zawar, 2024). Prebiotics promote beneficial bacteria by selective fermentation, microbial fermentation, and produce SCFAs that act as a nutrient source for beneficial bacteria (Liu et al., 2024).

Inulin helps promote the growth of gut bacteria, improves digestion, reduces inflammation, reduces blood cholesterol level, and increases blood sugar level (Slavin, 2013). FOS improves gut health, reduces the risk of colon cancer, improves mineral absorption, and enhances immunity (Sabater-Molina et al., 2009). Beta-Glucan improves gut health (Davani-Davari et al., 2019), while Pectin improves digestion and reduces inflammation (Jackson et al., 2007).

Once in the colon, prebiotics like inulin and oligosaccharides are fermented by the enzymes of gut bacteria, specifically by healthful bacteria like bifidobacteria and lactobacilli. The fermentation process produces short-chain fatty acids such as acetate, propionate, butyrate, along with gases like hydrogen, methane, and carbon dioxide. These help maintain a somewhat acidic environment in the colon, which suppresses the growth of noxious bacteria and pathogens while promoting the growth and activity of beneficial bacteria (Zhou et al., 2024; Peredo-Lovillo et al., 2020).

SCFAs improve nutrient absorption and are energy sources for colonocytes, particularly butyrate (Mishra et al., 2023), which serves as a favored energy source for colonocytes, promoting their health, integrity, and enhancing the production of mucins (Song et al., 2023). Mucins play a crucial role in keeping the integrity of the mucosal barrier, providing protection against pathogens and preventing inflammation. This strengthens the gut barrier function, reduces permeability, and prevents the translocation of harmful substances from the gut into the bloodstream (Ney et al., 2023).

Prebiotics in the colon promote the proliferation of beneficial bacteria, which can have various positive effects on health, including enhanced nutrient absorption, improved gut barrier function, immune system modulation, and potential reduction in inflammation (Peredo-Lovillo et al., 2020). Upon prebiotics fermentation by gut bacteria, short-chain fatty acids, including butyrate, propionate, and acetate, are produced (Kim, 2023). SCFAs have immunomodulatory effects and maintain immune system balance.

Research Indicating Therapeutic Effect of Prebiotic on Atopic Diseases

Moderate evidence is available for prebiotic supplementation to reduce the risk of eczema in high-risk children (Sestito et al., 2020). A shift from healthy gut microbiota to gut microbiota dysbiosis can lead to conditions like atopic dermatitis and allergic diseases (Pantazi et al., 2023). Prebiotics, probiotics, and synbiotics can be used to restore gut microbiota balance and manipulate it like healthy gut microbiota (Sestito et al., 2020).

Human milk contains 200 Human Milk Oligosaccharids (HMO), which induce tolerance and stimulate gut microbiota (Oozeer et al., 2013). Infants who are breastfed have a reduced risk of atopic dermatitis (Lodge et al., 2015). Studies have shown that short-chain galactooligosaccharides (ScGOS) and long-chain fructooligosaccharides (lcFOS) mixtures have prebiotic activities and create a similar gut microbiota to breastfed infants (Knol et al., 2005; Rinne et al., 2005).

Randomized Controlled Trials (RCTs) analyzing prebiotics in children have shown long-term benefits for the prevention of atopic eczema and common infections in healthy infants (Thomas, Greer, Bhatia, et al., 2010). Prebiotics like XOS and Red ginseng Extract (RGE) have been shown to improve the Firmicutes/Bacteroidetes ratio, increase beneficial bacteria, and lower harmful bacteria, helping to restore gut microbiota health distorted by antibiotics (Ibáñez et al., 2018).

