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Prebiotics, probiotics and synbiotics in human health

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Abstract

The human gastrointestinal tract harbours a diverse microbial ecosystem that plays a fundamental role in maintaining physiological balance, immune regulation, and metabolic homeostasis. In recent years, considerable scientific interest has focused on functional food components such as probiotics, prebiotics, and synbiotics because of their ability to modulate the gut microbiota and promote human health beneficially. Probiotics are defined as live microorganisms that, when consumed in adequate amounts, confer health benefits to the host. Common probiotic genera, including *Lactobacillus* and *Bifidobacterium*, help maintain intestinal microbial balance, inhibit the proliferation of pathogenic microorganisms, and enhance host immune responses. Prebiotics are non-digestible dietary components, mainly oligosaccharides and specific dietary fibres, that selectively stimulate the growth and metabolic activity of beneficial gut bacteria. Fermentation of these substrates by the intestinal microbiota produces short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate. These metabolites help maintain intestinal epithelial integrity, regulate lipid and glucose metabolism, and reduce inflammatory processes. Synbiotics represent a synergistic combination of probiotics and prebiotics designed to enhance the survival, colonisation, and functional activity of beneficial microorganisms within the gastrointestinal tract. By simultaneously providing beneficial microbial strains and their selective substrates, synbiotics promote improved microbial stability and metabolic efficiency. Emerging evidence suggests that synbiotics may improve digestive health, strengthen immune function, influence the gut-brain axis, and potentially reduce the risk of metabolic and gastrointestinal disorders. Therefore, these functional components represent promising strategies for promoting long-term human health and disease prevention.

Keywords: Dietary fibres, functional food, gut microbiota, human health, prebiotics, probiotics, synbiotics

Introduction

Since the beginning of the 21st century, the composition and functionality of the intestinal microbiota have gained significant attention within the scientific community. In comparison to microbial populations inhabiting other regions of the human body, the gut microbiota is markedly more abundant and exhibits greater diversity and complexity. In adults, the colon harbors an estimated 3.9×10^{13} microbial cells, a quantity that slightly exceeds the total number of human somatic and germ cells. This dense and diverse microbial ecosystem plays a critical role in maintaining host physiological homeostasis [36]. The intestinal microbiota plays a vital role in the digestion and metabolism of dietary components and contributes to a wide range of systemic physiological processes in the host, thereby exerting a significant influence on overall human health. Based on their functional effects on the host, gut microorganisms can be broadly classified into three groups: beneficial microorganisms (probiotics), commensal or neutral bacteria, and pathogenic microorganisms [16]. In healthy individuals, these microbial populations coexist in a state of dynamic equilibrium, where mutual competition and regulatory interactions contribute to the maintenance of intestinal homeostasis. The gastrointestinal tract, often referred to as the "second brain" due to its extensive neural network and regulatory functions, plays a pivotal role in overall health. The intestinal microbiota engages in complex interactions with the host, facilitating the digestion and absorption of nutrients, biotransformation and detoxification of intestinal metabolites, and the synthesis of essential bioactive compounds. These include amino acids, vitamins, and short-chain fatty acids (SCFAs), which are critical for maintaining physiological functions and metabolic balance [8].

Disruption of the intestinal microbiota, commonly referred to as dysbiosis, can adversely impact host health and is associated with the development of various disorders, including obesity, diabetes mellitus, irritable bowel syndrome, and colorectal cancer [48]. Therefore, the maintenance of microbial homeostasis within the gut is essential for preserving normal physiological function and preventing disease. Therefore, to maintain a balanced and functionally stable intestinal microbiota, it is essential to employ external interventions aimed at modulating microbial composition, particularly by enhancing the abundance of beneficial microorganisms while suppressing the proliferation of pathogenic species.

Probiotics are defined as viable microorganisms that confer health benefits to the host when administered in adequate amounts. These beneficial microbes contribute to the modulation of the intestinal microbial community by promoting a favorable microbial balance and inhibiting the establishment and proliferation of pathogenic organisms within the gut. Furthermore, probiotics play a significant role in maintaining intestinal integrity by supporting the formation of a protective mucosal barrier, enhancing epithelial barrier function, and modulating immune responses, thereby improving overall host immunity [45]. Based on the functional attributes of probiotics, it is essential to elucidate their mechanisms of action within the host and to develop strategies that facilitate their survival, proliferation, and metabolic activity in the gastrointestinal environment (Fig 1).

