

An Evidence-Based Review of Probiotics and Prebiotics

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Probiotics and prebiotics have a variety of beneficial effects on the host's health. Extensive studies have established probiotic strains such as *Lactobacillus* and *Bifidobacterium*, and further the concept of next-generation probiotics has been advocated. Clinical trials and mechanism of action research have demonstrated that the gut microbiota and host health are inextricably linked, and that probiotics can benefit intestinal-related disorders such as inflammatory bowel disease by controlling the gut microbiota. Accordingly, the host's gut microbiota has the greatest direct effect on the efficiency of probiotics and prebiotics. Due to the highly individualized gut microbiota, supplementation with probiotics and prebiotics must take the host's gut microbiota into account. Personalized and specific interventions, as well as the development of next-generation probiotics, will be the new focus of research.

Keywords: Probiotics; Prebiotics; Gut Microbiota; Inflammatory Bowel Disease; Intervention

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THE term “probiotic” originates in Greek and means “for life.” It was coined in 1953 by German scientist Werner Kollath to refer to “a material necessary for the health and development of life” (1). The World Health Organization defined it in 2001 as “a living microorganism that, when supplemented appropriately, benefits the host's health” (2). Probiotics are acid and bile salt resistant and can survive safely in the digestive system and colonize the intestinal mucosa (3). While different probiotic strains may have varying degrees of efficiency, they can have favorable synergistic effects on the host. Currently, the majority of probiotics belong to the genera *Lactobacillus* and *Bifidobacterium* (4). It is critical to emphasize that probiotics are a strain-level notion. A probiotic's effect does not necessarily imply that the strain or genus to which it belongs has the effect.

The term “prebiotics” refers to a family of substances that

the body cannot digest, such as fructooligosaccharides and galactose. The International Scientific Association for Probiotics and Prebiotics (ISAPP) defined prebiotics as “substances that are selected for use by microorganisms within the host and are advantageous to the host's health” in 2017 (5). Prebiotics are distinct from the majority of dietary fibers (fruit gum, cellulose, xylan, etc.). While most dietary fibers can promote the growth of most microorganisms in the gut, prebiotics promote the growth of beneficial microorganisms within the host, or probiotics ingested into the body (6). As a result, prebiotics are defined in terms of probiotics. Prebiotics are nutrients that encourage the growth of *Lactobacillus* and *Bifidobacterium*. With the growth of the spectrum of probiotics comes an update to the concept of prebiotics. They are currently referred to as prebiotics and should exhibit the following three characteristics: (i) resistance to host digestive enzymes; (ii) fermentation by intesti-

nal microbes; and (iii) the ability to selectively boost the growth of health-promoting gut flora.

Probiotics and prebiotics have grown in popularity as dietary supplements in recent years. As consumers become more aware of the tight connection between gut microbiota and health, market demand for probiotics has risen, and a huge number of enterprises have begun producing and selling various probiotics. However, studies on probiotics have trailed behind the market's growth, resulting in an unequal distribution of product quality. This paper organizes recent advances in probiotics and prebiotics research to facilitate scientific comprehension and theoretical advice for all.

Brief Research History of Probiotics and Prebiotics

In 1907, Mechnikov discovered that the secret to the elderly's lifespan in Bulgaria's Longevity Village was yogurt (7). German soldiers utilized fresh camel excrement to treat diarrhea in Africa during World War II, and the active element was eventually identified as *Bacillus subtilis* (8). In 1921, Rettger et al. demonstrated that *Lactobacillus* increased in abundance in the human intestine following carbohydrate consumption, and this sparked interest in the link between probiotics, prebiotics, and health (9). Over two decades ago, a class of substances called prebiotics was identified to promote health by supporting the growth of *Bifidobacteria* and *Lactobacilli*.