Studies Exploring Therapeutic Effect of Prebiotic on Atopic Diseases

However, a comprehensive review of studies shed light on the potential benefits of prebiotic supplementation in infants' reveals varying positive outcomes. Boehm et al. (2002) found that adding oligosaccharides to preterm infants formula increased *Bifidobacteria* levels significantly similar to breast fed infants. Moro et al. (2002), conducted a study on term infants at high risk of atopy and founded that prebiotic supplementation significantly reduced the incidence of atopic dermatitis at 6 months of age. Schmelzle et al. (2003), reported good tolerance and no adverse effects when prebiotics were added to infant formula in a multi-center trial. Scholtens et al. (2006) found that adding prebiotics to solid food had a bifidogenic effect. The GOS was given to healthy term infants resulted in high *Bifidobacteria* (Sierra et al., 2015). Ziegler et al. (2007) observed that infants fed formula with a pre-biotic mixture had growth and stool characteristics similar to breastfed infants, with a lower incidence of eczema. Gruber et al. (2010) demonstrated that a formula containing a specific mixture of oligosaccharides (ScGOS/lcFOS) reduced the risk of atopic dermatitis in low atopy risk infants. Pontes et al. (2016) showed that a cow's milk based beverage with prebiotics reduced allergic manifestations (atopic dermatitis, wheezing, allergic rhinitis) compared to controls. Partially hydrolyzed whey formula containing oligosaccharides pHF-OS showed immune modulatory effects and increased T cells in infants at high risk of allergic diseases stating that may protect against later allergic diseases (Boyle et al., 2016). Study discovered that prebiotic supplementation reduced the commutative incidences of allergic manifestations (allergic wheezing and allergic urticaria) at 2 years of age and atopic dermatitis were significantly reduced at 5 years of age. Concluding prebiotic supplementation in early infancy reduced the risk of atopic diseases at high risk infants (Nisticò and Conti, 2013).

Ranucci et al. (2018) found that prebiotic enriched formula reduced the risk of atopic dermatitis by 35% conferred to standard formula. Wopereis et al. (2018) observed infants fed with prebiotic (partially hydrolyzed formula) showed differences in gut microbiota composition and altered levels of certain compounds, potentially influencing eczema development. Prebiotics have also been shown to increase beneficial gut bacteria and short-chain fatty acids, while decreasing harmful bacteria in a study by Francavilla et al. (2012). Additionally, prebiotics have been found to reduce the concentration of Ig-Free light chain, which is associated with atopic diseases (Schouten et al., 2011).

In adults, prebiotics have been found to have numerous benefits as well. They can help promote a healthy gut microbiome, boost the immune system, and even reduce symptoms of certain diseases (Biagioli et al., 2024).

Prebiotics may be a complementary approach to reducing atopic diseases, particularly when combined with human milk or supplemented feed in early infancy and dietary or supplementary prebiotics in adulthood (Biagioli et al., 2024). The European Commission's Scientific Committee on food has no objections to adding oligosaccharides to infant formula, and the FAO of UNWHO supports prebiotic products as infant formula for infants over 5 months old (Leuschner et al., 2010).

Potential Benefits and Limitations

Regardless of prebiotics studies showing its benefits in improving gut microbiota, increasing healthy bacteria, decreasing harmful bacteria, enhancing selective growth to produce SCFAs, and reducing the severity of atopic conditions like eczema, asthma allergies. Still there are some limitations in therapeutic effect of prebiotics.

The relationship between atopic diseases and gut microbiota is quite complex making it even more challenging (Donald and Finlay, 2023), and individual responses to prebviotics vary due to unique microbes and factors (Li et al., 2014). Improper dosage may also lead to gastrointestinal issues (Ballan et al., 2020). Moreover, due to limited clinical evidence (Kang et al., 2023) and varied prebiotic studies, this makes it difficult to draw a concrete conclusion about its therapeutic results in atopic diseases management. Prebiotics may interact with other treatments or other diets, which may not produce desirable results. Therefore, more research is needed to fully understand its method and their results.

