Journal of Multidisciplinary Healthcare

Dovepress
Taylor & Francis Group

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REVIEW

Probiotics and Synbiotics: Applications, Benefits, and Mechanisms for the Improvement of Human and Ecological Health

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Abstract: This review explores the multifaceted roles and applications of probiotics, emphasizing their significance in maintaining and enhancing host health through microbial interactions. It includes the concept of holobionts and the symbiotic relationships between hosts and their microbiomes, illustrating how various microbiota can enhance immunity, support growth, and prevent diseases. It delves into the customization of probiotics using molecular and genomic techniques, focusing *Enterococcus, Bifidobacterium*, and *Lactobacillus* species. Furthermore, it discusses the symbiotic effects of symbiotics which aids in enhancing the survivability and beneficial effects of probiotics. The role beneficial microbes in gut is emphasized, noting its impact on preventing diseases and maintaining a stable microbial community. The potential therapeutic value of probiotics includes the ability to treat gastrointestinal diseases, as well as to strengthen the immune system and reduce the number of free radicals that are present in the body. Additionally, it explores secondary metabolites produced by bacteria in the gut, such as bacteriocins and exopolysaccharides, and their effect on the health of human, particularly in the gastrointestinal tract. The review concludes by addressing the use of probiotics in traditional medicine and their potential in novel therapeutic applications, including the treatment of endangered wildlife species and various human ailments.

Keywords: human health, gut microbiota, secondary metabolites, synergistic effects

Introduction

Most organisms depend on their innate microbiome, which gives rise to the term "holobiont" or "metaorganism". By supplying nutrients, encouraging growth and development, detoxifying, and reducing disease, microbes support host health and development in several ways. For instance, certain bee microbiota can affect host immunity, certain rhizosphere bacteria can help plants tolerate drought, and the human gut microbiome can help prevent disease. Together with their significant metabolic potential, microbiomes are also robust, adaptable, and quick to react to environmental changes. These characteristics form the foundation for the successful application of probiotics and other microbial therapies to modify host functioning.[1] Focusing on the intestinal microbiome and its resistome could be a promising way to address this problem. "Probiotics are live microorganisms that give the host health benefits when consumed in sufficient amounts." The extracellular polysaccharides that are produced by lactic acid bacteria (LAB) have been chosen for a wide range of applications. This is because microbial polysaccharides are generally accepted as safe (GRAS) and can be utilised for biological activities in both in vitro and in vivo settings.[2] While their metabolites, known as postbiotics and secreted by these microorganisms, can be significant as antimicrobials against a wide range of pathogenic bacteria,

Received: 30 October 2024
Accepted: 5 February 2025
Published: 11 March 2025

probiotics are known to promote health through stimulating the natural gut microbiota, host immunity, cholesterol reduction, and several other functions.[3] Prebiotics, first described in 1995, are non-digested dietary ingredients that support the expansion and activity of microbes in the gastrointestinal tract (GIT). They were redefined in 2004 as fermentation components, benefiting the host's health. FAO/WHO experts defined prebiotics as nonviable dietary ingredients that modulate the microbiota, benefiting host health. Prebiotics can replace probiotics or support natural gut flora, but their effects are specific to individual strains and species.[4] Recent research and clinical data highlight the role that the intestinal microbiota plays in the pathogenesis of Inflammatory Bowel Syndrome (IBS). This has resulted in the development of novel therapeutic approaches, including faecal microbiota transfer, probiotics, synbiotics, and prebiotics, with the goal of modifying the gut microbiota to a composition that is beneficial for IBS patients.[5] However, this research will focus upon the prebiotics that will be extracted from the wild plants to increase the efficacy of probiotics as a treatment against multidrug resistance organisms.

Probiotics, Prebiotics and Synbiotics

Up until this point, various types of bacteria and fungi have been utilised for the purpose of improving human health. The species of bacteria, including *Bifidobacterium* as well as *Lactobacillus*, have been investigated for their possibility as positive probiotic agents. The most common species of *Lactobacillus* and *Bifidobacterium* are shown in Figure 1. *Lactobacillus, Bifidobacterium*, and *Saccharomyces boulardii* are the three kinds of bacteria and fungi that are most frequently found in probiotic product.[6] When probiotics and prebiotics are mixed into formulations, the resulting functional goods are known as synbiotics. Synbiotics are mixtures of active cultures and substrates used by host bacteria to provide benefits for health. Prebiotics can increase probiotics' lifespan and include carbohydrate-based molecules like GOS (Galactooligosaccharides) FOS (Fructooligosaccharides), inulin, and fructans. They offer advantages for the host microbiota and health.[7] The human body contains a vast array of germ and somatic cells, equivalent to the adult gut microbiota. These microbiomes contain over 500 times as many genes as the human genome. A healthy microbiome includes a diverse array of microbes and butyrate-producing.[8] Exceeding 400 distinct species of bacteria, the human GIT is a complex microbial ecology. During infancy and childhood, the microbiota develops into a stable population of microorganisms in adults. There are many things that can influence autochthonous bacteria, one of which is the food of the host individual.[9]

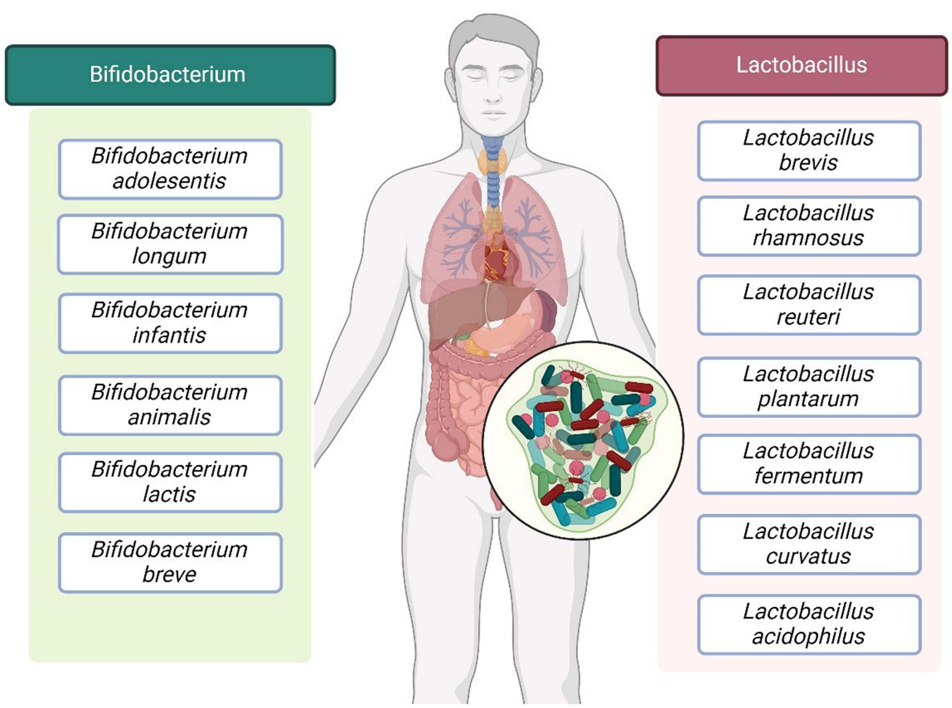

Figure 1 Most common species of genus *Lactobacillus* and *Bifidobacterium*. Created in BioRender. Izzati, N. (2025) https://BioRender.com/o26e467.