The proliferation and metabolic activity of probiotic microorganisms are significantly influenced by the presence of prebiotics. Prebiotics are selectively fermentable dietary components, predominantly non-digestible polysaccharides,

that resist digestion in the upper gastrointestinal tract and are subsequently utilized by beneficial gut microbiota. Through this selective utilization, prebiotics stimulate the growth and activity of advantageous microorganisms within the host [23]. Prebiotics play a significant role in modulating immune function, enhancing resistance against pathogenic microorganisms, and influencing host metabolic processes. Additionally, they facilitate the absorption of essential minerals and contribute to the overall improvement of host health and physiological well-being [29]. Prebiotics generally encompass a diverse group of bioactive substrates, including polysaccharides, oligosaccharides, microalgal derivatives, and compounds derived from natural plant sources. These substances are widely distributed across various biological materials. In recent years, novel prebiotic candidates have been increasingly identified in sources such as algae, fruit juices, fruit peels, seeds, traditional medicinal plants, and microbial systems. These emerging prebiotics predominantly comprise complex biomolecules, including polysaccharides, polyphenolic compounds, and polypeptide-based polymers, which contribute to their functional properties.

Most earlier research has focused on elucidating the health-promoting effects of prebiotics and probiotics [25]. However, comprehensive, systematic investigations addressing the diversity of prebiotics and probiotics, their mechanisms of action, and their interactions remain limited. Accordingly, this study presents an extensive overview of commonly recognized prebiotics, along with emerging sources and their functional roles within the intestinal environment. It further examines the classification, functional attributes, and practical applications of probiotics, with particular emphasis on elucidating their mechanisms of action in the host.

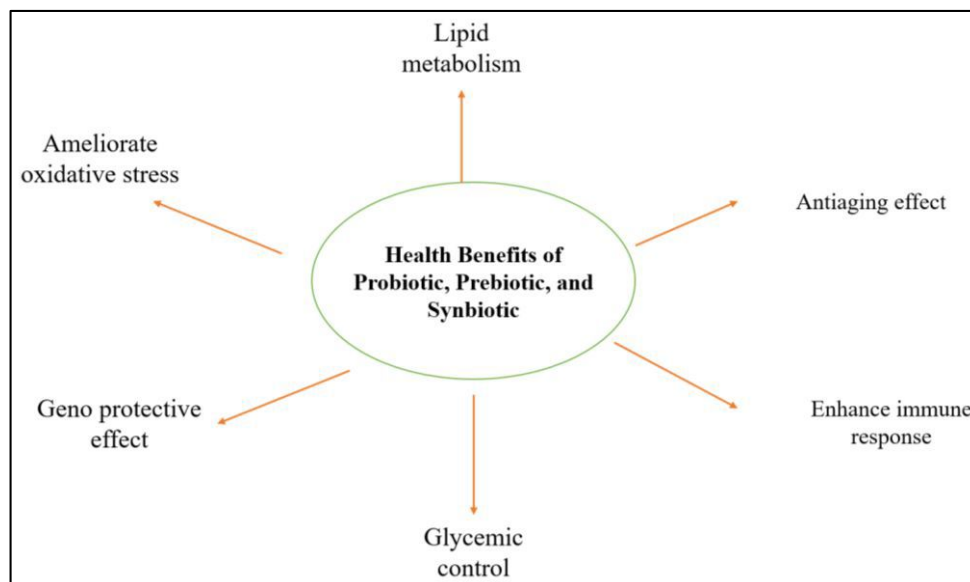


Fig 1: Overall health benefits related to Probiotic Probiotic and Synbiotic

Mechanisms of action of prebiotics

Prebiotics serve as fermentable substrates for beneficial gut microorganisms, leading to the generation of metabolites such as short-chain fatty acids (SCFAs). These bioactive compounds play a crucial role in maintaining intestinal homeostasis and exert systemic physiological effects beyond the gastrointestinal tract [26]. Elucidating the precise mechanisms through which prebiotics improve gastrointestinal health and mitigate the risk of various