Combination of prebiotics and probiotics can produce more productive result than prebiotic and probiotics alone for atopic conditions. A study showed positive results in reducing atopic dermatitis severity with oral administration of synbiotic supplementation in children. An improved SCORAD index regardless of underlying treatments (Ibáñez et al., 2018).

Conclusion

In conclusion atopic diseases, including allergies and asthma, have become increasingly prevent globally. Factors like genetics, environment, lifestyle and microbial imbalances contribute to their development. Dysbiosis, or disruption of the good microbiota, is linked to atopic diseases. Prebiotic, non-digestible food components that promote beneficial gut bacteria, show promise in modulating the gut microbiota and reducing the risk of atopic diseases. They promote short chain fatty acids production, immune modulation, and gut barrier function, reducing inflammation and allergic responses. While studies have shown varying outcomes, there is growing evidence supporting prebiotics role, especially in high risk infants. Dietary sources rich in prebiotics foods and considering supplementation, especially during infancy and early childhood, may contribute to better overall health and reduce the burden of atopic diseases. Further research is needed to fully understand prebiotic supplementation's mechanism and long-term effects.

REFERENCES

Aachary, A. A., Gobinath, D., Srinivasan, K., and Prapulla, S. G. (2015). Protective effect of xylooligosaccharides from corncob on 1, 2-dimethylhydrazine induced colon cancer in rats. *Bioactive Carbohydrates and Dietary Fibre*, *5*(2), 146–152.

Alderete, T. L., Autran, C., Brekke, B. E., Knight, R., Bode, L., Goran, M. I., and Fields, D. A. (2015). Associations between human milk oligosaccharides and infant body composition in the first 6 mo of life. *The American Journal of Clinical Nutrition*, *102*(6), 1381–1388.

Araya, M., Morelli, L., Reid, G., Sanders, M., Stanton, C., Pineiro, M., and Ben Embarek, P. (2002). Joint FAO/WHO Working Group report on drafting guidelines for the evaluation of probiotics in food. *London, Canada: World Health Organization, Food and Agriculture Organization of the United Nations*.

Arslanoglu, S., Moro, G. E., Schmitt, J., Tandoi, L., Rizzardi, S., and Boehm, G. (2008). Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. *Journal of Nutrition*, *138*(6), 1091–1095. https://doi.org/10.1093/jn/138.6.1091

Ballan, R., Battistini, C., Xavier-Santos, D., and Saad, S. M. I. (2020). Interactions of probiotics and prebiotics with the gut microbiota. *Progress in Molecular Biology and Translational Science*, *171*, 265–300.

Biagioli, V., Volpedo, G., Riva, A., Mainardi, P., and Striano, P. (2024). From birth to weaning: a window of opportunity for microbiota. *Nutrients*, *16*(2), 272.

Björkstén, B. (1999). The intrauterine and postnatal environments. *Journal of Allergy and Clinical Immunology*, *104*(6), 1119–1127.

Boehm, G., Lidestri, M., Casetta, P., Jelinek, J., Negretti, F., Stahl, B., and Marini, A. (2002). Supplementation of a bovine milk formula with an oligosaccharide mixture increases counts of faecal bifidobacteria in preterm infants. *Archives of Disease in Childhood-Fetal and Neonatal Edition*, *86*(3), F178–F181.

Boyle, R. J., Tang, M. L. K., Chiang, W. C., Chua, M. C., Ismail, I., Nauta, A., Hourihane, J. O. B., Smith, P., Gold, M., Ziegler, J., Peake, J., Quinn, P., Rao, R., Brown, N., Rijnierse, A., Garssen, J., Warner, J. O., Axelrad, C., Jeffries, S., and Knipping, K. (2016). Prebiotic-supplemented partially hydrolysed cow's milk formula for the prevention of eczema in high-risk infants: A randomized controlled trial. *Allergy: European Journal of Allergy and Clinical Immunology*, *71*(5), 701–710. https://doi.org/10.1111/all.12848

Candela, M., Rampelli, S., Turroni, S., Severgnini, M., Consolandi, C., De Bellis, G., Masetti, R., Ricci, G., Pession, A., and Brigidi, P. (2012). Unbalance of intestinal microbiota in atopic children. *BMC Microbiology*, *12*, 1–9.