Properties of Probiotics, Prebiotics and Synbiotics

Probiotics enhance innate and acquired immunity by increasing phagocytic activity, regulating receptor expression, and activating neutrophils. They also increase host tolerance to infections and reduce hypersensitivity reactions. Probiotics improve digestion, food absorption, and gastrointestinal motility in farm animals. Probiotic *Bifidobacterium* is another extensively used probiotic bacterium. It was shown to boost antitumor immunity and alleviate irritable bowel syndrome in women.[10] A perfect probiotic formulation should have a dosage of $5x10^9$ CFU/day, Microorganisms that are categorised as GRAS, decreased intestinal permeability, the production of lactic acid, anti-carcinogenic effects, and resistance to bile, HCl, and digestive juice are all characteristics of this substance. It is also important that they can tolerate the acidic and alkaline conditions that are present in the stomach and the duodenum. Foods for human consumption such as wine, sausages, fermented milk, and cheeses are mostly made of LAB. Preparations containing live microorganisms might be either single or mixed cultures.[11] *Bacillus* species are popular in the feed industry due to their stability and enzyme production. They can influence fish microbiota and mucosal immunity, and probiotics can control antioxidant metabolites. Consuming *Lactobacillus acidophilus* La1 yogurt significantly enhances folate and vitamin B12 levels in children.[12] The GIT's mucosa is the primary contact point for the immune system. Pathogenic bacteria interact with immune cells and gut epithelial cells, promoting gut defences. Reduced gut microbiota leads to increased antigen transmission. Probiotic microbes regulate immunoglobulin synthesis, strengthen mucosal immunity, and increase cytokine profiles. Yogurt with fermented milk and probiotics enhances IgA production.[13] Studies conducted in academic institutions on the antioxidant characteristics of synbiotics are limited because the various processes that synbiotics use to perform antioxidant activities need to be differentiated from those of prebiotics, probiotics, metabolites, or bio-converted prebiotic.[7] The study evaluated the impact of *Malva neglecta* (MN) and lactulose as prebiotic substances on *Lactobacillus fermentum* survival in half-fat synbiotic stirred yogurt. Results showed that increasing MN and lactulose concentrations increased *Lb. fermentum* count, firmness, chewiness, and adhesiveness. Additionally, incorporating MN and lactulose in yogurt formulation could create a novel functional product.[14]

Colonising Microbiota and Host Microbial Interactions

The human gut microbiota, influenced by factors like human milk, is vital for maintaining health, preventing pathogen colonization, promoting host cell differentiation, boosting immune system, and aiding nutrient breakdown.[15] A stable bacterial community that is resistant to disease proliferation and foreign bacterial invasion is formed by the typical gut microbiota. This tendency is referred to as "colonization resistance", having been identified in the 1950s. For instance, bacteriocins are proteinaceous substances that can inhibit closely related species or species that occupy similar habitats or resources. Both Gram-positive and Gram-negative bacteria can produce them at the ribosome level.[16]

Multi-Omics Approach in Studying Host-Microbial Interaction

With the rise of omics technologies, more studies are using multi-omics profiling to track host tissue and gut microbiota changes in IBD patients. Lloyd-Price and the other scientist's part of the US Integrative Human Microbiome Project, collected longitudinal multi-omics data from 110 patients with IBD (CD = 68, UC = 38) and 27 non-IBD controls over a year, including intestinal tissues (bulk transcriptomics, epigenetic reduced representation bisulfite sequencing [RRBS], and 16S rRNA gene amplicon sequencing) and stool samples. The open-access IBD Multi omics Database (IBDMDB) (https://ibdmdb.org/) 19 found dysbiotic samples in IBD patients, with an enrichment of facultative anaerobes like Escherichia coli and a depletion of beneficial species. Integrative study showed that *Faecalibacterium prausnitzii* was strongly correlated with many dysbiosis-related downregulated microbial enzymes, while Escherichia coli was strongly correlated with upregulated enzymes. *Roseburia* genus members were connected to bile acids and acylcarnitines, suggesting a role in IBD carnitine and bile acid dysregulation. In addition, chemokines such CXCL6 and CCL20 were negatively associated with *Eubacterium rectale, Streptococcus*, and *Eikenella*. The study pioneered longitudinal multi-omics profiling to identify differences between IBD patients and non-IBD controls, but a heterogeneous population and simple correlation methodology prevented mechanistic insights into specific HMIs contributing to IBD pathogenesis.[17,18]

CRISPR Based Genetic Engineering of Probiotics

The introduction of CRISPR-Cas systems has greatly boosted probiotic engineering by allowing targeted gene insertions, deletions, or alterations. This precision is essential for therapeutic probiotic development. CRISPR-Cas9 is frequently utilized because it creates double-strand breaks at precise DNA locations, which are repaired by NHEJ or HDR processes. This method allows regulated genetic alterations to improve probiotic efficacy in various applications. Engineering probiotics with targeted genome editing addresses complex disease pathways. A type I-E CRISPR-Cas system has been added to *Escherichia coli* Nissle 1917 (EcN), a model probiotic, to target and degrade antibiotic resistance genes (ARGs) and reduce gut microbiome ARG transmission. This change promotes therapeutic efficacy and clinical safety. CRISPR systems are tailored to reduce off-target effects, ensuring therapeutic safety. Beyond Cas9, other Cas proteins like Cas12 have wider protospacer adjacent motif (PAM) compatibility, making probiotic genome targeting more flexible. The diversity of CRISPR-Cas subtypes, including type I and type II systems, expands the toolkit for editing a wide range of probiotic species, supporting the idea of probiotics as "living therapeutics" that dynamically respond to host environmental cues. In precision medicine, probiotics must be adaptable to deliver therapeutics and respond to individual health demands.[19]

Action Mechanism of Probiotics

Through four primary mechanisms—competitive exclusion of pathogens, enhancement of intestinal barrier functions, host-body immunomodulation, and neurotransmitter production—probiotics may have a beneficial effect on the human body. Probiotics make it harder for infections to survive in the gut by competing with them for resources and receptor-binding sites. By generating compounds including hydrogen peroxide, organic acids, short chain fatty acids (SCFA), and bacteriocins, probiotics also function as antimicrobial agents by reducing the number of harmful bacteria in the gut. Additionally, probiotics enhance the function of the intestinal barrier by promoting the synthesis of mucin proteins, controlling the expression of tight junction proteins, such as occluding and claudin 1, and controlling the gut's immunological response.[20] The stepwise action occurrence of the probiotics can be seen in Table 1 and its mechanism of action can be seen in Figure 2.

Action Mechanism of Prebiotics

Since the enzymes needed to hydrolyze the prebiotics' polymer bonds are typically absent from the human gut, they can withstand small-intestinal digestion and make it to the colon undigested, where they are fermented by good bacteria like *Lactobacilli* and *Bifidobacteria*. Dietary methods to alter gut microbiota are becoming more and more popular as they have been linked to the pathophysiology of several GI disorders. Because the gut microbiota can metabolize several of these polysaccharides, resulting in the generation of SCFAs (such as acetate, butyrate, and propionate), research has therefore concentrated on the use of prebiotics. There is ongoing discussion over how prebiotics affect the diversity of microbes in the colon. In fact, conflicting findings of SCFA levels were found in the limited human studies that have been carried out. The possible representation of action mechanism of prebiotics can be seen in Figure 3.

Table 1 Stepwise Representation of Probiotics' Action Mode

Probiotics' mechanism of action	References
Antibacterial activity	[21–23]
Reduce luminal pH by secreting antimicrobial peptides	
Bacterial invasion is prevented.	
Prevent bacterial adhesion	
Barrier function improvement	[21–23]
Boost mucus production	
Improve the barrier's integrity.	

(*Continued*)

Table 1 (Continued).

Probiotics' mechanism of action	References
Immunomodulation	[21–23]
Epithelial cell effects	
Dendritic cell effects	
Monocyte/macrophage effects	
Lymphocyte effects	[21–23]
B lymphocytes	
NK cells	
Thymus derived cells	
Redistribution of T cells	

Probiotics as Medicine

Throughout the years, probiotics have been utilised in human medicine, agriculture, and aquaculture with the purpose of enhancing the health of the host which can be seen as its potential benefits in Figure 4. Recently, they're being studied for endangered wildlife species like bees, amphibians, bats, plants, and corals, aiming to conserve and restore populations by addressing ecosystem-scale stress.[1] Traditional Chinese medicine, a healing system, uses herbal remedies, acupuncture, and food therapy. Probiotic-fermented CHM for *Helicobacter pylori* infection improved gastrointestinal symptoms, and reduced glucose levels in Japanese healthy subject.[24]