digestive disorders and associated comorbidities is essential for fully harnessing their therapeutic potential. Prebiotics, including inulin, fructo-oligosaccharides (FOS), and galacto-oligosaccharides (GOS), are non-digestible dietary fibers that resist enzymatic digestion in the upper gastrointestinal tract and are delivered intact to the colon, where they undergo selective fermentation by the resident microbiota [21]. These non-digestible fibers function as selective substrates for beneficial gut microorganisms,

including probiotic genera such as *Lactobacillus* and *Bifidobacterium*. Through this targeted utilization, prebiotics facilitate the growth, colonization, and metabolic activity of these advantageous microbes, thereby contributing to the maintenance of a balanced intestinal microbiota^[24].

Short-chain fatty acids (SCFAs) generated through the microbial fermentation of prebiotics contribute to a reduction in intestinal pH, typically from approximately 6.5 to around 5.5. This acidification of the gut environment inhibits the proliferation of pathogenic microorganisms while favoring the growth and metabolic activity of beneficial bacteria that are well adapted to such conditions. Consequently, this shift in the intestinal milieu supports the maintenance of microbial balance and overall gut health^[34]. In a study conducted by^[47], substrates including inulin, lactose, galacto-oligosaccharides (GOS), and fructo-oligosaccharides (FOS) were evaluated using an *in vitro* colon model to investigate the influence of pH gradients, representative of physiological colonic conditions, on gut microbiota composition and metabolite production. The findings demonstrated that lower pH conditions significantly altered microbial composition, characterized by an increased relative abundance of *Bifidobacterium* spp. and a reduction in *Bacteroides* spp.

Furthermore, short-chain fatty acid (SCFA) production was modulated by higher simulated colonic pH in a manner dependent on both the microbial donor and substrate type. Elevated pH conditions enhanced butyrate production from inulin fermentation, accompanied by an increased abundance of butyrate-producing bacteria such as *Butyrivibrio*. Additionally, higher colonic pH levels were associated with increased relative abundances of *Phascolarctobacterium*, *Bacteroides*, and members of the *Rikenellaceae* family, along with enhanced propionate production when GOS and FOS were utilized as substrates.

The gut-associated lymphoid tissue (GALT) constitutes a critical component of the host immune system. Prebiotics promote the proliferation of beneficial gut microbiota, which interact with GALT and contribute to the modulation and regulation of immune responses^[38]. This interaction facilitates the maintenance of immune homeostasis and attenuates inflammatory responses through the regulation of immune activity within the intestinal environment^[50]. Within the intestinal environment, short-chain fatty acids (SCFAs) play a significant role in modulating immune responses. They promote immune tolerance and regulate the activity of immune cells, particularly regulatory T cells (Tregs). Through these immunomodulatory effects, SCFAs contribute to the maintenance of gut homeostasis and support overall immune function^[28]. Prebiotics contribute to the preservation of intestinal barrier integrity by promoting the proliferation of beneficial microbiota, which stimulate the production of key structural components such as tight junction proteins and mucins^[29].

Tight junction proteins play a critical role in maintaining epithelial integrity by sealing intercellular spaces, thereby