Probiotic and prebiotic research can be loosely divided into four stages. The first stage is the isolation and screening of probiotics, which is also the most fundamental effort, involving the use of pure culture and biochemical methods to separate and screen superior *Lactobacillus* and *Bifidobacterium* strains. The probiotic effect is then validated in the second stage using in vitro research replicating the gastrointestinal fluid environment and animal experiments using mouse models. For example, it was discovered that *Lactobacillus casei Zhang* can increase blood osteocalcin levels in patients with type 2 diabetes and enhance oral glucose tolerance in a rat model on a high fructose diet (10). Clinical experiments are conducted in the third step, and strains with superior probiotic qualities as determined by animal models are employed in clinical controlled trials. The conduct of population trials on a variety of scales has determined the efficacy of probiotics. For example, a meta-analysis of almost 6,000 adults from 19 trials found that probiotics can successfully prevent *C. difficile* infection and that the preventative effect is enhanced when probiotics are administered immediately after antibiotic treatment (11). Another clinical research paper published the same year demonstrated that synbiotics containing *Lactobacillus plantarum* and oligofructose dramatically reduced neonatal sepsis in India (12). Clinical research findings, on the other hand, are inconsistent. The *New England Journal of Medicine* published a clinical study in November 2018 on the use of probiotics in the treatment of children with gastroenteritis in the United States and Canada, concluding that rhamnose LGG was ineffective in children with gastroenteritis (13). Numerous clinical trials progressively convinced that probiotics are not a panacea, and they began to focus on the fourth stage – the probiotics' mechanism of action. The advancement of high-throughput sequencing technologies revealed that hu-

man and animal intestines contain tens of thousands of microbes. These microorganisms contribute to the regulation of host immunity and physiological metabolism, prompting individuals to consider and demonstrate the relevance of probiotics and prebiotics in relation to the gut microbiota (14). Probiotics and prebiotics research has also made significant strides as a result of the boom in gut microbiota studies. Healthy people in rural Thailand who had *Bacillus* in their intestinal tract did not colonize *Staphylococcus aureus* in their intestinal tract or nasal cavity and revealed the mechanism by which *Bacillus subtilis* eliminates *Staphylococcus aureus* through mouse experiments (15). It removes harmful germs by interfering with *Staphylococcus aureus* colonization via the lipopeptide feninterference generated (16). Researchers have made significant progress in elucidating the mechanism of action of probiotics.

Therefore, studies on probiotics and prebiotics have turned gradually away from basic screening and efficacy verification and toward in-depth investigation of the mechanism of action. Scientists have increased their focus on the relationship between probiotics, prebiotics, and gut microbiota. For instance, one study suggested that dysbiosis of the gut microbiota may contribute to mastitis in dairy cows and that probiotics may be used to treat mastitis by restoring gut microbiota balance (17). The gut, on the other hand, is a complex and open microecological environment that is influenced by a variety of factors. More comprehensive and effective studies are required to demonstrate how probiotics and prebiotics function in the human gut. Different probiotics may benefit different people. Probiotics, prebiotics, and their interactions with the gut microbiota remain a work in progress.

Probiotics, Prebiotics, and Inflammatory Bowel Diseases

Probiotics have been shown to protect the integrity of tight junction proteins in intestinal epithelial cells, to prevent excessive penetration, and to decrease pathogenic bacteria colonization (18). As a result, probiotics have been utilized as adjuvant therapy in numerous clinical investigations for inflammatory bowel disease (IBD). IBD is caused by aberrant immune responses in genetically vulnerable individuals in response to specific environmental conditions, with the gut microbiome playing a critical role. The patient's intestinal epithelial cells' tight junction protein is damaged, and commensal bacteria enter the mucosal lamina propria, activating the immune system to resist the inflammatory response and resulting in damage to the intestinal mucosa. IBD is a term that refers to ulcerative colitis (UC) and Crohn's disease (CD). Gut microbiota have been shown to play a critical role in intestinal inflammation, and germ-free animals are not encouraged to develop intestinal inflammation (19, 20). Although animal models of inflammatory bowel disease are nearly totally suppressed in gut sterility, healthy animals transplanted with the gut microbiota of mice with colitis produce intestinal inflammation (21, 22).

A clinical study involving 200 IBD patients and a 36-month follow-up period revealed that the longer the duration of probiotics in CD patients, the lower the incidence of adverse events; CD and UC patients who took probiotics for 75% of the treatment time had the lowest incidence of adverse events, and

the adverse events were reduced by 100% and 93%, respectively, implying that probiotics may be used adjuvantly to treat inflammatory bowel disease (23). Additionally, another study demonstrated that prebiotics significantly reduced the intestinal injury score in a rat model of inflammatory bowel disease and improved inflammatory response indicators in rats (24). However, not all probiotics and prebiotics are beneficial against IBD (25), and in other studies, probiotics had no meaningful effect on remission of active UC in nine of the twelve randomized clinical trials included in the study (26-28). Moreover, another study showed that different dietary fibers have varying effects on colitis in rats, with inulin exacerbating the condition while pectin alleviates it (29).

