

Advancements in Prebiotics

Industry Research, Applications & Insights

Prebiotics are non-digestible components of food that promote the growth of beneficial microorganisms in the intestines. They are often found in high-fiber foods such as fruits, vegetables, mushrooms, and whole grains, and can also be added to foods or taken as supplements.

According to the International Scientific Association for Probiotics and Prebiotics

(ISAPP)¹, and the Global Prebiotics Association (GPA)², a prebiotic is:

"A substrate that is 'selectively' utilized by host microorganisms conferring a health or performance benefit for the host."

This definition implies that prebiotics can include a variety of substances. The central aspects of this definition are the selective utilization by beneficial host microorganisms and the resultant health benefits to the host. This definition also opens the possibility for prebiotics to be effective in body sites other than the gastrointestinal tract and in various categories beyond food³.

The market for prebiotics has been growing rapidly, driven by increasing consumer awareness of their health benefits. According to GM Insights, the North American market for prebiotics in 2022 was roughly 6.2B USD with a 14.5% CAGR⁴. Prebiotics are being used in a variety of food products, including dairy, baked goods, and dietary supplements. The market growth is fueled by research showing the benefits of prebiotics in gut health, immunity, and metabolic syndrome-related diseases, among others. Moreover, the expanding functional food industry and the growing demand for health-promoting ingredients have contributed to the rise of the prebiotic market. Companies are focusing on developing efficient production methods to meet increasing demand and reduce costs. The market is also influenced by regulatory developments and consumer education regarding the health benefits of prebiotics.⁵

Key challenges for the prebiotics market include:

- 1) *ensuring the stability and effectiveness of prebiotic ingredients in different food matrices,*
- 2) *meeting regulatory standards, and*
- 3) *substantiating health claims with strong scientific evidence.*

Of these three main challenges, ***ProDigest is a recognized global leader in providing innovative food and supplement companies with a one-stop-shop to substantiate a product's prebiotic activity with high quality research and data***⁶.

To qualify a product as a prebiotic, it is first important to understand how prebiotics exert a beneficial effect on the host and how to measure these effects in practice.