Cukrowska, B. (2018). Microbial and nutritional programming—the importance of the microbiome and early exposure to potential food allergens in the development of allergies. *Nutrients*, *10*(10), 1541.

Dahiya, D., and Nigam, P. S. (2023). Biotherapy Using Probiotics as Therapeutic Agents to Restore the Gut Microbiota to Relieve Gastrointestinal Tract Inflammation, IBD, IBS and Prevent Induction of Cancer. *International Journal of Molecular Sciences*, *24*(6). https://doi.org/10.3390/ijms24065748

Davani-Davari, D., Negahdaripour, M., Karimzadeh, I., Seifan, M., Mohkam, M., Masoumi, S. J., Berenjian, A., and Ghasemi, Y. (2019). Prebiotics: Definition, types, sources, mechanisms, and clinical applications. *Foods*, *8*(3). https://doi.org/10.3390/foods8030092

Donald, K., and Finlay, B. B. (2023). Early-life interactions between the microbiota and immune system: impact on immune system development and atopic disease. *Nature Reviews Immunology*, *23*(11), 735–748.

Fassio, F., and Guagnini, F. (2018). House dust mite-related respiratory allergies and probiotics: a narrative review. *Clinical and Molecular Allergy*, *16*(1), 15.

Faye, O., Flohr, C., Kabashima, K., Ma, L., Paller, A. S., Rapelanoro, F. R., Steinhoff, M., Su, J. C., Takaoka, R., Wollenberg, A., Yew, Y. W., Postigo, J. A. R., Schmid-Grendelmeier, P., and Taïeb, A. (2023). Atopic dermatitis: A global health perspective. *Journal of the European Academy of Dermatology and Venereology*, *November*, 1–11. https://doi.org/10.1111/jdv.19723

Francavilla, R., Calasso, M., Calace, L., Siragusa, S., Ndagijimana, M., Vernocchi, P., Brunetti, L., Mancino, G., Tedeschi, G., and Guerzoni, E. (2012). Effect of lactose on gut microbiota and metabolome of infants with cow's milk allergy. *Pediatric*

Allergy and Immunology, *23*(5), 420–427.

Gibson, G. R., Probert, H. M., Van Loo, J., Rastall, R. A., and Roberfroid, M. B. (2004). Dietary modulation of the human colonic microbiota: updating the concept of prebiotics. *Nutrition Research Reviews*, *17*(2), 259–275.

Gray, L. E. K., O'Hely, M., Ranganathan, S., Sly, P. D., and Vuillermin, P. (2017). The maternal diet, gut bacteria, and bacterial metabolites during pregnancy influence offspring asthma. *Frontiers in Immunology*, *8*(MAR), 1–13. https://doi.org/10.3389/fimmu.2017.00365

Grüber, C., van Stuijvenberg, M., Mosca, F., Moro, G., Chirico, G., Braegger, C. P., Riedler, J., Boehm, G., Wahn, U., and Group, M. 1 W. (2010). Reduced occurrence of early atopic dermatitis because of immunoactive prebiotics among low-atopy-risk infants. *Journal of Allergy and Clinical Immunology*, *126*(4), 791–797.

Hotel, A. C. P., and Cordoba, A. (2001). Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. *Prevention*, *5*(1), 1–10.

Ibáñez, M. D., Rodríguez del Río, P., González-Segura Alsina, D., and Villegas Iglesias, V. (2018). Effect of synbiotic supplementation on children with atopic dermatitis: an observational prospective study. *European Journal of Pediatrics*, *177*, 1851–1858.

