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REVIEW

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Probiotics: friend or foe to the human immune system

Devendra Singh[1*], Archana Singh[2] and Sunil Kumar[3]

Abstract

Background Live microorganisms known as probiotics have been shown to improve or restore the gut microbiota, which in turn has been linked to improved health. Probiotics are the modern equivalent of a panacea, with claims that they may treat or prevent anything from colic in babies to obesity, diarrhea, and respiratory infections.

Main body of the abstract It has been proven by a few researchers that probiotics are effective in treating numerous ailments by controlling the host's immunological response. But on the other side, the probiotic industry takes a more straightforward, "one-formula-fits-all" approach to probiotic therapy. As the unique native microbiota of each person is another crucial factor in recommending probiotic therapy. Approximately 1000 distinct bacterial species reside in the human gut. It will take further research into how probiotic strains interact with the microbiota, so there is still a long way to go before probiotics can be used to their full potential.

Short conclusion This review study provides a thorough description of probiotics and seeks to establish whether they are beneficial to or harmful to the human immune system and their mode of action.

Keywords Probiotics, Gut, Immune response, Microbiota, Probiotic therapy

Background

In particular, gut maturation, nutrition uptake, energy metabolism, as well as the immune system are all profoundly influenced by the gut microbiota, the complex ecology of billions of microorganisms that live in our gastrointestinal tract (Rusch et al. 2023).

It is generally established that various disease processes are related to compositional as well as metabolic alterations to the gut microbiota or dysbiosis (Manos 2022). In fact, mounting evidence implicates gut microbial dysbiosis in the etiology of a number of illnesses, including cancer, obesity, extra-intestinal diseases as well as type 2 diabetes (Canfora et al. 2019). In this review paper, we are trying to explain the role of probiotics. The term Probiotic is derived from the Latin, which means 'for life. Werner Kollath, a German chemist, gave the term "probiotic" in the year 1953 to describe "active substances that are required for the proper development of life." This phrase was first used in the year 1965 by Lilly and Stillwell to refer to "substances released by one microorganism which promote the growth of another" in a different context (Fernández-Veledo and Vendrell 2019). Probiotics were more clearly described by Fuller in 1992 as "a live microorganisms feed supplement that improves the intestinal flora of the host animal to the benefit of the animal" (de Miranda et al. 2023).

Probiotic bacteria are mostly derived from fermented dairy products as well as vegetables, which have been consumed historically for ages (Zucko et al. 2020). They have already been taken for their beneficial health effects, particularly on digestive issues (Zucko et al. 2020). It's interesting to note that as their use has expanded, so too has our approach to using them. Probiotics are

*Correspondence:
Devendra Singh
devendrasingh.ibst@srmu.ac.in
[1] Faculty of Biotechnology, Institute of Biosciences and Technology, Shri Ramswaroop Memorial University, Barabanki, Uttar Pradesh 225003, India
[2] Department of Zoology, National PG College, Lucknow, India
[3] Department of Biotechnology, Faculty of Allied Health Sciences, Mahayogi Gorakhnath University, Arogya Dham, Balapar Road, Sonbarsa, Gorakhpur, Uttar Pradesh 273007, India

progressively more being ingested as nutritive supplements in the form of pills or capsules, even if fermented milk products and drinks are still their most common sources (de Simone 2019). The amount of live bacteria or yeast consumed has grown by a thousand times on average with this switch from the traditional fermented products to dietary/nutritive supplements in pills, or from 10^5–10^8 of live bacteria/gm of fermented products to 10^9–10^{12} per dose, consumed as a diet supplement (Lin et al. 2023). There is no universal agreement on what constitutes an appropriate daily intake, but some nations have suggested that a dose of live microorganisms should contain no less than 10^9 colony-forming units (Reid et al. 2018). Probiotics must be produced and prepared, regardless of quantity, in a way that ensures microbial survivability in a significant amount during the full shelf life (Ozen and Dinleyici 2015). They are widely used in the food sector as a component in the creation of food products or as supplements (Rezac et al. 2018).