¹ <https://isappscience.org/>

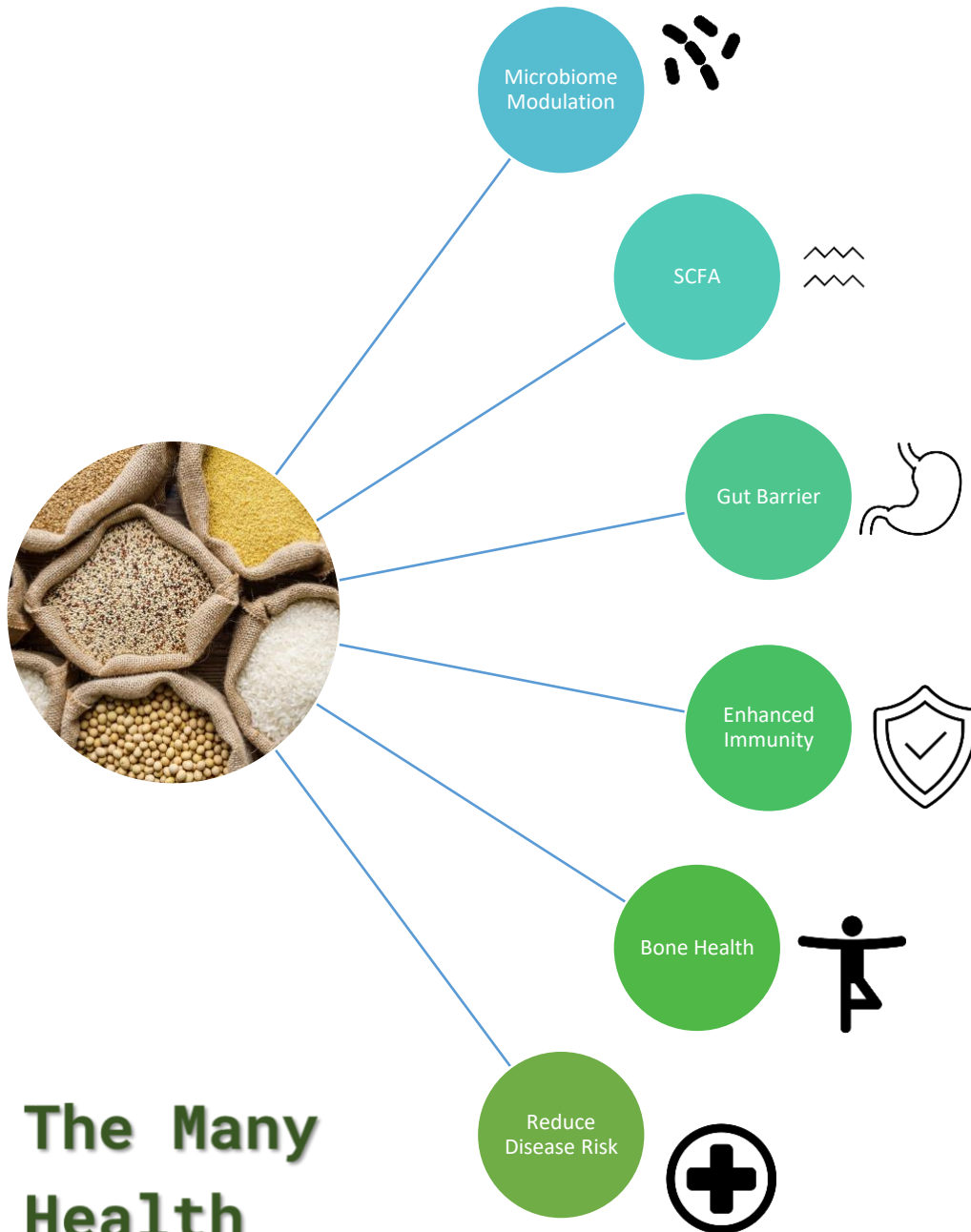
² <https://prebioticassociation.org/>

³ Gibson, G., Hutkins, R., Sanders, M., Prescott, S., Reimer, R., Salminen, S., Scott, K., Stanton, C., Swanson, K., Cani, P., Verbeke, K., & Reid, G. (2017). Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nature Reviews Gastroenterology & Hepatology*, 14, 491-502. <https://doi.org/10.1038/nrgastro.2017.75>.

⁴ Prebiotics Market Size - By Type (Inulin, Fructo-Oligosaccharides, Galacto-Oligosaccharides, Oligosaccharides), Source (Roots, Grains, Vegetables), Application (Food & Beverages, Dietary Supplements, Animal Feed), Functionality & Global Forecast, 2023 – 2032. GM Insights. Nov 2023

⁵ Amorim, C., Silvério, S., Prather, K., & Rodrigues, L. (2019). From lignocellulosic residues to market: Production and commercial potential of xylooligosaccharides. *Biotechnology advances*. <https://doi.org/10.1016/j.biotechadv.2019.05.003>.

⁶ <https://prodigest.eu/application/prebiotics-and-fibers/>



The Many Health Benefits of Prebiotics

Prebiotics contribute to health improvement through several mechanisms:

- 1) **Modulation of Gut Microbiota:** Prebiotics alter the composition of intestinal microbiota, favoring beneficial bacteria and inhibiting pathogenic organisms. This can lead to improved gut health and overall