As a result, the efficacy of various probiotics and prebiotics on IBD cannot be generalized. The efficacy of each probiotic and prebiotic should be supported by clinical evidence, and they should not be mutually exclusive. A single probiotic is beneficial for a single individual. This is not to say that all probiotics are effective for everyone.

Future Generation of Probiotics

With the advancement of research into gut microorganisms, public awareness of the critical nature of host gut health has progressively expanded, prompting researchers to begin exploring for novel probiotic microbes. Along with the classic *Lactobacilli* and *Bifidobacteria*, the concept of next-generation probiotics has been advocated on a number of occasions. At the moment, researchers have identified several health-related gut bacteria, including *Bacteroides*, *Clostridium flexis*, and *Akkermansia*, as prospective microorganisms for the next generation of probiotics (30, 31). While people are actively expanding the scope of probiotics, the majority of these intestinal indigenous bacteria has high nutritional requirements and is extremely sensitive to oxygen, which complicates pure culture and makes large-scale manufacturing difficult (32). Additionally, the safety of these bacteria found in the healthy gut has not been determined, which means that the next generation of bacteria represents a new challenge for industry and research. *Bacteroides*, one of the most prevalent gut bacteria, has several probiotic characteristics, including the ability to ferment a range of carbohydrates to create short-chain fatty acids that are helpful to the host's gut health (33). *Bacteroides polymorpha* and *Bacteroides fragilis* are effective carbohydrate metabolizers and may convert complicated polysaccharides to monosaccharides, which are favorable for the growth of other bacteria (34). *Bacteroides polymorpha* and *Bacteroides fragilis*, on the other hand, are frequently isolated at the infection site. Certain *Bacteroides fragilis* strains, in particular, can form abscesses in order to elude the host's immune response and create enterotoxins that can cause intestinal epithelial tight junction protein damage (35). Additionally, because its decrease or deletion is

connected with illnesses such as metabolic abnormalities, *Akkermansia muciniphila* is a viable next-generation probiotic. However, *Akkermansia muciniphila* has been documented to recur following antibiotic therapy, and its drug resistance is unknown (36). Thus, the next generation of probiotics is a "double-edged sword," and it is critical to assess strain safety, including strain resistance genes, horizontal transfer of drug resistance genes, antibiotic susceptibility, and other issues that require additional research (37).

Probiotics and Prebiotics Research Trends in the Future - Individualized Intervention

Israeli researchers elicited a strong response from the probiotic sector. The study also discovered that probiotic colonization of the host exhibits clear individual and strain uniqueness (38). The identical probiotic product colonized differently in the intestines of 19 healthy volunteers, and it was rather easy for some people to colonize their intestines, while it was completely unable to colonize the guts of another subgroup of the population. The study demonstrated that the human gut is resistant to probiotic colonization, implying that probiotic colonization in the gut is highly dependent on the inherent flora in the guts of volunteers (39). Indeed, individual variances in gut microbiota may dictate whether probiotic strains can be planted, and this is also why the same probiotic may not be helpful for everyone or for the same type of inflammatory bowel disease (40). Not only must we put an end to the "universal theory" of probiotics, but we must also be aware of their "ineffectiveness," scientifically understand probiotics products, use clinical research as a guide, consider the characteristics of the host's gut microbiota, and have a large number of probiotics based on data research that are beneficial to human health.

Furthermore, long-term consumption of dietary fibers such as inulin, oligofructose, and pectin has been linked to an increased risk of liver cancer when the gut microbiota is disturbed (41). Although not all dietary fiber is a prebiotic, the majority of prebiotics are classified as dietary fiber. This cautions us that even the consumption of dietary fiber or prebiotics should take into consideration the host's intrinsic gut flora and that even healthy individuals should consume them in moderation (42).

Probiotics and prebiotics should be used in the future based on the features of the host's gut microbiota, and targeted intervention should be based on a full understanding of the gut microbiota's composition and structure. Considering the interplay of probiotics, prebiotics, and the host's innate flora, elucidating the microorganisms that serve as probiotics and prebiotics, and examining the impact of probiotics and prebiotics on the host's physiological metabolism are all novel study avenues. By controlling gut microbiota, individualized intervention with probiotics and prebiotics may promote host health. ■

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