Jackson, C. L., Dreaden, T. M., Theobald, L. K., Tran, N. M., Beal, T. L., Eid, M., Gao, M. Y., Shirley, R. B., Stoffel, M. T., and Kumar, M. V. (2007). Pectin induces apoptosis in human prostate cancer cells: correlation of apoptotic function with pectin structure. *Glycobiology*, *17*(8), 805–819.

Kalliomäki, M., Kirjavainen, P., Eerola, E., Kero, P., Salminen, S., and Isolauri, E. (2001). Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. *Journal of Allergy and Clinical Immunology*, *107*(1), 129–134.

Kang, M., Jung, J.-H., Kim, J.-Y., Hong, S.-H., and Her, Y. (2023). Therapeutic and preventive effect of orally administered prebiotics on atopic dermatitis in a mouse model. *Allergy, Asthma and Immunology Research*, *15*(3), 303.

Khan, F. F., Sohail, A., Ghazanfar, S., Ahmad, A., Riaz, A., Abbasi, K. S., Ibrahim, M. S., Uzair, M., and Arshad, M. (2023). Recent innovations in non-dairy prebiotics and probiotics: Physiological potential, applications, and characterization. *Probiotics and Antimicrobial Proteins*, *15*(2), 239–263.

Kim, C. H. (2023). Complex regulatory effects of gut microbial short-chain fatty acids on immune tolerance and autoimmunity. *Cellular and Molecular Immunology*, *20*(4), 341–350. https://doi.org/10.1038/s41423-023-00987-1

Knol, J., Scholtens, P., Kafka, C., Steenbakkers, J., Gro, S., Helm, K., Klarczyk, M., Schöpfer, H., Böckler, H.-M., and Wells, J. (2005). Colon microflora in infants fed formula with galacto-and fructo-oligosaccharides: more like breast-fed infants. *Journal of Pediatric Gastroenterology and Nutrition*, *40*(1), 36–42.

Koh, A., De Vadder, F., Kovatcheva-Datchary, P., and Bäckhed, F. (2016). From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. *Cell*, *165*(6), 1332–1345.

Kunst, C., Schmid, S., Michalski, M., Tümen, D., Buttenschön, J., Müller, M., and Gülow, K. (2023). The influence of gut microbiota on oxidative stress and the immune system. *Biomedicines*, *11*(5), 1388.

Leuschner, R. G. K., Robinson, T. P., Hugas, M., Cocconcelli, P. S., Richard-Forget, F., Klein, G., Licht, T. R., Nguyen-The, C., Querol, A., and Richardson, M. (2010). Qualified presumption of safety (QPS): a generic risk assessment approach for biological agents notified to the European Food Safety Authority (EFSA). *Trends in Food Science and Technology*, *21*(9), 425–435.

Li, M., Wang, M., and Donovan, S. M. (2014). Early development of the gut microbiome and immune-mediated childhood disorders. *Seminars in Reproductive Medicine*, *32*(01), 74–86.

Lin, T. L., Fan, Y. H., Chang, Y. L., Ho, H. J., Wu, C. Y., and Chen, Y. J. (2022). Early-life infections in association with the development of atopic dermatitis in infancy and early childhood: a nationwide nested case–control study. *Journal of the European Academy of Dermatology and Venereology*, *36*(4), 615–622. https://doi.org/10.1111/jdv.17908

Liu, J., Lu, X., Fang, F., Wu, K., Wu, J., and Gao, J. (2024). Comparison of the in-vitro effect of five prebiotics with different structure on gut microbiome and metabolome. *Food Bioscience*, 103810. https://doi.org/10.1016/j.fbio.2024.103810

Lodge, C. J., Tan, D. J., Lau, M. X. Z., Dai, X., Tham, R., Lowe, A. J., Bowatte, G., Allen, K. J., and Dharmage, S. C. (2015). Breastfeeding and asthma and allergies: a systematic review and meta-analysis. *Acta Paediatrica*, *104*, 38–53

Logoń, K., Świrkosz, G., Nowak, M., Wrześniewska, M., Szczygieł, A., and Gomułka, K. (2023). The Role of the Microbiome in the Pathogenesis and Treatment of Asthma. *Biomedicines*, *11*(6). https://doi.org/10.3390/biomedicines11061618

Markowiak-Kopeć, P., and Śliżewska, K. (2020). The effect of probiotics on the production of short-chain fatty acids by human intestinal microbiome. *Nutrients*, *12*(4), 1107.