Impact of Probiotics on Intestinal Diseases

The gut plays a crucial role in maintaining the mucosal barrier, facilitating nutrient digestion and absorption, with numerous commensal bacteria influencing human physiology.[25] The microbes in gut can be changed by faecal transplants, probiotics, prebiotics, and antibiotics. The metabolic activities of the intestinal microbiome are thought to have both beneficial and detrimental consequences on the health of the host. When the precise balance in the microflora (eubiosis) is upset, it can lead to both acute and long-term clinical conditions such as ulcers, IBS, IBD, and antibiotic-associated diarrhea (AAD).[26] Likewise, a very small number of researchers have expressed their support for the concept that microbial dysbiosis plays a part in the development of specific cancers that affect humans.[27] To restore a healthy gut When it comes to treating intestinal diseases, microbiota is an effective treatment method. Probiotics can enhance the immunological microenvironment, stimulate the production of the enzyme lactase, contribute to an increase in the richness and diversity of microorganisms, and enhance the permeability of the intestinal tract.[28]

Gastroenteritis

The most important course of treatment is rehydration, which deaths worldwide needs to start right away. Following the first round of rehydration, regular feeding should continue without interruption. Drugs are not required, yet some do affect the length and symptoms of AGE. It is estimated that children in Europe who are up to the age of three have an incidence of AGE that ranges from 0.5 to 1.9 occurrences per child on a yearly basis.[29] Animal resistance to STEC was found to be increased by the probiotic mixture of *Lactobacillus acidophilus* NP51 and *P. freudenreichii* in a 2007 systematic study.[28] Probiotics have also been shown to dramatically lower faecal STEC levels in ruminant animals, which are repositories for the pathogenic bacteria, according to a 10-year research.[30] Probiotics' beneficial benefits are attributed to a variety of processes, including direct antagonistic interactions linked to the production of certain chemicals like bacteriocins, competition with pathogens for nutrients and adherence to the epithelium, and host immunomodulation.[31] Prebiotic supplements in nursing rats improve rotavirus defence by inhibiting viral replication

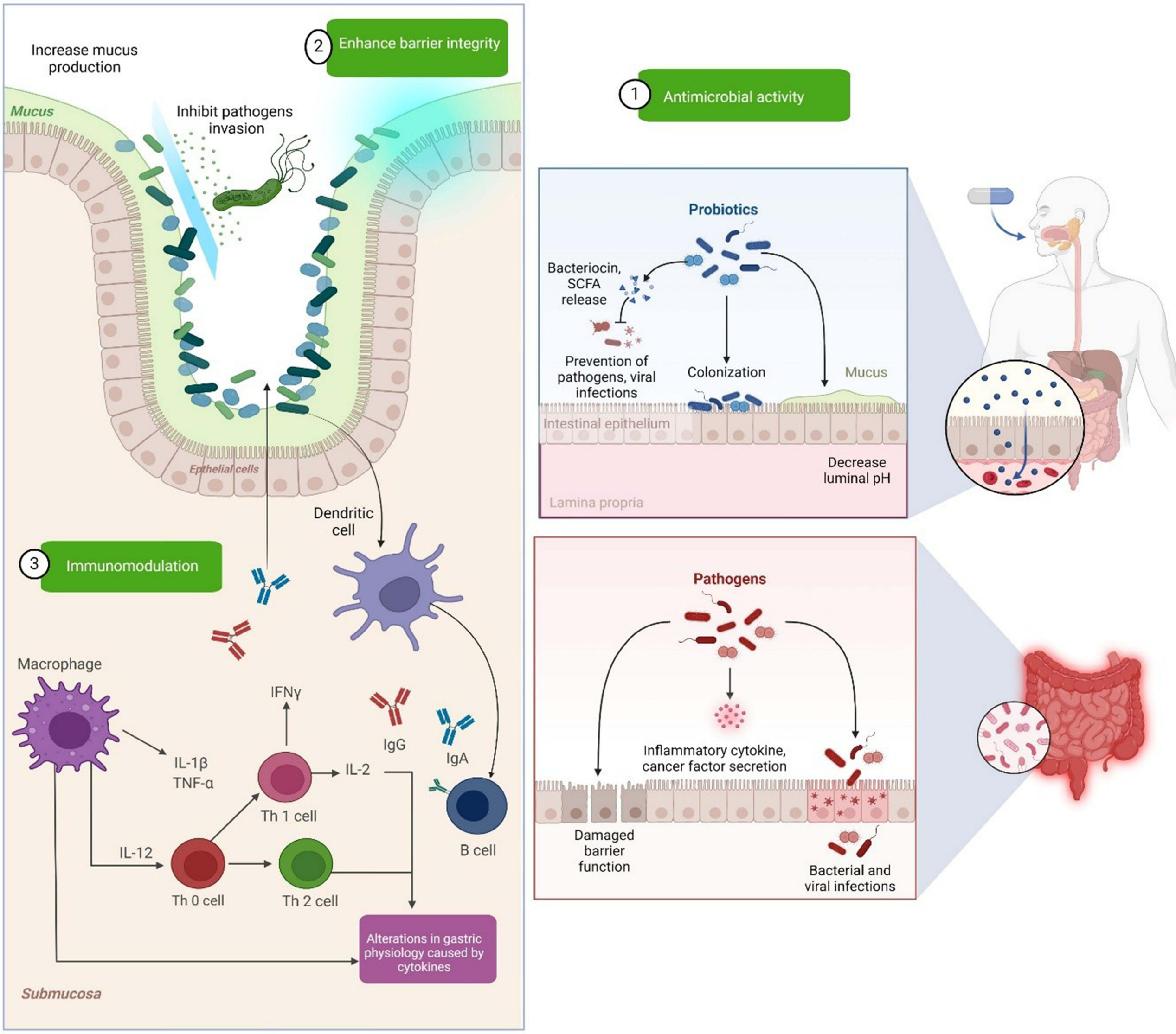

Figure 2 Demonstration of the action Mechanism of Probiotics. Probiotics serve as antimicrobial agents by producing bacteriocins and promoting gut barrier integrity, while also modulating immune responses by stimulating anti-inflammatory cytokine production. Created in BioRender. Izzati, N. (2025) https://BioRender.com/d49e142.
Abbreviations: IL-1β, −12, −2, Interleukin-1 beta, −12, −2; TNF-α, Tumor Necrosis Factor-alpha; IFNγ, Interferon-gamma; Th 1, −2, T helper cell type 1, Type 2; IgA, Immunoglobulin A; IgG, Immunoglobulin G.

and altering the interferon signalling pathway. In vitro research suggests synbiotics as adjuncts to traditional therapy for severe rotavirus enteritis, but more study is needed.[32]

Probiotics and Mental Health

Gut microbiota impacts brain function through neuronal, endocrine, and immunological mechanisms, disrupting intestinal barrier and releasing cytokines. Brain regulates gut microbiota through neuronal, endocrine, and health habits.[33] Elevated kynurenine levels in petrochemical workers can lead to brain illnesses and oxidative stress, causing damage to DNA, RNA, and proteins. Treatments include a balanced diet, vitamin intake, antioxidant supplements, and probiotics, which may help with mood and mental health issues.[34] Research suggests gut microbiota significantly influences emotions and behavior, making it crucial in mental health treatment. Stress can disrupt gut balance, and psychobiotics can enhance cognitive function in psychiatric patients. Gut microbial species produce neuromolecules regulating mood.[35] The regulation of BDNF expression and the inhibition of histone deacetylase (HDAC) by butyrate produced by