- well-being⁷. For instance, inulin-type fructans and galacto-oligosaccharides, are known to stimulate the growth of beneficial bacteria like Bifidobacteria and Lactobacilli. These changes in the gut microbiota composition are associated with various health benefits, including improved gut barrier function and immune modulation⁸.
- 2) **Production of Short-Chain Fatty Acids:** The fermentation of prebiotics by gut microbiota leads to the production of short-chain fatty acids (SCFAs), which have various health benefits including modulation of gut health and immune response⁹. For instance, SCFAs, including acetate, propionate, and butyrate, exhibit anti-inflammatory properties. They modulate immune responses, which can be beneficial in conditions like inflammatory bowel disease (IBD) and may also have protective effects against colon cancer¹⁰. SCFAs are also crucial for maintaining gut integrity. They regulate the luminal pH, enhance mucus production, provide energy for epithelial cells, and affect mucosal immune function, thus maintaining the overall health of the gastrointestinal tract¹¹.
 - 3) **Enhancement of Gut Barrier Integrity:** Prebiotics help in maintaining the integrity of the gut epithelium, which is crucial for preventing pathogen invasion and maintaining gut health¹².
 - 4) **Immune System Stimulation:** They can stimulate the immune system directly or indirectly by increasing the population of beneficial microbes. This results in the production of cytokines and antibodies, thereby enhancing immunity¹³.
 - 5) **Improvement in Bone Health:** Prebiotics like glucans and fructans have been shown to improve mineral absorption, particularly calcium, which contributes to better bone health¹⁴.
 - 6) **Reduction in Disease Risk:** Consumption of prebiotics has been linked to reduced risks of certain diseases, including cardiovascular diseases and certain types of cancer, through their impact on gut microbiota and immune function¹⁵.

Of the above listed 6 ways prebiotics can exert a health benefit on the host, ProDigest can help companies quantify all of them!

⁷ Ashwini, A., Ramya, H., Ramkumar, C., Reddy, K., Kulkarni, R., Abinaya, V., Naveen, S., & Raghu, A. (2019). Reactive mechanism and the applications of bioactive prebiotics for human health: Review. *Journal of microbiological methods*, 159, 128-137. <https://doi.org/10.1016/j.mimet.2019.02.019>.

⁸ Gibson, G., & Roberfroid, M. (1995). Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *The Journal of nutrition*, 125 6, 1401-12. <https://doi.org/10.1093/JN/125.6.1401>.

⁹ Cummings, J., Macfarlane, G., & Englyst, H. (2001). Prebiotic digestion and fermentation. *The American journal of clinical nutrition*, 73 2 Suppl, 415S-420S. <https://doi.org/10.1093/ajcn/73.2.415s>.

¹⁰ Carretta, M., Quiroga, J., López, R., Hidalgo, M., & Burgos, R. (2021). Participation of Short-Chain Fatty Acids and Their Receptors in Gut Inflammation and Colon Cancer. *Frontiers in Physiology*, 12. <https://doi.org/10.3389/fphys.2021.662739>.

¹¹ Peng, L., Li, Z., Green, R., Holzman, I., & Lin, J. (2009). Butyrate enhances the intestinal barrier by facilitating tight junction