Maslowski, K. M., and Mackay, C. R. (2011). Diet, gut microbiota and immune responses. *Nature Immunology*, *12*(1), 5–9.

Maslowski, K. M., Vieira, A. T., Ng, A., Kranich, J., Sierro, F., Yu, D., Schilter, H. C., Rolph, M. S., Mackay, F., and Artis, D. (2009). Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature*, *461*(7268), 1282–1286.

Mishra, P., Badiyani, V. M., Jain, S., Subramanian, S., Maharaj, S. V., Kumar, A., and Singh, B. N. (2023). Prebiotics: Ignored player in the fight against cancer. *Cancer Reports*, *6*(11), 1–12. https://doi.org/10.1002/cnr2.1870

Moro, G., Minoli, I., Mosca, M., Fanaro, S., Jelinek, J., Stahl, B., and Boehm, G. (2002). Dosage-related bifidogenic effects of galacto-and fructooligosaccharides in formula-fed term infants. *Journal of Pediatric Gastroenterology and Nutrition*, *34*(3), 291–295.

Muir, A. B., Benitez, A. J., Dods, K., Spergel, J. M., and Fillon, S. A. (2016). Microbiome and its impact on gastrointestinal atopy.

Allergy: European Journal of Allergy and Clinical Immunology, *71*(9), 1256–1263. https://doi.org/10.1111/all.12943
Neaville, W. A., Tisler, C., Bhattacharya, A., Anklam, K., Gilbertson-White, S., Hamilton, R., Adler, K., DaSilva, D. F., Roberg, K. A., and Carlson-Dakes, K. T. (2003). Developmental cytokine response profiles and the clinical and immunologic expression of atopy during the first year of life. *Journal of Allergy and Clinical Immunology*, *112*(4), 740–746.
Ney, L. M., Wipplinger, M., Grossmann, M., Engert, N., Wegner, V. D., and Mosig, A. S. (2023). Short chain fatty acids: key regulators of the local and systemic immune response in inflammatory diseases and infections. *Open Biology*, *13*(3). https://doi.org/10.1098/rsob.230014
Nisticò, G., and Conti, P. (2013). Journal of Biological Regulators and Homeostatic Agents: Introduction. *Journal of Biological Regulators and Homeostatic Agents*, *27*(2 SUPPL.).
Oozeer, R., Van Limpt, K., Ludwig, T., Amor, K. Ben, Martin, R., Wind, R. D., Boehm, G., and Knol, J. (2013). Intestinal microbiology in early life: specific prebiotics can have similar functionalities as human-milk oligosaccharides. *The American Journal of Clinical Nutrition*, *98*(2), 561S-571S.
Pantazi, A. C., Mihai, C. M., Balasa, A. L., Chisnoiu, T., Lupu, A., Frecus, C. E., Mihai, L., Ungureanu, A., Kassim, M. A. K., Andrusca, A., Nicolae, M., Cuzic, V., Lupu, V. V., and Cambrea, S. C. (2023). Relationship between Gut Microbiota and Allergies in Children: A Literature Review. *Nutrients*, *15*(11), 1–15. https://doi.org/10.3390/nu15112529
Peredo-Lovillo, A., Romero-Luna, H. E., and Jiménez-Fernández, M. (2020). Health promoting microbial metabolites produced by gut microbiota after prebiotics metabolism. *Food Research International*, *136*(April), 109473. https://doi.org/10.1016/j.foodres.2020.109473
Piccioni, A., Covino, M., Candelli, M., Ojetti, V., Capacci, A., Gasbarrini, A., Franceschi, F., and Merra, G. (2023). How do diet patterns, single foods, prebiotics and probiotics impact gut microbiota? *Microbiology Research*, *14*(1), 390–408.
Pontes, M. V, Ribeiro, T. C. M., Ribeiro, H., Mattos, A. P. De, Almeida, I. R., Leal, V. M., Cabral, G. N., Stolz, S., Zhuang, W., and Scalabrin, D. M. F. (2016). Cow ' s milk-based beverage consumption in 1- to 4-year-olds and allergic manifestations : an RCT. *Nutrition Journal*, 1–10. https://doi.org/10.1186/s12937-016-0138-0
Ranucci, G., Buccigrossi, V., Borgia, E., Piacentini, D., Visentin, F., Cantarutti, L., Baiardi, P., Felisi, M., Spagnuolo, M. I., Zanconato, S., Baraldi, E., Giaquinto, C., and Guarino, A. (2018). Galacto-oligosaccharide/polidextrose enriched formula protects against respiratory infections in infants at high risk of atopy: A randomized clinical trial. *Nutrients*, *10*(3). https://doi.org/10.3390/nu10030286