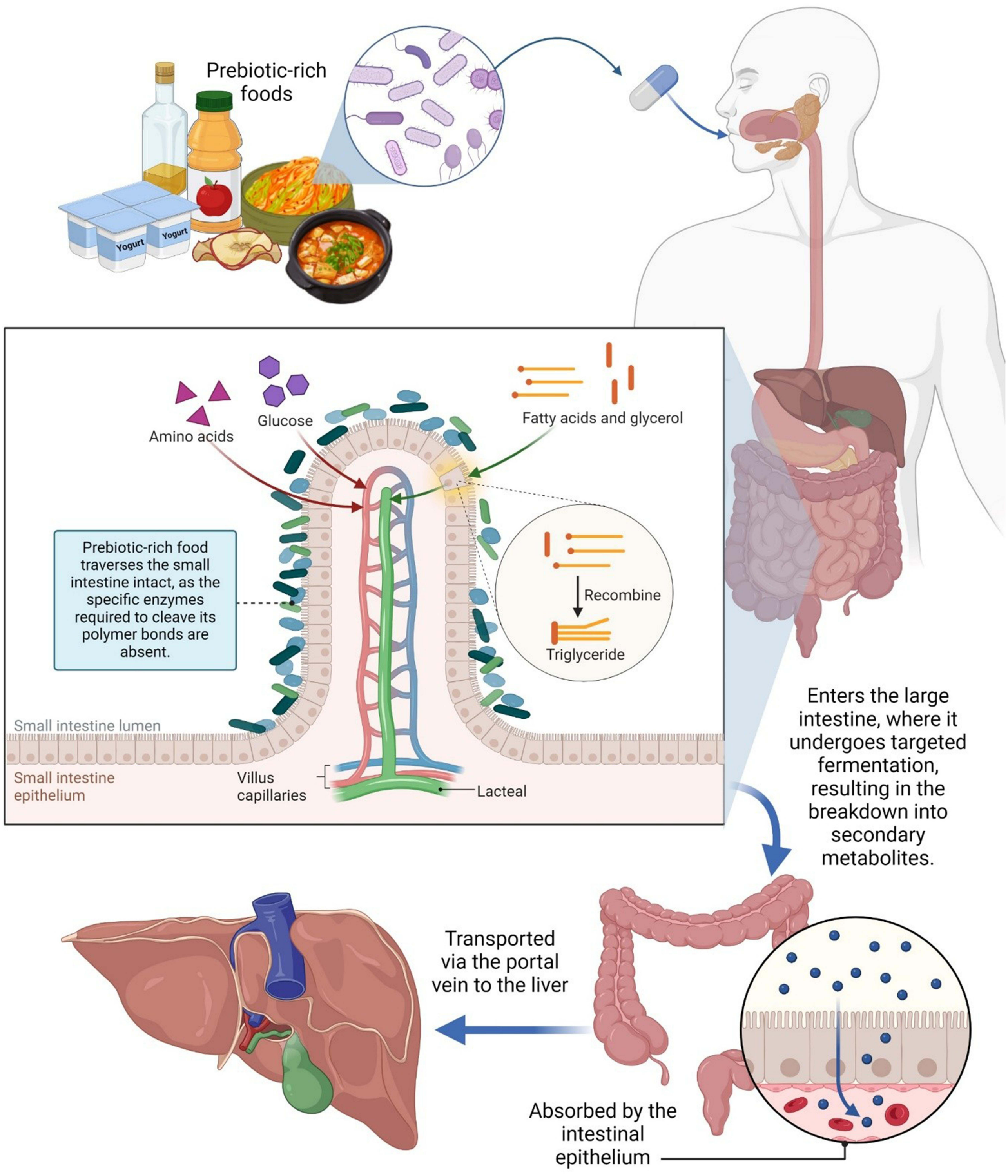

Figure 3 Representing the action mechanism of prebiotics. Created in BioRender. Izzati, N. (2025) https://BioRender.com/m78x231.

probiotics implies that they may have epigenetic potential in this context, even if no research has specifically examined the epigenetic mechanism of probiotics in depression.[36] In the early 1920s, interest in oral "bacteriotherapy" for mental health resurged, with North American manufacturers advertising acidophilus milk. Probiotics with *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 reduced depression and anxiety, but did not improve schizophrenia

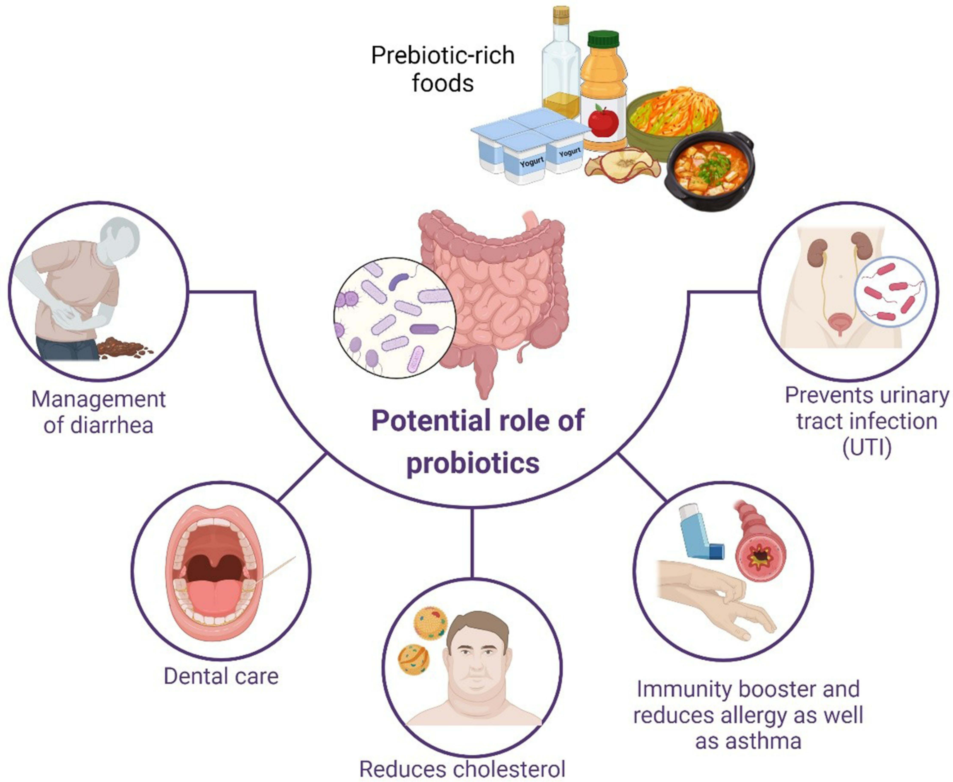

Figure 4 Representing the potential role of probiotics. Created in BioRender. Izzati, N. (2025) https://BioRender.com/e18h133.

symptom.[34] When given peripherally, gut-derived bacterial compounds like *Staphylococcal* enterotoxin B can make people anxious. Robust investigations, however, indicate that systemic injection of LPS endotoxins is a critical element of the gut microbiota-brain link. Acute anxiety, despair, cognitive decline, and increased sensitivity to visceral pain have all been associated with low doses of liposomal protein (LPS; 0.4 ng/kg).[37] Research shows that probiotics can be as powerful as antidepressants. Probiotics offer few negative effects and are not connected with stigma. Probiotics have been demonstrated in recent meta-analyses and systematic reviews to be beneficial for treating depressed symptoms. Interconnected MGBA processes in the pathophysiology of depression have been connected to the antidepressant effects of probiotics. Probiotics—more especially, *Lactobacillus* and *Bifidobacterium* species—have been studied in depression for a long time. Probiotics' efficacy raises the possibility that they could be a suitable medication for precision psychiatry.[36] Because of the close connection between the gut and the central nervous system, it may be helpful to modify the gut microbiota in individuals suffering from depression or anxiety. Studies have shown that probiotics can lessen anxiety and depressive symptoms. Probiotics have anti-inflammatory properties that make them a potential adjunctive treatment for Parkinson's disease.[38]

Probiotics and Women Health

Probiotics are essential for maintaining a healthy gut microbiome, promoting female wellness, and preventing vaginal infections. They are used in obstetrics to reduce preterm labor and preeclampsia. Probiotics can alleviate symptoms of PCOS, improve insulin sensitivity, inflammation, and fertility, and contribute to overall health.[39] The female reproductive tract's principal malignant tumour is cervical carcinoma. A study discovered that oral *Lactobacillus curlicus* can influence the status. CST can enhance HPV clearance. Persistent high-risk HPV infection and changes in the cervical microenvironment can promote the establishment of cervical precancerous lesions. *Lactobacillus casei* and *Lactobacillus rhamnosus* activate NK and dendritic cell maturation, leading to anticancer activity.[40] The vaginal ecosystem maintains balanced vaginal health by preventing harmful organisms from colonizing. *Lactobacilli* produce antimicrobial molecules to stabilize the microbiota, but their role in preventing colonization has been misinterpreted, suggesting they are not necessary for vaginal health.[41] Probiotics, either as dietary supplements or vaginal capsules, can improve vaginal health by balancing gut microbiota, preventing pathogens, and boosting the immune system, unlike orally supplemented probiotics.[42] Despite an increasing number of studies on probiotics and mental health in non-pregnant populations, as well as probiotics and other outcomes (such as metabolic), there is a lack of data on the impact of probiotic consumption on pregnant women's mental health. A study found that probiotic *Lactobacillus rhamnosus* HN001 significantly reduced anxiety and melancholy scores in the postnatal period when compared to placebo-treated pregnant women with a history of asthma, eczema, or hay fever.[43] The risk of preterm delivery or other pregnancy-related complications was not increased or decreased when pregnant women were given probiotics. Researchers discovered *E. coli, Staphylococcus aureus, Bifidobacterium*, and *Firmicutes* as possible obesity inhibitors.[44]