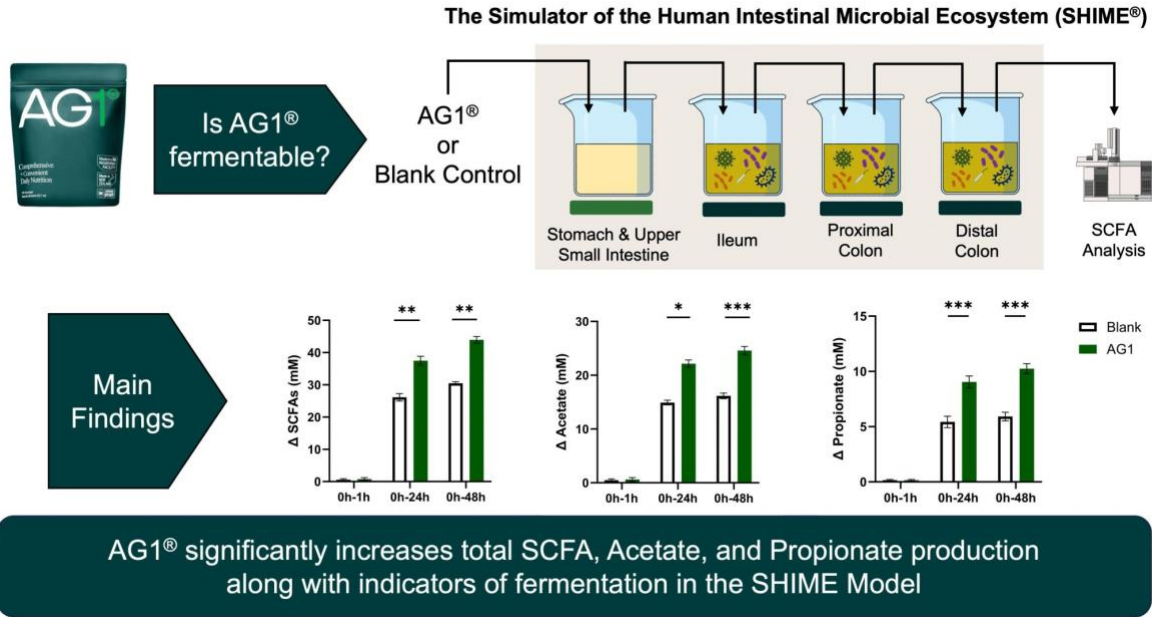
assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers. *The Journal of nutrition*, 139 9, 1619-25. <https://doi.org/10.3945/jn.109.104638>.

¹² Teng, P., & Kim, W. (2018). Review: Roles of Prebiotics in Intestinal Ecosystem of Broilers. *Frontiers in Veterinary Science*, 5. <https://doi.org/10.3389/fvets.2018.00245>.

¹³ Boder, P. (2008). Influence of prebiotics on the human immune system (GALT). *Recent patents on inflammation & allergy drug discovery*, 2 2, 149-53. <https://doi.org/10.2174/187221308784543656>.

¹⁴ Whisner, C., & Castillo, L. (2017). Prebiotics, Bone and Mineral Metabolism. *Calcified Tissue International*, 102, 443 - 479. <https://doi.org/10.1007/s00223-017-0339-3>.

¹⁵ Dubert-Ferrandon, A., Newburg, D., & Walker, W. (2009). Part 2- Prebiotics: New Medicines for the Colon, Health Benefits. *Nutrition Today*, 44, 85-91. <https://doi.org/10.1097/NT.0b013e31819df7bc>.



ProDigest offers the best in class, ex-vivo human and animal gut simulations. ProDigest’s gut simulation platforms, like the Simulator of the Human Microbial Ecosystem (SHIME®), have been used by thousands of researchers and companies globally to investigate the functional impact of probiotics, prebiotics, live biotherapeutic products, functional foods, supplements, and drugs.

For example, in recent series of studies, ProDigest evaluated the performance of Athletic Greens’ AG1® in a SHIME model.