Rinne, M. M., Gueimonde, M., Kalliomäki, M., Hoppu, U., Salminen, S. J., and Isolauri, E. (2005). Similar bifidogenic effects of prebiotic-supplemented partially hydrolyzed infant formula and breastfeeding on infant gut microbiota. *FEMS Immunology and Medical Microbiology*, *43*(1), 59–65.
Rø, A. D. B., Simpson, M. R., Rø, T. B., Storrø, O., Johnsen, R., Videm, V., and Øien, T. (2017). Reduced Th22 cell proportion and prevention of atopic dermatitis in infants following maternal probiotic supplementation. *Clinical and Experimental Allergy*, *47*(8), 1014–1021.
Roberfroid, M., Gibson, G. R., Hoyles, L., McCartney, A. L., Rastall, R., Rowland, I., Wolvers, D., Watzl, B., Szajewska, H., and Stahl, B. (2010). Prebiotic effects: metabolic and health benefits. *British Journal of Nutrition*, *104*(S2), S1–S63.
Sabater-Molina, M., Larqué, E., Torrella, F., and Zamora, S. (2009). Dietary fructooligosaccharides and potential benefits on health. *Journal of Physiology and Biochemistry*, *65*, 315–328.
Schmelzle, H., Wirth, S., Skopnik, H., Radke, M., Knol, J., Böckler, H.-M., Brönstrup, A., Wells, J., and Fusch, C. (2003). Randomized Double-Blind Study of the Nutritional Efficacy and Bifidogenicity of a New Infant Formula Containing Partially Hydrolyzed Protein, a High β-Palmitic Acid Level, and Nondigestible Oligosaccharides. *Journal of Pediatric Gastroenterology and Nutrition*, *36*(3). https://journals.lww.com/jpgn/fulltext/2003/03000/randomized_double_blind_study_of_the_nutritional.8.aspx
Scholtens, P. A. M. J., Alles, M. S., Bindels, J. G., van der Linde, E. G. M., Tolboom, J. J. M., and Knol, J. (2006). Bifidogenic effects of solid weaning foods with added prebiotic oligosaccharides: a randomised controlled clinical trial. *Journal of Pediatric Gastroenterology and Nutrition*, *42*(5), 553–559.
Schouten, B., Van Esch, B. C. A. M., Kormelink, T. G., Moro, G. E., Arslanoglu, S., Boehm, G., Knippels, L. M. J., Redegeld, F. A., Willemsen, L. E. M., and Garssen, J. (2011). Non-digestible oligosaccharides reduce immunoglobulin free light-chain concentrations in infants at risk for allergy. *Pediatric Allergy and Immunology*, *22*(5), 537–542.
Scott, K. P., Gratz, S. W., Sheridan, P. O., Flint, H. J., and Duncan, S. H. (2013). The influence of diet on the gut microbiota. *Pharmacological Research*, *69*(1), 52–60.
Sestito, S., D'Auria, E., Baldassarre, M. E., Salvatore, S., Tallarico, V., Stefanelli, E., Tarsitano, F., Concolino, D., and Pensabene, L. (2020). The Role of Prebiotics and Probiotics in Prevention of Allergic Diseases in Infants. *Frontiers in Pediatrics*, *8*(December). https://doi.org/10.3389/fped.2020.583946
Shirsath, N. R., and Zawar, L. R. (2024). Role of Food Supplements in Gut Health. In *Food Supplements and Dietary Fiber in Health and Disease* (pp. 337–357). Apple Academic Press
Sierra, C., Bernal, M.-J., Blasco, J., Martínez, R., Dalmau, J., Ortuno, I., Espín, B., Vasallo, M.-I., Gil, D., and Vidal, M.-L. (2015). Prebiotic effect during the first year of life in healthy infants fed formula containing GOS as the only prebiotic: a multicentre, randomised, double-blind and placebo-controlled trial. *European Journal of Nutrition*, *54*, 89–99.
Slavin, J. (2013). Fiber and prebiotics: mechanisms and health benefits. *Nutrients*, *5*(4), 1417–1435.
Song, C., Chai, Z., Chen, S., Zhang, H., Zhang, X., and Zhou, Y. (2023). Intestinal mucus components and secretion mechanisms: what we do and do not know. *Experimental and Molecular Medicine*, *55*(4), 681–691. https://doi.org/10.1038/s12276-