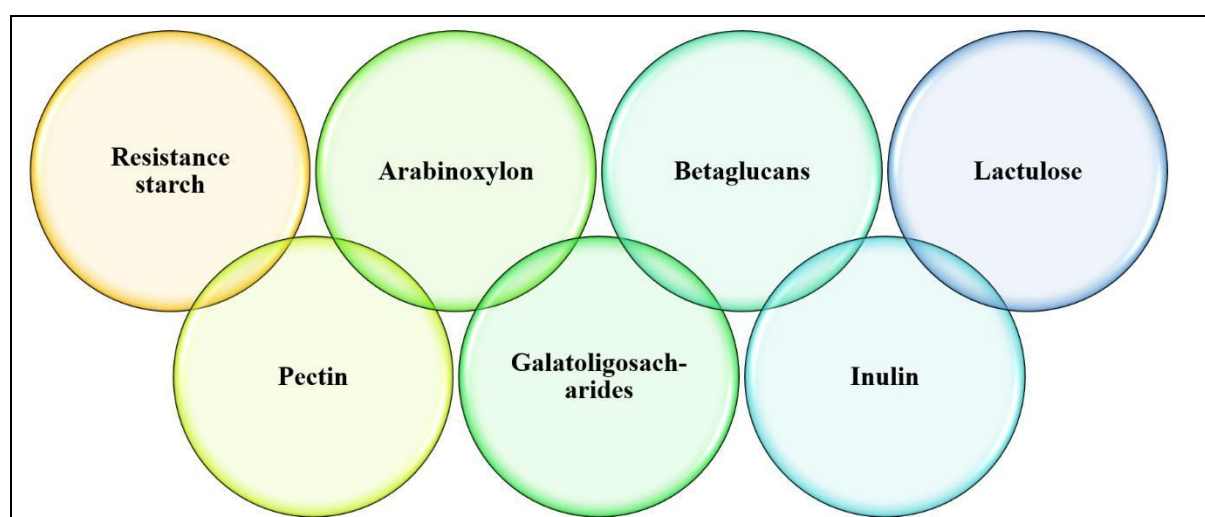
preventing the translocation of pathogens and harmful substances into the systemic circulation. Mucins, on the other hand, form a protective mucus layer over the intestinal epithelium, providing an additional barrier against luminal insults. Colonocytes, the epithelial cells of the colon, primarily derive their energy from short-chain fatty acids (SCFAs), particularly butyrate. By serving as an energy source, SCFAs support epithelial cell metabolism, promote mucosal regeneration, and contribute to the maintenance of intestinal barrier integrity^[12]. Prebiotics have been shown to enhance the functional activity of key immune cells, including phagocytes and lymphocytes, which play essential roles in the recognition and elimination of pathogenic microorganisms^[27]. Prebiotics facilitate the functional activity of immune cells by promoting the proliferation of beneficial microbiota and modulating host immune responses. Through these mechanisms, they enhance the host's defense against infections and contribute to the maintenance of intestinal health^[2]. Short-chain fatty acids (SCFAs), generated through the microbial degradation of prebiotics in the intestine, also play a significant role in supporting and modulating the host immune defense system^[39], reported that prebiotic interventions exert differential effects in individuals with non-alcoholic fatty liver disease (NAFLD) and in obese patients who have undergone gastric bypass surgery, proposing several mechanistic hypotheses based on molecular and biochemical pathways. Specifically, the partial fermentation of non-digestible carbohydrates into short-chain fatty acids (SCFAs), along with a reduction in endogenous intestinal alcohol production, may contribute to a decreased risk of NAFLD progression, primarily through improvements in insulin sensitivity. Prebiotics indirectly suppress the proliferation of pathogenic microorganisms by promoting the growth and metabolic activity of beneficial gut microbiota, thereby contributing to a competitive and inhibitory intestinal environment^[35]. Within the intestinal environment, beneficial microorganisms compete with pathogenic bacteria for available nutrients and occupy adhesion sites on the epithelial surface. This competitive exclusion limits the attachment, colonization, and subsequent proliferation of pathogenic organisms^[33].

Health benefits of Prebiotic

Prebiotics are beneficial microorganisms that help maintain a balanced intestinal microbiota by inhibiting the growth of harmful pathogens. Prebiotics, such as inulin, Lactulose galactooligosaccharides, arabinosyl, resistance starch, pectin and betaglacans (Fig 2), serve as selective substrates that promote the growth of these beneficial microbes (Fig 2). They play a crucial role in improving digestive health, enhancing nutrient absorption, and strengthening the intestinal barrier. Additionally, prebiotics support immune function by modulating immune responses, thereby contributing to overall health and reducing the risk of various gastrointestinal and metabolic disorders, as shown in Table 1.