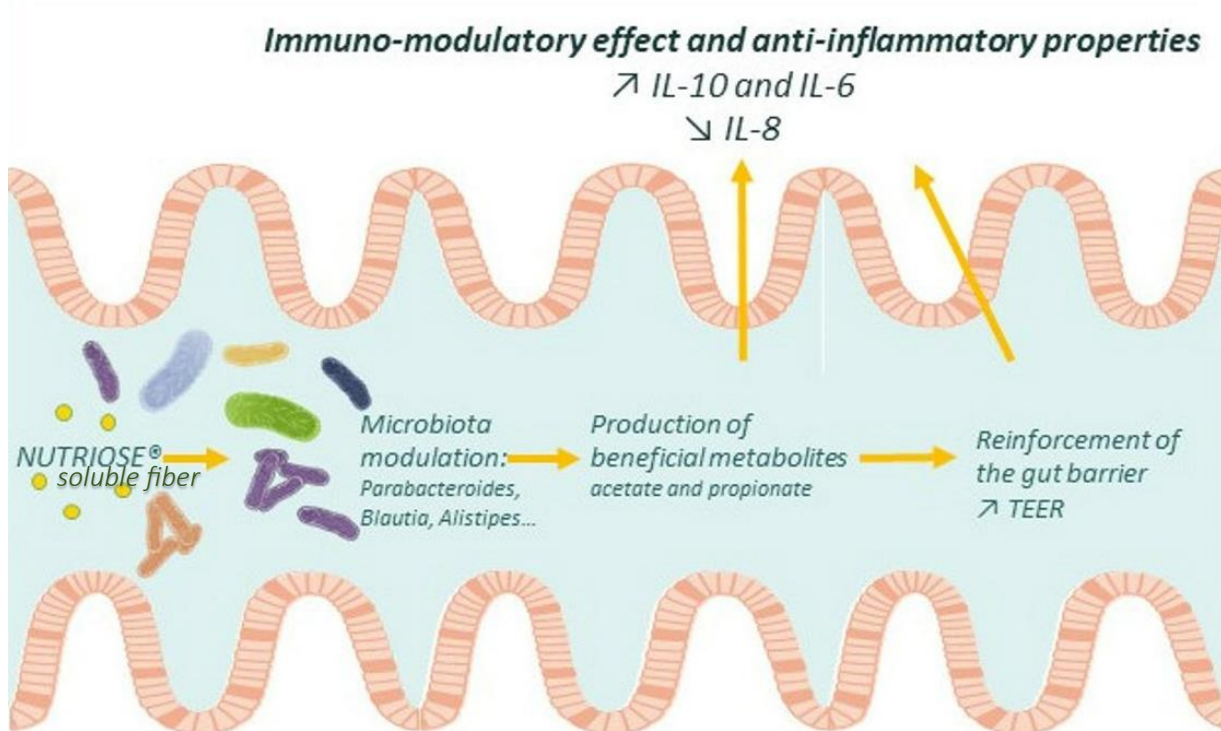
In one study, AG1®, a novel nutritional supplement which contains vitamins, minerals, phytonutrients, adaptogens, and probiotics, demonstrated properties of a synbiotic (a combination of prebiotics and probiotics)¹⁶. In this study, AG1® significantly increased the production of total SCFAs, including acetate and propionate, which are beneficial for gut health. This suggests that AG1® enhances the fermentation process of human gut microbiota.

In a complementary study, AG1® was shown to modulate the gut microbiome, enhancing eight specific taxa of microbes¹⁷. Of interest, *Faecalibacterium prausnitzii* and *Walteria intestinalis* increased in prevalence. *F. prausnitzii* is known to produce butyrate. Butyrate is a SCFA that is crucial for colon health and has been associated with reduced risk of colon cancer and anti-inflammatory properties, particularly in the context of inflammatory bowel diseases (IBD) like Crohn's disease and ulcerative colitis. While *W. intestinalis* are native to the intestinal environment and play a role in digestion, nutrient absorption, and immune system modulation. The study also showed an enhancement of important microbial metabolic pathways.

Taken together, these two studies clearly demonstrate that AG1® has prebiotic activity, whereby the supplement enhances SCFA production while also modulating the gut microbiome, enhancing beneficial taxa such as *F. prausnitzii*.

¹⁶ Kirby, T.O.; Townsend, J.R.; Sapp, P.A.; Govaert, M.; Duysburgh, C.; Marshall, T.M.; Marzorati, M.; Esposito, R. The Novel Synbiotic, AG1®, Increases Short-Chain Fatty Acid Production in the Simulator of Human Intestinal Microbial Ecosystem (SHIME) Model®. *Nutraceuticals* 2023, 3, 489-498. <https://doi.org/10.3390/nutraceuticals3040035>