Main text

History

According to a number of academic and popular sources, probiotics were first used by humans in 2000 BC, when they learned how to store milk over longer periods of time. Despite being unaware of their existence, the first food producers used bacteria and yeasts to turn the milk into fermented dairy products (Talib et al. 2019). Fermented foods have been used to treat illnesses for two main reasons: they are very nutritious and contain live microorganisms that can fight off some infections (Leeuwendaal et al. 2022).

But according to recent scientific articles, our ancestors employed yeasts to make beverages far earlier, before 2000 BC (Sicard and Legras 2011). The fermenting dairy products "Laban Rayad" and "Laban Khed," which are still popular in the Middle East today, can be found being used as earlier as 3500 BC based on artifacts from ancient Egypt (Ozen and Dinleyici 2015).

However, because they are strongly tied to the consumption of fermented foods, probiotics have a history that is as old as that of humans (Ozen and Dinleyici 2015). It should be assumed that man started making fermented foods and drinks approximately 10,000 years ago when farming began to supplant hunting and gathering. In actuality, the domestication of animals took place during the Neolithic era of the Age of the Stone (Sicard and Legras 2011). The first population to settle and perfect animal husbandry were the Sumerians. The use of dairy products and milk is linked to a healthy and long life, as in ancient Indian Ayurveda literature (Mahalak et al. 2022).

Recent scientific articles, however, have made it clear that our ancestors used yeasts in the manufacture of beverages far early than 2000 BC (Sicard and Legras 2011). Even, in 1856, a guy who was having issues with his distillery and was making alcohol from sugar beet fermentation asked Pasteur for assistance. He was not getting alcohol; he was getting something like sour milk. Pasteur examined the sour substance's chemical composition and discovered it contained a sizable quantity of lactic acid. When he analyzed the sediments from various containers under a microscope, he discovered that specimens from the containers where alcoholic fermentation had taken place revealed significant levels of yeast (Some et al. 2020).

He discovered "far smaller cells than that of the yeast" in the lactic acid-contaminated containers, in comparison. According to Pasteur's research, there are two different types of fermentation: alcoholic as well as lactic acid. Bacteria along with the yeast contribute to the production of lactic acid and alcohol, respectively (Mazzarello 2002).

Beginning in the early 1900s, a Russian research scientist there at Paris Pasteur Institute named Elie Metchnikoff conducted groundbreaking investigations on probiotics (Gordon 2016). These findings would later earn him the Nobel Prize. In contrast to Metchnikoff, who first sought to determine whether these germs would have any impact on human health, Louis Pasteur discovered the organisms essential for the fermentation process (Gordon 2016). He attributed the habitual eating of fermented dairy foods like yogurt to the longer life expectancy of rural Bulgarians (Ozen and Dinleyici 2015).

Previously because probiotic formulations carrying the bacterial species have been utilized by human beings, the historical use of camel feces carrying *Bacillus subtilis* for the cure of dysentery seems probable. However, as there are few adequate trials, it is challenging to determine whether *B. subtilis* is effective as a probiotic for treating diarrhea (Lee et al. 2019).

A wide variety of bacteria have been identified as prospective probiotic candidates in the fish gallbladder, but *Lactobacillus* and *Bacillus* species have received particular interest due to their potent antagonistic activity, availability, and synthesis of extracellular enzymes and were commonly used by the subcontinent ayurvedic physicians in earlier days (El-Saadony et al. 2021).

An expert consensus agreement on the definition and proper application of the term "probiotic"—live microbes that, when given in sufficient quantities, benefit the host—was released in 2013 (Salminen et al. 2021). Additionally, more than other strains, modern technology has chosen those strains that produce

fermented milk having good nutritional and organoleptic features. As per a consensus document, yogurt and other products created from fermented milk could be regarded as the first functional foods (Savaiano and Hutkins 2021; Szydłowska and Sionek 2022).