Table 1: Functional Profile of Prebiotics and Their Health Effects

Prebiotic	Specific selective microbial growth	Short chain fatty acid produced	Specific health Benefit	Source
Inulin	<i>Bifidobacterium longum</i> , <i>Lactobacillus acidophilus</i> , <i>Catenibacteria</i> , <i>Bifidobacteria</i> and <i>Collinsella</i>	Enhanced production of acetate and butyrate	Promotes better digestion, increases mineral uptake, and supports immune function.	[49]
Fructooligosaccharides (FOS)	<i>Bifidobacterium lactis</i> , <i>Lactobacillus rhamnosus</i>	Elevated synthesis of acetate and butyrate	Enhances satiety, lowers blood glucose levels, and supports intestinal health	[6]
Galactooligosaccharides (GOS)	<i>Bifidobacterium</i> , <i>Lactobacillus</i>	Enhanced production of propionate and butyrate	Supports immune function, enhances calcium absorption, and promotes gut health	[22]
Type 2 Resistant Starch	Selectively promotes <i>Bifidobacteria</i> while suppressing <i>Bacteroides</i> , <i>Dorea</i> , and <i>Blautia</i> , and is utilized by microbes such as <i>Bifidobacterium adolescentis</i> and <i>Ruminococcus bromii</i> .	Elevated synthesis of acetate and butyrate	Improved insulin sensitivity, reduced appetite, enhanced gut health	[32]
Pectin	Promotes the proliferation of <i>Sutterella</i> , <i>Lachnospira</i> , <i>Bifidobacteria</i> , and <i>Clostridia</i> , while decreasing the abundance of other microbial populations.	Leads to higher acetate and butyrate levels while reducing propionate production	Results in reduced cholesterol levels and enhanced gut barrier integrity	[3]
Arabinogalactan	Promotes the proliferation of <i>Faecalibacterium</i> , <i>Coprococcus</i> , <i>Bifidobacterium</i> , <i>Lactobacillus</i> , and <i>Bacteroides</i>	Enhances the production of acetate and butyrate	Strengthens immune function and supports overall gut health	[6]
Beta-glucan	Promotes the growth of <i>Lactobacillus</i> , <i>Enterococcus</i> , and <i>Coprobacillus</i> species while suppressing <i>Dorea</i> populations	Boosts acetate and butyrate production	Leads to lower cholesterol levels while improving immune function	(Yang <i>et al.</i> , 2013)
Xylooligosaccharides (XOS)	Encourages the growth of <i>Bifidobacteria</i> , <i>Bacteroides</i> , and members of the <i>Lachnospiraceae</i> family	Enhances the production of propionate and butyrate	Promotes regular bowel movements and strengthens immune function	[44]
Lactulose	<i>Bifidobacteria</i> , <i>Lactobacillus</i>	Elevates the levels of acetate, lactate, propionate, and butyrate	Helps relieve constipation while promoting better gut health	[7]
Soy Oligosaccharides	Promotes the growth of <i>Lactobacilli</i> and <i>Clostridia</i> while inhibiting <i>Bifidobacterium</i> and <i>Bacteroides</i>	Enhances the production of acetate, lactate, propionate, butyrate, and branched-chain fatty acids (BCFAs)	Promotes better lipid metabolism and strengthens immune function.	[11]
Type 3 Resistant Starch	Specifically promotes the proliferation of <i>Bifidobacteria</i> .	Elevates acetate and butyrate production	Supports colonocyte health, reduces inflammation, and may lower the risk of colorectal cancer.	[17]

**Fig 2:** Types of Prebiotics**Synbiotics**

The concept of prebiotics was first introduced by [14], also proposed the potential for combining prebiotics and probiotics to form synbiotics [14]. Subsequently, synbiotics

were classified into two major categories based on their functional interactions: complementary and synergistic synbiotics, as described [19]. Complementary synbiotics consist of probiotics and prebiotics selected independently,

where each component exerts distinct physiological effects or health benefits. In such systems, the prebiotic is not necessarily selectively utilized by the probiotic strain and may instead be metabolized by other members of the gastrointestinal microbiota. Consequently, the probiotic organism may not gain a competitive ecological advantage and, in some cases, may not be capable of fermenting the substrate. Therefore, the overall effect of complementary synbiotics is typically additive, reflecting the independent contributions of each component^[19].