023-00960-y

Stec, A., Sikora, M., Maciejewska, M., Paralusz-Stec, K., Michalska, M., Sikorska, E., and Rudnicka, L. (2023). Bacterial metabolites: a link between gut microbiota and dermatological diseases. *International Journal of Molecular Sciences*, *24*(4), 3494.

Thomas, D. W., Greer, F. R., Bhatia, J. J. S., Abrams, S. A., Daniels, S. R., Schneider, M. B., Silverstein, J., Stettler, N., Heitlinger, L. A., Baker, R. D., Gremse, D. A., Gugig, R., and Lightdale, J. R. (2010). Clinical report - Probiotics and prebiotics in pediatrics. *Pediatrics*, *126*(6), 1217–1231. https://doi.org/10.1542/peds.2010-2548

Thomsen, S. F. (2015). Epidemiology and natural history of atopic diseases. *European Clinical Respiratory Journal*, *2*(1), 24642. https://doi.org/10.3402/ecrj.v2.24642

Wopereis, H., Sim, K., Shaw, A., Warner, J. O., Knol, J., and Kroll, J. S. (2018). Intestinal microbiota in infants at high risk for allergy: Effects of prebiotics and role in eczema development. *Journal of Allergy and Clinical Immunology*, *141*(4), 1334-1342.e5. https://doi.org/https://doi.org/10.1016/j.jaci.2017.05.054

Zhou, P., Chen, C., Patil, S., and Dong, S. (2024). Unveiling the therapeutic symphony of probiotics, prebiotics, and postbiotics in gut-immune harmony. *Frontiers in Nutrition*, *11*, 1355542.

Ziegler, E., Vanderhoof, J. A., Petschow, B., Mitmesser, S. H., Stolz, S. I., Harris, C. L., and Berseth, C. L. (2007). Term infants fed formula supplemented with selected blends of prebiotics grow normally and have soft stools similar to those reported for breast-fed infants. *Journal of Pediatric Gastroenterology and Nutrition*, *44*(3), 359–364