Uses of microorganisms as probiotics

The gut microbiota serves as a microbial ecosystem, and current probiotics research aims to characterize and analyze its composition. It is important to note that probiotic effects vary based on the strain (Yang et al. 2022). Therefore, each probiotic strain has a unique health claim, and the probiotic potential of bacterial strains of the same species varies greatly (Karaseva et al. 2023).

Because of this, it is advised that strain identification be made in order to attribute each probiotic's functions to a particular strain. This could be done by strain-typing pulsed-field gel electrophoresis, DNA-DNA hybridization, and 16S RNA sequencing, among other molecular techniques.

In addition, the PCR technique can provide quick qualitative and quantitative data on the composition of intestinal microbes. A solitary strain may have various advantages, and it has been reported that many probiotics supplements comprise one strain both separately and in a mixture (Li et al. 2021).

Every person is born with a unique gut microbiota that contributes to unique processes like the metabolism of nutrients, maintenance of the gut mucosal barrier's structural coherence, as well as immunomodulation. The term "probiotics" has historically been used to refer to the most common strains of *Lactobacillus* and *Bifidobacterium* (Khatoon et al. 2023).

The term "probiotics" has historically been used to refer to the most common strains of *Bifidobacterium* and *Lactobacillus*; on the other hand, it can also refer to bacteria like *Streptococcus*, *Bacillus*, *Enterococcus*, and *Saccharomyces*.

Probiotics may also include bacteria like *Leuconostoc, S. thermophilus,* and *L. bulgaricus* bacterial species, which do not typically colonize the intestinal tract. These bacteria don't colonize the gut and have little to no impact on the microbial balance there (Messina 2004). However, they do have a significant impact on the food industry (Chauhan et al. 2022). Numerous studies are being conducted to identify the futuristic genre as well as new varieties that may be used as probiotics (Mishra and Acharya 2021). Before being used, these new strains must be evaluated and analyzed using recognized and validated selection criteria.

Immune system

Innate immunity triggers the immune response after encountering foreign materials as well as tissue damage. By activating adaptive immune reactions against recurring insults and causing inflammation, innate immunity plays a protective role in maintaining the homeostasis of the host (Vanderpool et al. 2008). However, an unbalanced immune response causes disease, unchecked tissue damage, and severe inflammation. The host mucosal immune system's ability to sense the intestinal microbiota is crucial for preserving intestinal homeostasis and triggering a range of protective responses throughout the body (Vanderpool et al. 2008). Therefore, altering the gut microbiome is an alternative strategy that may be used to promote health and/or prevent and/or treat diseases (Vanderpool et al. 2008).

Three probiotics that have been extensively studied and are frequently used in both humans and animals are *Saccharomyces, Bifidobacterium,* and *Lactobacillus*. Probiotics have been shown to have a number of advantageous effects on the host's intestinal mucosal defense system (Kiani et al. 2022). The production of bacteriocidal substances, which block the effects of pathogenic bacteria, is one of these. Another is preventing pathogens and toxins from adhering to the gut wall. Probiotics support intestinal epithelial survival, improve barrier performance, and elicit barrier protection responses from intestinal epithelium to maintain intestinal epithelial homeostasis (Gou et al. 2022). Most importantly, one of the most likely mechanisms underlying the positive effects of probiotic strains on human health is immune system modulation. Through toll-like receptor-regulated signaling pathways, probiotics have been shown to improve/enhance innate immunity as well as control pathogen-induced inflammation (Vanderpool et al. 2008).

The good effect of probiotics

The natural and predominant components of the intestinal microbiota are hundreds of different species of bacteria. Among the many intestinal microbes, those thoughts to likely have the potential to improve the host's health by altering the gut microbiome are frequently chosen as probiotics (Mahalak et al. 2022). According to reports, healthy probiotic bacterial strains include species from the genera and *Bifidobacterium* (Iqbal et al. 2021).

Bifidobacterium lactis, Lacticaseibacillus casei, Bifidobacterium bifidum, Bifidobacterium longum, Lactobacillus acidophilus, as well as *Lactiplantibacillus plantarum* are some of the representative species (Żółkiewicz et al. 2020). Probiotics are thought to have a number of important health advantages, such as enhancing the immune system, lowering cholesterol levels, preventing cancer,

treating diarrhea brought on by IBS, reducing blood pressure, and improving lactose metabolism (Dash et al. 2023).