In contrast, synergistic synbiotics are specifically formulated so that the prebiotic substrate selectively enhances the growth and metabolic activity of the co-administered probiotic strain^[19]. This targeted interaction promotes improved survival, colonization, and functional efficacy of the probiotic within the gut environment. Unlike complementary synbiotics, these formulations do not depend on the presence of other microbial populations capable of fermenting the prebiotic substrate. Furthermore,

considering the well-established inter-individual variability in gut microbiota composition and response to dietary interventions^[37], synergistic synbiotics provide a significant advantage by reducing non-responder outcomes. By delivering both the probiotic strain and its specific growth substrate simultaneously, they enhance the consistency and effectiveness of microbiota modulation.

Health benefits related to synbiotics

Synbiotics, a combination of probiotics and prebiotics, provide enhanced health benefits by synergistically improving the growth and activity of beneficial gut microorganisms. They help restore microbial balance, promote the production of short-chain fatty acids, and improve digestive health. Additionally, synbiotics strengthen the intestinal barrier, support immune function, and reduce inflammation, thereby contributing to overall gut health and lowering the risk of various metabolic and gastrointestinal disorders (Table 2).

Table 2: Health Benefits and Mechanisms of Synbiotics

Health Aspect	Mechanism of Action	Observed Benefits	Source
Gut microbiota modulation	Selective stimulation of beneficial bacteria	Improved microbial balance and diversity	[43]
Short-chain fatty acid production	Enhanced fermentation producing acetate, propionate, butyrate	Improved colon health and energy metabolism	[42]
Digestive health	Improved gut motility and microbial activity	Relief from constipation and better digestion	[10]
Immune system support	Modulation of gut-associated lymphoid tissue (GALT)	Enhanced immune response and reduced infections	[4]
Gut barrier function	Strengthening of intestinal epithelial integrity	Reduced intestinal permeability	[18]
Anti-inflammatory effects	Reduction in pro-inflammatory cytokines	Lower inflammation and improved gut health	[31]
Lipid metabolism	Regulation of cholesterol metabolism	Reduced serum cholesterol levels	[1]
Glycemic control	Modulation of glucose metabolism and insulin sensitivity	Improved blood glucose regulation	[46]
Colon health	Increased butyrate production and colonocyte nourishment	Reduced risk of colorectal disorders	[13]
Pathogen inhibition	Competitive exclusion and antimicrobial compound production	Reduced growth of harmful bacteria	[30]

Commercial Synbiotics: Challenges, Limitations, and Future Perspectives

By 2018, the global probiotic market was projected to surpass USD 40 billion, while the prebiotic sector was expected to approach USD 5 billion, reflecting substantial commercial growth and consumer interest^[5]. Despite this expansion, significant scientific and industrial challenges persist, particularly in establishing robust clinical evidence to substantiate health benefits^[40]. A major limitation identified is the difficulty in demonstrating consistent clinical efficacy, further complicated by variations in regulatory requirements for health claims across different regions^[41].

At present, neither the European Food Safety Authority (EFSA) nor the United States Food and Drug Administration (FDA) has approved specific health claims for probiotic or synbiotic formulations. Regulatory classification also presents a challenge, as such products may be categorized either as foods or pharmaceutical agents depending on their intended use^[15]. According to FDA guidelines, any substance, including probiotics, intended for the prevention, treatment, or diagnosis of disease is regulated as a drug and must comply with stringent pharmaceutical approval processes. Similarly, European Union regulations mandate that health claims must be scientifically substantiated, clear, and not misleading to consumers^[41]. Consequently, well-designed human

intervention studies are essential to validate the efficacy of these products.

Synbiotic formulations are commonly incorporated into food matrices, particularly fermented dairy and non-dairy products. While prebiotics are generally stable and compatible with a wide range of food applications, the viability of probiotics is often compromised by environmental factors such as temperature, oxygen, and processing conditions, thereby limiting their use in non-refrigerated products (Saulnier, 2008). Advances in microencapsulation technologies, however, have shown promise in enhancing the stability and survival of probiotic microorganisms during processing and storage. These innovations may facilitate the development of novel synbiotic products, including confectionery, beverages, dairy products, and chocolate-based systems^[20].