Probiotics, Prebiotics and Synbiotics in Paediatrics

Because breastfeeding has both short- and long-term benefits for early growth and development, it is advised for all-term neonates. Bioactive substances found in human milk enhance immune system performance, microbial colonization, and gut health.[45] Gut microbes can influence the nutritional status of their hosts through a variety of processes. These processes include the fermentation of food components that would otherwise be indigestible, the de novo synthesis of micronutrients, the stimulation of hunger through interactions with the central nervous system, and the modification of the assimilation and metabolism of nutrients by the host. Using this potential could help develop strategies for treating or preventing child malnutrition, one of the most important global health concerns of our day.[26] Childhood obesity is increasingly linked to psychological issues, insulin resistance, hypertension, metabolic syndrome, dyslipidaemia, and non-alcoholic fatty liver disease (NAFLD). The gut microbiota plays an important role in paediatric obesity by regulating blood lipopolysaccharide levels, satiety, and fat distribution, as well as delivering extra calories.[46] Pre-, Pro-, and synbiotics may reduce inflammation by modulating gut microbiota, influencing immune function, and directly interacting with immune cells and signalling pathways. However, the exact mechanisms are unclear. Probiotics can create short-chain fatty acids, which show anti-inflammatory properties by inhibiting pathogenic bacteria and their products through colonization resistance.[47]

The gut microbiota affects inflammation and enteropathy, perhaps leading to growth issues. The gut microbiota regulates IGF-1 and growth hormone synthesis, impacting growth. Changing the microbiota by nutrition, antibiotics, probiotics, prebiotics, synbiotics, or fecal microbiota transplantation can promote healthy growth and development.[45] Synbiotics successfully mimic milk-driven colonisation and the formation of a *Bifidobacterium*-dominated environment in the infant gut. Synbiotics containing a 9:1 ratio of short-chain galactooligosaccharides to long-chain fructooligosaccharides (scGOS/lcFOS) and B. breve M-16V have been shown to restore delayed bifidobacteria colonisation in C-section infants25 and improve symptoms of IgE-associated atopic dermatitis2.[48]

Synbiotics in Mental Health

Research on the gut and brain axis suggests dietary changes can affect gut microbiota, increasing health risks and disease vulnerability. Depression is linked to altered gut microbiomes, lowering stress tolerance.[34] The Gut-Brain Axis connects gut microorganisms to the brain, prompting research for safer alternatives. Prenatal supplements such as pre, pro and synbiotics are being utilized to minimize the risk of maternal mental health disorders during the perinatal period. However, their effectiveness has not been thoroughly studied.[49] For those with low prebiotic intake and mild psychological distress, a high-prebiotic diet can improve mood, anxiety, stress, and sleep. Adding a probiotic supplement to a high-prebiotic diet did not improve mental health outcomes.[50] Recent research indicates a connection between gut microbiota and mental health. Gut bacteria like *Bacteroides uniformis, Roseburia inulinivorans, Eubacterium rectale*, and *Faecalibacterium prausnitzii* support mental health through the production of short-chain fatty acids, amino acids, taurine, and cortisol metabolism pathway.[51] A placebo-controlled RCT found that supplementing with *Lactobacillus* and *Bifidobacterium* reduced self-reported depressed symptoms, inflammation, and metabolic parameters significantly.[52] The link between depression and gut microbiota modification or stress response activation is unclear, yet both play a role in its pathophysiology.

Clinical Applications

For most people with IBD, diarrhea is a prominent symptom and indicator. It might be the first apparent manifestation of intestinal inflammation that alerts physicians to these patients, and it will continue to be a concern as the illness develops.[53] One of the most important factors influencing a child's mortality and morbidity rate is diarrhea, a common condition. In developing countries, this is the primary cause of death for children most frequently. More than a million kids die from illnesses linked to diarrhea every year. Diarrhoea is India's third biggest cause of mortality and morbidity. Approximately 4–5 million deaths worldwide are ascribed to diarrheal illness annually. Within the first two years of life, eight of their 10 fatalities take place. In India, around 20% of hospitalized paediatric cases are due to diarrhea.[54]

Treatment and Prevention

Diarrhea management involves refuelling electrolyte and fluid loss, using Gatorade, Pedialyte, or diluted fruit juice, and IV fluid rehydration. A simple "BRAT" diet can alleviate symptoms. Anti-diarrheal therapy, anti-secretory or anti-motility medications, oral fluoroquinolone medication, empiric antibiotic therapy, and probiotic supplementation may be recommended for severe symptoms. Avoiding these medications can exacerbate serious intestinal illnesses.[55]

Likewise, the common causes, symptoms and their diagnosis can be seen in Table 2.

Prevention of Antibiotic-Associated Diarrhea (AAD)

AAD, a common consequence of antibiotic treatment, affects up to one-third of patients, causing diarrhea and can occur weeks or months after medication is prescribe.[29] The purpose of this study was to investigate the efficacy of *Lactiplantibacillus plantarum* ELF051 in preventing colon inflammation and to establish its influence on the microbiota of the gut in mice with Alzheimer's disease. Following an exposure period of 14 days, the bacteria were found to

Table 2 The Most Common Causes of gastroenteritis, Their Symptoms and Diagnosis

The most common causes of Gastroenteritis				
	Causative agent/organism	**Symptoms of infection**	**Diagnosis**	**References**
Virus				
1. a	*Norovirus*	Vomiting, Diarrhea, Dehydration	Stool Test	[56,57]
1. b	*Rotavirus*	Diarrhea and Dehydration	Stool Test	[56,57]
1. c	*Astrovirus*	Diarrhea and dehydration	Stool Test	[56,57]
1.d	*Adenovirus*	Diarrhea and Dehydration	Stool Test	[56,57]
Bacteria				
2. a	*Campylobacter*	Bacteraemia (Bloodstream infection), Guillain barre syndrome, Reactive arthritis	Culture of stool sample, Culture of blood sample	[56,57]
2. b	*C. difficile*	Food poisoning	Stool samples	[56,58,59]
2. c	*E. coli*	Severe Diarrhea, Abdominal pain, Traveller's Diarrhea	Culture of a stool sample	[56,60,61]
2.d	*Salmonella aureus*	Nausea, Crampy abdominal pain	Stool sample, Swab from rectum	[56,60,62]
2.e	*Shigella*	High fever (up to 106°F) sometimes with delirium seizures and coma, Severe dehydration, or weight loss.	Culture of Stool sample	[56,63]
2.f	*Staphylococcus aureus*	Bloodstream infections, Endocarditis, Osteomyelitis	Culture of blood or infected body fluids	[56]

(*Continued*)

Table 2 (Continued).