Probiotics are living microorganisms that give their hosts health benefits when given in sufficient doses. Probiotics have been studied for their outcomes for patients with afflicted intestines and stomachs in a number of systematic reviews and meta-analyses. According to a recent systematic review, *B. infantis* has demonstrated effectiveness in treating IBS symptoms (McFarland et al. 2021; Zhang et al. 2022). Probiotics may be useful in the treatment of IBS, according to a number of other authors (McFarland et al. 2021). However, the information on this topic is still inconclusive.

There isn't much research on using probiotics to cure IBS (Irritable bowel syndrome) in Asia. In a Japan-based single-blind follow-up study, 68 IBS patients were randomized to probiotics containing *L. helveticus, L. acidophilus, Bifidobacterium*, or a control group. Significant reductions in pain, as well as bloating, were noted in the treated group after 6 weeks of treatment when compared to the control group (Oh et al. 2023; Zhang et al. 2022).

In contrast to Traveler's Diarrhea, probiotics had no discernible effects on pouchitis, IBS, *C. difficile*, *H. pylori* disease, necrotizing enterocolitis, or antibiotic-associated diarrhea, according to Ritchie and Romanuk's meta-analysis (Ritchie and Romanuk 2012).

All of the tested strains and mixtures had positive effects, with the exception of *Lactobacillus acidophilus, Lactobacillus plantarum*, and *Bifidobacterium infantis*. Ganji-Arjenaki and Rafieian-meta-analysis Kopaei's of probiotics in cure of bowel inflammation discovered a significant difference in ulcerative colitis patients and children with bowel inflammation, but not for Chron's disease (Ganji-Arjenaki and Rafieian-Kopaei 2018). Mixtures of different probiotic strains were the most productive in this case.

Irrespective of the probiotics chosen to take, most of the reported earlier research that is centered on the effectiveness of probiotic usage, as well as gastrointestinal illnesses, is still insufficient (Onofrei et al. 2023). When the effectiveness of the two probiotic strains with the best documentation, namely *L. rhamnosus* GG (LGG) as well as *B. animalis* subsp. lactis BB-12 are examined, and the situation is comparable (BB-12). "The current evidence signifies that LGG, as well as BB-12 supplementation, could promote human health and enhance the daily wellness of customers, even though most (previous) trials do not meet the rigorous requirements required for science-based corroboration of a health claim in Europe," Flach et al. (2018) wrote in their conclusion.

A recent study from Korea revealed B-containing composite probiotics. Treatment of IBS patients with *B. bifidum* BGN4, *L. acidophilus* AD031, as well as other species, was risk-free and productive (Chlebicz-Wójcik and Śliżewska 2021). A Chinese study found that treating IBS-like patients with severe diarrhea with a probiotic preparation reduced their signs of abdominal discomfort, bowel movement frequency, urgency, and distension (Xiao et al. 2003).

Bad effects of probiotics

Probiotics are being used more frequently for their health advantages in treating a variety of illnesses and diseases, including cancer, depression, bacterial vaginosis, obesity, allergies, and even obesity (Byakika et al. 2019; Tomé-Castro et al. 2021; Masiá et al. 2021).

Worrying reports that claim probiotics can even also have harmful effects on the person's health only serve to compound the issue of the lack of proper evidence for the medicinal advantages of probiotics (Luo et al. 2022). This idea has been around for a while, particularly for at-risk groups like patients who are immunocompromised, have an abnormal gastrointestinal mucosal layer, or are recovering from surgery. Fungemia and bacteremia were the most frequently reported probiotic side effects, but the list is likely just getting started (Lerner et al. 2019). However, it seems that research rarely focuses on the probiotics' safety. After the published studies on the advantages of probiotics, articles were published about the safety of probiotic administration follow. This may be partially a result of the researchers' reluctance to publish adverse effects (Bafeta et al. 2019).