It is noteworthy that many commercially available prebiotic and synbiotic products contain relatively low concentrations of prebiotic components, which may be insufficient to elicit significant physiological effects. Such low inclusion levels are often employed to minimize gastrointestinal discomfort and reduce production costs^[9].

The formulation of clinically effective synbiotic combinations remains complex and requires careful consideration of several factors. Determination of the minimum effective dose for both probiotic and prebiotic components is essential. Additionally, the design of clinical

trials should incorporate appropriate controls, including placebo, probiotic-only, and prebiotic-only groups, to accurately assess additive or synergistic effects. Clear justification for the selection and pairing of probiotic strains with specific prebiotic substrates is also necessary. Furthermore, establishing causality requires precise detection, quantification, and monitoring of the administered probiotic strain within the gastrointestinal tract. Comprehensive evaluation of changes in gut microbiota composition is equally important to understand underlying ecological interactions, such as cross-feeding, niche competition, niche partitioning, and exclusion phenomena within the resident microbial community.

Future Perspectives on Sustainable Prebiotics, Probiotics, and Synbiotics

The future development of prebiotics, probiotics, and synbiotics is increasingly driven by the need for sustainability, innovation, and personalized nutrition. These functional components are gaining attention as eco-friendly and health-promoting alternatives to synthetic additives and antibiotics, aligning with global efforts to promote sustainable food systems and improve public health. Their integration into dietary and therapeutic strategies offers significant potential to enhance gut health while minimizing environmental impact. One of the most promising areas is the utilization of sustainable and low-cost sources for prebiotic production. Agricultural by-products, food processing residues, fruit peels, and algal biomass are being explored as novel substrates for extracting prebiotic compounds. This approach not only reduces food waste but also supports the development of a circular bioeconomy by converting underutilized resources into valuable functional ingredients. Such innovations are expected to improve the economic feasibility and large-scale production of prebiotics. In the field of probiotics, future research is focused on the development of next-generation probiotics (NGPs), which include newly identified microbial strains with specific health benefits. Advances in omics technologies, such as genomics and metagenomics, are enabling the identification of targeted probiotic strains with enhanced functional properties. These developments will facilitate the design of precision probiotics tailored to individual gut microbiota profiles, thereby improving their efficacy and consistency in different populations. Synbiotics are expected to play a central role in future microbiome-based interventions due to their synergistic effects. The rational design of synbiotic formulations, where specific prebiotics are paired with compatible probiotic strains, will enhance microbial survival, colonization, and metabolic activity. This targeted approach can help overcome inter-individual variability in gut microbiota composition and improve therapeutic outcomes. Technological advancements, such as microencapsulation and controlled-release delivery systems, will further support the stability and viability of probiotics during processing and storage. These innovations will enable the incorporation of synbiotics into a wider range of food products, including plant-based and non-refrigerated systems. Additionally, the application of prebiotics, probiotics, and synbiotics in sustainable agriculture and animal nutrition is gaining importance. Their use as alternatives to antibiotics in livestock can improve animal health, reduce antimicrobial resistance, and contribute to environmentally sustainable farming practices.

Conclusion

The intestinal microbiota is a complex and essential component of human health, playing a key role in metabolism, immune regulation, and maintenance of gut integrity. An imbalance in this microbial ecosystem (dysbiosis) is associated with various chronic diseases, highlighting the need for effective strategies to maintain microbial homeostasis. Probiotics and prebiotics serve as important tools for modulating gut microbiota. Probiotics enhance microbial balance and immune function, while prebiotics selectively stimulate the growth of beneficial bacteria and promote the production of short-chain fatty acids (SCFAs), which support gut health and metabolic functions. Synbiotics, combining both probiotics and prebiotics, offer a more effective approach by improving probiotic survival and activity. However, challenges such as limited clinical evidence, regulatory issues, and stability of formulations still exist. Future research should focus on well-designed clinical studies and advanced technologies to optimize synbiotic formulations. Overall, prebiotics, probiotics, and synbiotics hold significant potential for improving gut health and preventing disease.

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