The most common causes of Gastroenteritis				
	Causative agent/organism	**Symptoms of infection**	**Diagnosis**	**References**
Parasites				
3. a	*Giardia*	Abdominal Cramps, lactose intolerance.	A stool test or endoscopy of the upper part of the digestive tract	[56,64,65]
3. b	*Cryptosporidium*	Abdominal cramps and watery diarrhea	Stool test	[56,66,67]

decrease the pathogenic modifications in colon tissue, increase the levels of IL-10, improve the levels of intestinal SCFAs, and decrease the levels of IL-1β and TNF-α.[68]

Prevention of C. Difficile Diarrhea

Clostridium difficile infection (CDI) is the most prevalent cause of diarrhoea that is associated with healthcare procedures. It is possible that older people, who are the most susceptible to CDI, are the ones who are most impacted by this infection. Probiotics have demonstrated the potential to reduce the incidence of CDI in the senior population. Furthermore, *Saccharomyces boulardii*, often known as *S. boulardii*, was the strain that was most commonly associated with favourable results.[69] Another study discovered that probiotic treatment significantly reduced the occurrence of *Clostridium difficile*-associated diarrhoea (CDAD) and acute asymptomatic diarrhoea (AAD) in individuals. The type of probiotic utilised was found to be more beneficial than the placebo. *Lactobacillus casei* was the most effective.[70]

Prevention of Radiation-Induced Diarrhea

Changes in the intestinal microbiome, endothelial cell remodelling and damage, epithelial cell injury and repair, fibroplasia, and alterations in the enteric nervous system all interact dynamically to induce radiation enteritis. Two elements comprise the fundamental pathogenic alterations: radiation-induced damage to the intestinal mucosa and damage to the vascular endothelium cells that line the vessels. Research indicates that patients with acute diarrhea following radiation therapy show significant changes in their gut microbiota, with lower *Firmicutes* to *Bacteroides* ratios and microbial alpha diversity, suggesting microbial taxa may be a predictive marker of radiation-induced diarrhea.[65]

Lactose Malabsorption

Elderly people have lower energy needs than younger people, yet they still need certain nutrients including proteins, minerals, and certain vitamins. It is true that after the age of fifty, adults require more vitamins and minerals. Milk and dairy products have been suggested by numerous experts as excellent sources of calcium and protein for older persons. Because of this, milk and other dairy products can help with adult lactose intolerance as well as provide an excellent nutritional supply for the elderly.[71] Lactose intolerance impacts more than 60% of the global population, as reduced lactase enzyme activity hampers the process of digestion. Probiotic microorganisms found in milk products can alleviate symptoms. Yoghurt and capsules containing exogenous *Bifidobacteria* can endure the presence of bile salt and gastric acid. Supplementation of *B. longum* impacts the microorganisms present in the colon and increases the diversity of bacteria. Additionally, it exhibits anti-inflammatory characteristics.[72] Altering the makeup of the microbiota in the colon and the metabolism of the microbiota can be accomplished by consuming fermented foods and taking dietary supplements such as probiotics, prebiotics, and synbiotics. This will result in improved lactose digestion. Consuming dairy products that include active and living cultures, probiotics, and the enzyme lactase, which breaks down lactose, may all be beneficial for individuals who are lactose intolerant.[73]

Prevention of Systemic Infections

Probiotics can interact with the epithelial cells that line the intestinal tract, which helps to eliminate infections. In addition to influencing the microecology of the intestines and the human body, they are responsible for the induction of intestinal crypt cell proliferation. *Lacticaseibacillus rhamnosus* is responsible for the production of the p40 protein, which is responsible for activating the epidermal growth factor and protects against damage caused by tumour necrosis factor.[63]

Bioactive Substances Produced by Probiotic Flora

One creature uses ribosome synthesis to produce antimicrobial peptides known as bacteriocins, which can kill other species.[74] Two domains manufacture these bacteriocins: some *Archaea* members and bacteria. Gram-positive and gram-negative bacteria of the bacterial category both create bacteriocins. The cytoplasmic membrane region of receptor binding on bacterial surfaces is where the bactericidal mechanism of bacteriocin activity occurs. Furthermore, unlike antibiotics, these bacteriocins are non-toxic peptides that are susceptible to protease.[75] Through probiotic organisms, biofilm, dendritic cells, naive T cells, and B cells, bioactive substances affect the health of their hosts. By inducing secretory IgA, stimulating dendritic cells, activating naive T cells, and modifying the immune system, these substances eventually stop harmful bacteria from colonising.[76] Several probiotic bacteria produce important bioactive compounds, as outlined in Table 3, including bacteriocins, short-chain fatty acids, and exopolysaccharides.[76–78]

Immunomodulation

Probiotic modulation affects the immune system by increasing cytokine production, mucin secretion, phagocytosis activity, activating T and natural killer T cells, stimulating immunoglobulin A synthesis, and decreasing T cell proliferation. Intestinal microbiota influences Th17 and Treg cell development, potentially reflecting immune system changes.[6] Probiotics produce energy by fermenting nondigestible prebiotics. They are effective on the brain and nerve system and possess antipathogenic, antiobesity, diabetic, anti-inflammatory, anticancer, and angiogenic qualities.[79] Gut microbes promote health through soluble substances secreted by bacteria. Identifying physiologically active chemicals can improve biotherapeutic formulations and allow purified fraction administration. Intestinal IgA targets commensal microorganisms' proteins.[80] Research on collagen-induced arthritis in mice reveals probiotics and prebiotics' immunomodulating capabilities are strain-specific and prebiotic-dependent, highlighting their potential to enhance gut microbiota composition and immunological reactivity.[81] Probiotics have been shown to improve intestinal flora balance, lactose tolerance, B-complex vitamin production, calcium absorption, and overall intestinal homeostasis. Other benefits include anti-

Table 3 Representing the Bioactive Compounds Produced by Different Probiotic Bacteria

Probiotic bacteria	Bioactive compound	References
Lactococcus lactis	Bacteriocins	[76–78]
Enterococcus casseliflavus	Enterocins	[76]
Bacillus Coagulans	Exopolysaccharide	[76,77]
Lactobacillus spp	Lactic acid	[76]
F.prausnitzii	Butyric acid	[76,78]
Lactobacillus gasseri	Inulin	[76]
Clostridium spp.	Lysine	[76]
B.adolescentis	Folate	[76,78]
Lactobacillus spp.	Amylase	[76]
Lactobacillus reuteri	Vitamin B_{12}	[76–78]

https://doi.org/10.2147/JMDH.S501056

mutagenic and anticancer action, cholesterol-lowering, anti-pathogen secretion, and immune system strengthening.[82] The host's gut mucosal immune system defends against foreign antigens by inducing inflammation and triggering an adaptive immune response. Gut microbiota provides crucial immune cues, but alteration can lead to inflammation-related disorders, such as decreased IgG and IgA levels in germ-free mice.[83]

Enhanced Probiotic Viability

Prebiotics can enhance probiotic growth, improving their survival and colonization. Consumer demand for healthier foods necessitates functional components like prebiotics and probiotic bacteria. *Lactobacillus helveticus*, a safe, thermophilic lactic acid bacterium, is ideal for dairy applications due to its high lactic acid levels.[84] Fruit peels, high in pectin and phenolic compounds, have been utilised to increase probiotics' biological efficacy. Fruit peels—orange, passion fruit, and pineapple—increased consumer acceptance, hardness, and *Lactobacillus* counts in fat- and sugar-free probiotic yoghurt while reducing syneresis, as previously noted.[85] Sesame seeds, rich in health benefits, can enhance probiotic stirred yogurt quality and customer acceptability after 28 days of cold storage. Both raw and roasted sesame can affect bacterial growth, but yogurt starter culture remains unaffected, especially when stored for extended periods.[86] *Lactobacillus acidophilus* was encapsulated in whey protein isolate, sodium alginate, and antacids such as CaCO3 and Mg (OH)2. The viability of microgels under demanding settings was investigated. Additionally, for a duration of 28 days, dried apple snacks were evaluated as a probiotic carrier. Ultimately, the results shown that probiotics' viability can be greatly extended under stressful circumstances by using alginate microgels containing CaCO3.[87]

Encapsulation of Probiotics

Emulsion cross-linking, spray drying, LBL (Layer by Layer) self-assembly, hydrogel, and freeze-drying and biofilm are the main probiotic encapsulation methods. Antioxidants, tea extract, and fatty acids can be encapsulated with probiotics. Encapsulation materials include sodium alginate (SA), chitosan, carrageenan, gums, gelatin, whey protein (WP), and starch. The encapsulating materials employed affect probiotic viability throughout storage/processing or in the GIT. The capsule-forming ability, strength, and increasing survivability of a substance, along with its cheapness, availability, and biocompatibility, determine its effectiveness. Thus, convenience and cheaper packaging costs may offset the expense of encapsulating one or more components.[88]

Safety

The FDA classifies probiotics as dietary supplements in the US, requiring less stringent safety, efficacy, and purity requirements. Some strains are generally safe, while others are not. Clinical trials have not reported cases of bacteraemia or fungemia, and no reports of sepsis in healthy individuals. Probiotic use is popular for treating diarrhea and short intestine.[89] Ongoing research will undoubtedly reveal new long-term safety implications that must be included in safety assessments. However, using biomarkers and other outcomes commonly employed in short-term assessments may not be adequate for addressing long-term safety concerns. If a strain colonizes the host, greater long-term studies are advised. However, assessing microbiome changes is likely insufficient for this task because the therapeutic implications of these changes are unknown. More research is needed to determine which high-risk groups deserve closer long-term follow-up.[90] Likewise a tabular representation is demonstrated in Box 1 which are granted with QPS status.