Mechanism of probiotics

Advancement of the epithelial barrier, enhanced adhesion to the intestinal mucosa, concurrent suppression of bacterial adhesion, production of anti-bacterial substances, competitive exclusion of microbial pathogens, and immune system modulation are some of the main probiotic mechanisms of action (Singh et al. 2021, 2022; Singh and Agarwal 2021; Singh and Agarwal 2022; Sartor 2006; Kang et al. 2022). Some probable mode of action of probiotics is shown in Fig. 1.

The complex interaction of host-microbe interactions will be clarified by the latest characterization of a host family of pattern-recognition molecules, like as TLR as well as NOD-like receptors, and modulating important signaling pathways, i.e., NF-B as well as MAPK, in terms of their ability to improve or suppress the activation as well as effect downstream pathways (Sartor 2006; Halloran and Underwood 2019; Peng et al. 2022).

Commensal bacteria must stimulate these receptors in order to trigger measured antibacterial responses with little inflammatory tissue damage (Dohare et al. 2021a, 2021b; Singh and Agarwal 2023; Liu et al. 2023).

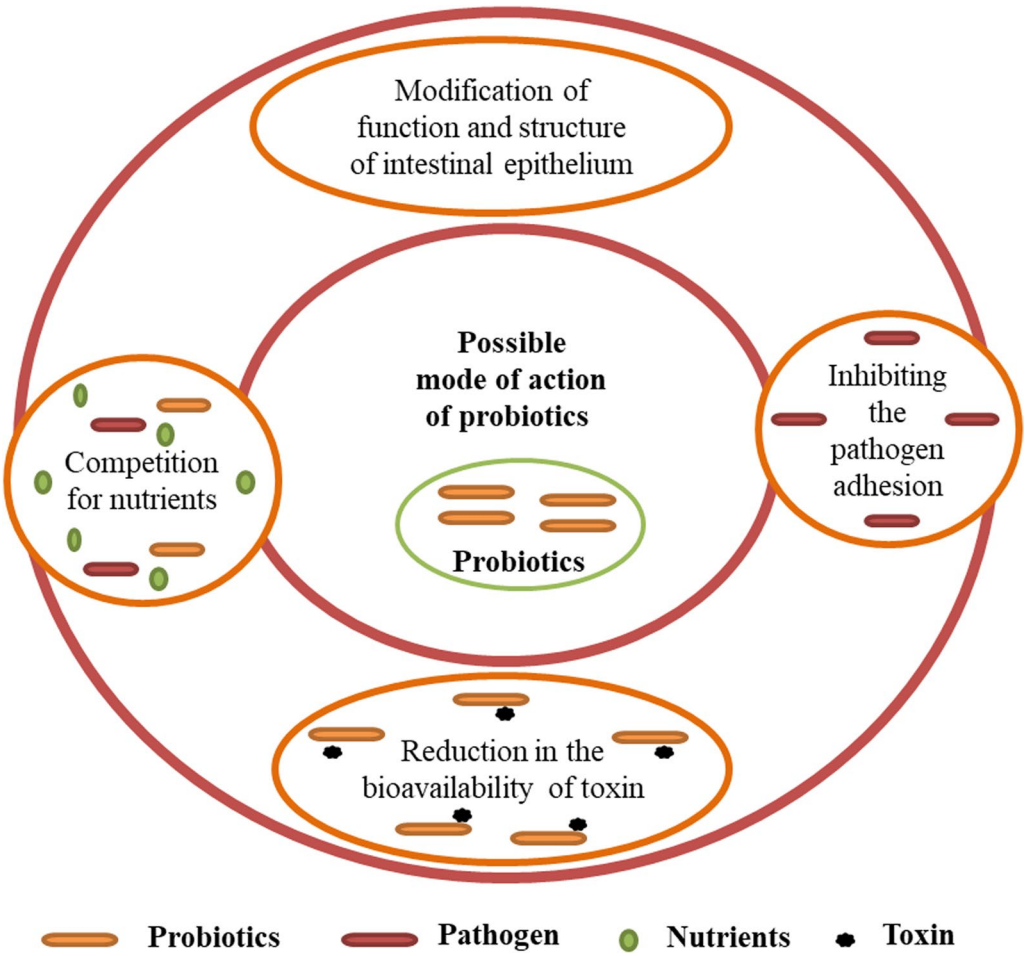

Fig. 1 Shows the diagrammatic representation of the probiotic's mode of action

Probiotics interact with their host through pattern recognition receptors, i.e., TLR as well as nucleotide-binding oligomerization domain (NBOD)-containing protein-like receptors that also modify vital signaling pathways such as NF-B as well as MAPK to enhance or suppress the activation and affect downstream pathways (Tao et al. 2006). This understanding is essential for inducing measured antimicrobial reactions with the least amount of inflammatory tissue damage.

Probiotics: are friend or foe

Probiotics have been used in a wide range of diseases by researchers and clinicians while adhering to safety precautions as well as scientific requirements (Dash et al. 2023). Different innovative technologies, such as cell immobilization and microencapsulation, can be developed to improve the stability as well as the viability of functional food. Aside from that, scientists are already experimenting with molecular technology to replace *Lactobacillus* with its active component or metabolite in order to create novel, clinically safe products (Chauhan et al. 2022; Dhiman et al. 2021; León Aguilera et al. 2022). Probiotics taken as dietary or health supplements frequently and in large doses can speed up these organic processes of developing resistance (Rad et al. 2020). Probiotics are linked to an increase in health advantages, including better immune function, improved nutrient absorption, and protection against cancer and heart-related illnesses (Vera-Santander et al. 2023).

Because the human intestinal bacteria functions like a bacterial community to strengthen the immune system by suppressing the formation of further pathogenic bacteria, taking probiotics as nutritional supplements may increase the health benefits (Cristofori et al. 2021).