¹⁷ Kirby, T.O.; Sapp, P.A.; Townsend, J.R.; Govaert, M.; Duysburgh, C.; Marzorati, M.; Marshall, T.M.; Esposito, R. AG1® Induces a Favorable Impact on Gut Microbial Structure and Functionality in the Simulator of Human Intestinal Microbial Ecosystem® Model. *Curr. Issues Mol. Biol.* 2024, 46, 557-569. <https://doi.org/10.3390/cimb46010036>



In another study, ProDigest evaluated Roquette's prebiotic NUTRIOSE[®] soluble fiber, a resistant dextrin with well-established prebiotic effects, for its ability to modulate immune function, gut barrier integrity, as well as changes in microbial community composition and fermentation-derived metabolites¹⁸. In this study, a Colon-on-a-Plate[®] simulation¹⁹ was used to evaluate the performance of NUTRIOSE[®] in 8 individual gut simulations. This study showed that:

- 1) NUTRIOSE[®] supplementation significantly increased transepithelial electrical resistance (TEER) across all donors, indicating enhanced protection of the intestinal epithelial barrier from inflammation-induced disruption.
- 2) There was a significant increase in the secretion of IL-6 (a pro- and anti-inflammatory cytokine) and IL-10 (an anti-inflammatory cytokine) with NUTRIOSE[®]-supplemented colonic suspensions. Additionally, levels of the neutrophil chemoattractant IL-8 were significantly decreased.
- 3) Enhanced fermentation activity as evidenced by decreased pH with NUTRIOSE[®] supplementation as compared to blank.
- 4) Supplementation led to increased levels of short-chain fatty acids (SCFAs) like acetate and propionate, which are important for carbohydrate metabolism in the colon.
- 5) There was a strong correlation between the production of certain metabolites (like acetate and propionate) and the enrichment of specific bacterial genera such as Blautia and Parabacteroides. This indicates direct and indirect effects of microbial enrichments on metabolite levels.

¹⁸ Perreau, C., Thabuis, C., Verstrepen, L., Ghyselincq, J., & Marzorati, M. (2023). Ex Vivo Colonic Fermentation of NUTRIOSE[®] Exerts Immuno-Modulatory Properties and Strong Anti-

Inflammatory Effects. *Nutrients*, 15(19), 4229. <https://doi.org/10.3390/nu15194229>

¹⁹ <https://prodigest.eu/technology/colon-on-a-plate/>

Overall, this study demonstrated 2 important points:

- 1) ***The findings highlight the significance of NUTRIOSE® as a prebiotic fiber with beneficial effects on gut health and immune modulation.***



- 2) ***ProDigest's Colon-on-a-Plate® ex-vivo technology accurately predicts the outcomes of clinical and animal trials concerning prebiotic effects and impacts on host inflammatory responses and epithelial integrity.***



The comprehensive analysis of prebiotics, their mechanisms of action, and health applications underscore the growing significance of prebiotics in nutrition science. Prebiotics, through their diverse actions such as modulation of gut microbiota, production of short-chain fatty acids, enhancement of gut barrier integrity, immune system stimulation, reduction in disease risk, and improvement in mineral absorption, offer multifaceted benefits that extend beyond traditional gut health.

Studies involving products like AG1® and NUTRIOSE® not only reinforce the efficacy of prebiotics in promoting gut health and immune response, but also highlight their potential in disease prevention and enhancing overall well-being.

Critically, ProDigest's advanced ex-vivo human and animal gut simulation platforms, like the SHIME® and Colon-on-a-Plate®, have proven instrumental in exploring the functional impacts of prebiotics and offering high quality data to support functional claims that a product has prebiotic activity and benefit. These studies not only validate the prebiotic activity of various compounds but also demonstrate the reliability and predictive power of such innovative methodologies in prebiotic research.

The growing body of research and the development of sophisticated testing methods signify a promising future for prebiotic applications in health and nutrition. As the market continues to expand, and consumer awareness increases, the role of prebiotics in enhancing human health is set to become widespread. This underlines the importance of continuous research, development, and innovation in this field, ensuring that the potential of prebiotics is fully harnessed for the betterment of global health.

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