Ecological Applications

Researchers are just beginning to study probiotics for endangered species. The devastating white-nose sickness (WNS), caused by the fungus *Pseudogymnoascus destructans*, threatens North American bat populations. The earliest probiotic applications in wildlife were to cure infectious disorders. Probiotics have reduced WNS severity and boosted brown bat (*Myotis lucifugus*) survival in laboratory and field experiments, making them a possible WNS treatment.[1] Through in-hive Bio Patty supplementation, this study showed how *Lactobacilli* can be used to increase honeybee survival and hive resilience against P. larvae, the spore-forming bacterium that causes AFB (American foulbrood). In contrast to vehicle controls that received only the base pollen patty ingredients, honeybee larvae treated with the Bio Patty exhibited much lower pathogen load and activity, according to endpoint measurements taken after the 12-day field study during which the

Box 1 Represents the Species of Lactobacillus Which are Granted With the QPS Status (Quality Presumption of Safety).[90]

Lactobacillus species granted QPS status
Lactobacillus kefiranofaciens, Lactobacillus gasseri, Lactobacillus aviaries, Lactobacillus reuteri, Lactobacillus plantarum, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus pentosus, Lactobacillus brevis, Lactobacillus paracasei, Lactobacillus paraplantarum, Lactobacillus diolivorans, Lactobacillus cellobiosus, Lactobacillus panis, Lactobacillus casei, Lactobacillus buchneri, Lactobacillus animalis, Lactobacillus curvatus, Lactobacillus kefiri, Lactobacillus coryniformis, Lactobacillus mucosae, Lactobacillus hilgardii, Lactobacillus crispatus, Lactobacillus amylovorus, Lactobacillus helveticus, Lactobacillus amylolyticus, Lactobacillus delbrueckii, Lactobacillus sakei,L.salivarius Lactobacillus fermentum, Lactobacillus collinoides, Lactobacillus farciminis, Lactobacillus alimentarius, Lactobacillus johnsonii, Lactobacillus gallinarum, Lactobacillus pontis

AFB epidemic unintentionally occurred.[91] The study evaluated five yeast or bacterial candidates' anti- *N. ceranae* activity in honeybees. The probiotics were administered two days before *N. ceranae* infection, and a *Pediococcus acidilactici* (PA) strain was administered two days after infection. The experiment also examined the effects of the PA strain on bees exposed to pesticides. RNAs were extracted from honeybees' midguts to evaluate gut microbiota composition and transcriptional changes. There isn't another treatment for the parasite *N. ceranae* because the antibiotic fumagillin has been taken off the European market. A growing number of researches have examined the effectiveness of probiotic therapy due to the significance of the gut flora.[92]

Future Prospectives

According to comparative microbiota assessments, next-generation probiotics are live bacteria that, when given in sufficient quantities, boost the host's health. However, LBPs (Live Biotherapeutic Products) are not vaccinations; rather, they are biological products that include living organisms and can be used to prevent, treat, or cure human diseases or conditions. These items represent microbial genera and species that have never been utilized in the food or pharmaceutical industries before and are the result of next-generation sequencing and bioinformatics study.[93] Studies show that fermented foods, including cheese, yogurt, and dairy sweets, contain health-promoting substances. The dairy sector uses these fermented goods to transport probiotic microorganisms. However, the growing demand for vegans, high cholesterol individuals, lactose intolerants, and dairy-allergic individuals has led to a surge in demand for non-dairy functional foods and beverages.[94] Probiotic strains vary in properties and potential health benefits, so incorporating them into a balanced diet is recommended. Probiotic formulations, combining beneficial bacteria, have shown efficacy in improving human health outcomes. These strains, often yeast or bacteria, have positive impacts on gut microbiota and general health.[95]

Conclusion

The lora in gut is crucial in GI diseases, and probiotics are a viable therapeutic intervention technique. According to the accompanying technical review, current evidence suggests that using specific probiotic strains or probiotic strain combinations may help adults and children on antibiotics avoid *C difficile* infections. Rapid onset medication resistance and the lack of effective immunization programs push people to choose a different approach to preventing viral illnesses from recurring. Because the viral particle is biomimetic, it can inhibit the host immune system by altering the activity of immune response cells. Nonetheless, enhancing the gastrointestinal and respiratory microbiota of the host may aid in lessening the complexity of viral infections.

 https://doi.org/10.2147/JMDH.S501056

Acknowledgments

The authors extend their appreciation to the Deanship of Research and Graduate Studies at King Khalid University for funding this work through Large Group Research Project under the grant number RGP2/162/45. This research was also supported by the Geran Universiti Penyelidikan (GUP)under the grant number GUP-2024-047 Universiti Kebangsaan Malaysia (UKM).

Disclosure

The authors report no conflict of interest in this work.