Additionally, during the manufacturing process, commercial probiotics are specifically designed to carry resilient determinants for selection purposes. Horizontal gene transfer can transfer the resistant genes present on probiotics' mobile elements to the resident gut microbes, which over time, may accumulate resilient determinants

which can be passed on to opportunistic microbes inside the intestinal infection (Sharma and Bajwa 2021). Others have also brought up this health risk. Based on research done on other probiotic foods, probiotic supplements probably pose a significant risk of trafficking resilient determinants, if not an even greater risk, due to the considerably higher quantities of probiotics consumed (Shahrokhi and Probiotics 2023). Very little is understood about the long-term protection of ingesting such large volumes of probiotic bacteria, in contrast to those other classes of functional foods. Contrary to the health claims made for probiotic supplements, it is unclear how well these organisms tolerate acids and bile salts, and when these properties have been studied, the results have been patchy, contradictory, erratic, strain-dependent, as well as restricted to in vitro settings (Anglenius et al. 2023; Naissinger et al. 2021). The absence of many other probiotics and resident microbes in the gut can cause the results of probiotic strain studies to be tilted in favor of the interests of manufacturers. Probiotic strains are also frequently tested in pure homogeneous cultures. Other issues with probiotics have also recently come to light, including poor or difficult research design, a lack of transparency, incomplete reporting and regulation of probiotics, as well as unreported safety of probiotics consumption (Lerner et al. 2019).

Lactic acidosis, gene transfer, mental fogginess, the introduction of particular bacteriophages, virulence factors, intestinal probiotic increased incidence, as well as many other conditions are common intestinal as well as systemic side effects of probiotic consumption (Oh et al. 2022). Since it can be transferred to local gut bacteria via gene transfer, which in turn causes opportunistic infection, antibiotic resistance determinants raise safety concerns (Wang et al. 2020). In future, the self-stool or human stool may be used for the collection of gut bacteria and can be used to treat various diseases (Ser et al. 2021).

Therefore, evaluating the clinical risk as well as rising reports of resistance to antibiotics globally, probiotic supplements will be not only ineffective but also counterproductive and even harmful (Anisimova et al. 2022). By bringing into sharp focus the long-standing problem of antibiotic resistance as well as intolerance to acids as well as bile salts, we are able to put into point of view the alleged health advantages and the long-term well-being of taking probiotic supplements (Marttinen et al. 2020) in Table 1 several microorganisms and their benefits.

Conclusions

Probiotics have a lot of potential as therapeutic or preventive treatments for different intestinal illnesses. It is crucial to remember that several probiotic marketing claims are still unsupported by experimental data. Our digestive tract can be replenished with beneficial microorganisms that will balance out the detrimental ones thanks to probiotics. Furthermore, the effectiveness shown for a specific bacteria cannot always be generalized to certain other probiotic organisms. Furthermore, the underlying mechanisms of probiotic action are still not completely understood.

The scientific community still needs to fully explain how native microbiomes affect the health of humans and well-being while accurately modeling predictions of interactions between probiotic strains as well as native gut microbiota. However, a long probiotic utilization history from conventional fermented products with a significant number of studies inferred friendliness to human health and well-being. This will make it possible to successfully customize probiotic supplements, figure out how long a therapy should last, and specify the ideal

Table 1 Shows the different microorganisms used as probiotics and their benefits

S. no	Microorganism	Claimed benefits	References
1	*Bifidobacterium infantis*	relief from the symptom of irritable bowel	Chang et al. (2022)
2	*Lactobacillus acidophilus*	Uses in the treatment of diarrhea, antimicrobial activity, relief from the symptom of irritable bowel	Mani-López et al. (2022)
3	*Lactobacillus plantarum*	Prevent the production of endotoxin, relieve from the symptom of irritable bowel, and antimicrobial activity	Michels et al. (2022)
4	*Bifidobacterium bifidum*	Reduces cholesterol, Used in the treatment of infant diarrhea	Robertson et al. (2020)
5	*Lactobacillus casei*	Use in treating diarrhea and constipation, relief from the symptom of irritable bowel	Michels et al. (2022)
6	*Saccharomyces boulardi*	Use in treating diarrhea, ulcerative colitis, a symptom of irritable bowel	Pramanik et al. (2023)
7	*Bacillus subtilis*	Use in treating diarrhea and also in the eradication of *H. pylori*	Roselli et al. (2019)
8	*Lactobacillus rhamnosus*	anti-diabetic activity, treating obesity, anti-viral activity	Wiciński et al. (2020)
9	*Bifidobacterium longum*	Use in treating diarrhea, relief from the symptom of irritable bowel	Rahkola et al. (2023)
10	*Enterococcus durans*	Antioxidant and antibiotic activity	Liu et al. (2022)

dosages for different people to maintain their health or treat various diseases.

The alteration of the gut microbes, competitive adhesion to the mucosa as well as an epithelial layer, enhancement of the intestinal epithelial barrier, and the immune system's modulation to benefit the host are a few significant potential mechanisms of action for probiotics that could explain their antagonistic effects on various microorganisms.

Future probiotic supplements and food additions are very likely to adopt the "bugs as drugs" theory, which is based on individualized treatment plans and well-researched probiotic strains that are tailored to each person's microbiota and target particular diseases. It would be entirely appropriate to refer to probiotics as human friends once all of these problems have been resolved, and positive effects on health have been supported by evidence.

Abbreviations

DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid
PCR	Polymerase chain reaction
B. lactis	*Bifidobacterium lactis*
L. casei	*Lacticaseibacillus casei*
NOD	Nucleotide oligomerization domain
B. bifidum	*Bifidobacterium bifidum*
B. longum	*Bifidobacterium longum*
L. acidophilus	*Lactobacillus acidophilus*
L. plantarum	*Lactiplantibacillus plantarum*
LGG	*Lacticaseibacillus rhamnosus* GG
IBS	Irritable bowel syndrome
C. difficile	*Clostridioides difficile*
H. pylori	*Helicobacter pylori*
TLR	Toll-like receptors

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DS conceived the idea and wrote the manuscript, drew figures and table AS, and SK, and read, edited, and proofread the manuscript. All authors have read and approved the manuscript.

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