References

1. Garcias-Bonet N, Roik A, Tierney B, et al. "Horiz on scanning the application of probiotics for wildlife. *Trends in Microbiol*. 2023;32(3):252–269. doi:10.1016/j.tim.2023.08.012
2. Angelin J, Kavitha M. Exopolysaccharides from probiotic bacteria and their health potential. *Int J Biol Macromol*. 2020;162:853–865. PMID: 32585269; PMCID: PMC7308007. doi:10.1016/j.ijbiomac.2020.06.190
3. Yadav MK, Kumari I, Singh B, Kant Sharma K, Kumar Tiwari S. "Probiotics, prebiotics and synbiotics: safe options for next-generation therapeutics. *Appl. Microbiol. Biotechnol*. 2022;106(2):505–521. doi:10.1007/s00253-021-11646-8
4. Markowiak P, Śliżewska K. "Effects of probiotics, prebiotics, and synbiotics on human health. *Nutrients*. 2017;9(9):1021. doi:10.3390/nu9091021
5. Simon E, Florina Călinoiu L, Mitrea L, Cristian Vodnar D. "Probiotics, prebiotics, and synbiotics: implications and beneficial effects against irritable bowel syndrome. *Nutrients*. 2021; 13: 2112.
6. Yousefi B, Eslami M, Ghasemian A, Kokhaei P, Salek Farrokhi A, Darabi N. "Probiotics importance and their immunomodulatory properties. *J Cell Physiol*. 2019;234(6):8008–8018. doi:10.1002/jcp.27559
7. Majid M, Ibijbijen A, Farih K, Rabetafika HN, Razafindralambo HL. "Synbiotics and their antioxidant properties, mechanisms, and benefits on human and animal health: a narrative review. *Biomolecules*. 2022;12(10):1443. doi:10.3390/biom12101443
8. Khan MT, Dwibedi C, Sundh D, et al.. "Synergy and oxygen adaptation for development of next-generation probiotics. *Nature*. 2023;620 (7973):381–385. doi:10.1038/s41586-023-06378-w
9. Shokryazdan P, Faseleh Jahromi M, Boo Liang J, Yin Wan H. "Probiotics: from isolation to application. *J Am Coll Nutr*. 2017;36(8):666–676. doi:10.1080/07315724.2017.1337529
10. Nair MS, Amalaradjou MA, Venkitanarayanan K. "Antivirulence properties of probiotics in combating microbial pathogenesis. *Adv. Appl. Microbiol*. 2017; 98: 1–29.
11. Gupta V, Garg R. "Probiotics. *Indian J Med Microbiol*. 2009;27(3):202–209. doi:10.4103/0255-0857.53201
12. Wang Y, Yanping W, Wang Y, et al.. "Antioxidant properties of probiotic bacteria. *Nutrients*. 2017;9(5):521. doi:10.3390/nu9050521
13. Phillip T, Kirkwood R. *Non-Traditional Feeds for Use in Swine Production*. CRC Press; 2017.
14. Jooyandeh H, Momenzadeh S, Alizadeh Behbahani B, Barzegar H. "Effect of Malva neglecta and lactulose on survival of Lactobacillus fermentum and textural properties of synbiotic stirred yogurt. *J Food Sci Technol*. 2023;60(3):1136–1143. doi:10.1007/s13197-023-05667-6
15. Milani C, Duranti S, Bottacini F, et al. "The first microbial colonizers of the human gut: composition, activities, and health implications of the infant gut microbiota. *Microbiol Mol Biol Rev*. 2017; 81: 10–1128.
16. Han S, Yanmeng L, Xie J, et al. "Probiotic gastrointestinal transit and colonization after oral administration: a long journey. *Front Cell Infect Microbiol*. 2021;11:609722. doi:10.3389/fcimb.2021.609722
17. Holzapfel WH, Schillinger U. "Introduction to pre-and probiotics. *Food Res Int*. 2002; 35: 09–116.
18. Zhang Y, Thomas JP, Korcsmaros T, Gul L. Integrating multi-omics to unravel host-microbiome interactions in inflammatory bowel disease. *Cell Rep Med*. 2024;5(9):101738. doi:10.1016/j.xcrm.2024.101738
19. Patra D. Synthetic biology-enabled engineering of probiotics for precision and targeted therapeutic delivery applications. *Exon*. 2024;1(2):54–66. doi:10.69936/en11y0024
20. Plaza-Diaz J, Gomez-Llorente C, Fontana L, Gil A. "Modulation of immunity and inflammatory gene expression in the gut, in inflammatory diseases of the gut and in the liver by probiotics. *World J Gastroenterol*. 2014;20(19):5632. doi:10.3748/wjg.v20.i19.5632
21. Ng SC, Hart AL, Kamm MA, Stagg AJ, Stella CK. "Mechanisms of action of probiotics: recent advances. *Inflamm Bowel Dis*. 2009;15(2):300–310. doi:10.1002/ibd.20602
22. Shanmugam H, Raja R, Ravikumar R, Isabel SC. "Mechanism of action of probiotics. *Brazilian Archives of Biology and Technology*. 2013;56: 113–119.
23. Dimidi, Eirini S, Scott M, Whelan K. "Probiotics and constipation: mechanisms of action, evidence for effectiveness and utilisation by patients and healthcare professionals. *Proceedings of the Nutrition Society*. 2020; 79: 147–157.
24. Zhang X, Miao Q, Pan C, et al.. "Research advances in probiotic fermentation of Chinese herbal medicines. *iMeta*. 2023;2(2):e93. doi:10.1002/imt2.93
25. Shehata AA, Yalçın S, Latorre JD, et al.. "Probiotics, prebiotics, and phytogenic substances for optimizing gut health in poultry. *Microorganisms*. 2022; 10: 395.
26. Saber A, Alipour B, Faghfoori Z, Yari Khosroushahi A. "Cellular and molecular effects of yeast probiotics on cancer. *Crit. Rev. Microbiol*. 2017;43 (1):96–115. doi:10.1080/1040841X.2016.1179622
27. Shih-Chi S, Chang L-C, Huang H-D, et al.. "Oral microbial dysbiosis and its performance in predicting oral cancer. *Carcinogenesis*. 2021;42 (1):127–135. doi:10.1093/carcin/bgaa062
28. Jang WJ, Min Lee J, Tawheed Hasan M, Lee B-J, Gu Lim S, Kong I-S. "Effects of probiotic supplementation of a plant-based protein diet on intestinal microbial diversity, digestive enzyme activity, intestinal structure, and immunity in olive flounder (Paralichthys olivaceus). *Fish Shellfish Immunol*. 2019;92:719–727. doi:10.1016/j.fsi.2019.06.056

29. Szajewska H, Guarino A, Hojsak I, et al.. "Use of probiotics for management of acute gastroenteritis: a position paper by the ESPGHAN working group for probiotics and prebiotics. *Journal of pediatric gastroenterology and nutrition*. 2014; 531–539.
30. Callaway TR, Carr MA, Edrington TS, Anderson RC, Nisbet DJ. "Diet, Escherichia coli O157: H7, and cattle: a review after 10 years. *Curr Issues Mol Biol*. 2009;11(2):67–80.
31. Schnadower D, Tarr PI, Charles Casper T, et al. Lactobacillus rhamnosus GG versus Placebo for Acute Gastroenteritis in Children. *N Engl J Med*. 2018;379(21):2002–2014. doi:10.1056/NEJMoa1802598
32. Guadalupe G-O, Flores-Mendoza LK, Icedo-Garcia R, Gomez-Flores R, Tamez-Guerra P. "Modulation of rotavirus severe gastroenteritis by the combination of probiotics and prebiotics. *Arch. Microbiol.* 2017;199(7):953–961. doi:10.1007/s00203-017-1400-3
33. Järbrink-Sehgal E, Andreasson A. "The gut microbiota and mental health in adults. *Curr. Opin. Neurobiol.* 2020;62:102–114. doi:10.1016/j.conb.2020.01.016
34. Mohammadi AA, Jazayeri S, Khosravi-Darani K, et al. "RETRACTED ARTICLE: the effects of probiotics on mental health and hypothalamic–pituitary–adrenal axis: a randomized, double-blind, placebo-controlled trial in petrochemical workers. *Nutr Neurosci*. 2016;19(9):387–395. doi:10.1179/1476830515Y.0000000023
35. Sivamaruthi BS, Iyer Prasanth M, Kesika P, Chaiyasut C. "Probiotics in human mental health and diseases-A mini review. *Trop J Pharm Res*. 2019;18: 889–895.
36. Johnson D, Letchumanan V, Choong Thum C, Thurairajasingam S, Lee L-H. "A microbial-based approach to mental health: the potential of probiotics in the treatment of depression. *Nutrients*. 2023;15(6):1382. doi:10.3390/nu15061382
37. Bested AC, Logan AC, Selhub EM. "Intestinal microbiota, probiotics and mental health: from Metchnikoff to modern advances. 2013.
38. Park JM, Chul Lee S, Ham C, Wook Kim Y. "Effect of probiotic supplementation on gastrointestinal motility, inflammation, motor, non-motor symptoms and mental health in Parkinson's disease: a meta-analysis of randomized controlled trials. *Gut Pathog*. 2023; 15: 9.
39. Nori W, Najatee Akram N, Mueen Al-kaabi M. "Probiotics in women and pediatrics health: a narrative review. *Al-Anbar Med J*. 2023. doi:10.33091/amj.2023.138442.1021
40. Mei Z, Dandan L. "The role of probiotics in vaginal health. *Front Cell Infect Microbiol*. 2022;12:963868. doi:10.3389/fcimb.2022.963868
41. Borges S, Silva J, Teixeira P. "The role of lactobacilli and probiotics in maintaining vaginal health. *Arch Gynecol Obstetrics*. 2014;289(3):479–489. doi:10.1007/s00404-013-3064-9
42. Lehtoranta L, Ala-Jaakkola R, Laitila A, Maukonen J. "Healthy vaginal microbiota and influence of probiotics across the female life span. *Front Microbiol*. 2022;13:819958. doi:10.3389/fmicb.2022.819958
43. Dawe JP, McCowan LME, Wilson J, Okesene-Gafa KAM, Serlachius AS. "Probiotics and maternal mental health: a randomised controlled trial among pregnant women with obesity. *Sci Rep*. 2020;10(1):1291. doi:10.1038/s41598-020-58129-w
44. Ranjha MMAN, Shafique B, Batool M, et al.. "Nutritional and health potential of probiotics: a review. *Appl Sci*. 2021;11(23):11204. doi:10.3390/app112311204
45. Janmohammadi P, Nourmohammadi Z, Fazelian S, et al.. "Does infant formula containing synbiotics support adequate growth in infants? A meta-analysis and systematic review of randomized controlled trials. *Crit. Rev. Food Sci. Nutr.* 2023;63(6):707–718. doi:10.1080/10408398.2021.1952548
46. Balas B, Reka LEM, Lupu A, Lupu VV, Oana Mărginean C. "Prebiotics, probiotics, and synbiotics—a research hotspot for pediatric obesity. *Microorganisms*. 2023;11(11):2651. doi:10.3390/microorganisms11112651
47. Kadia BM, John allen S. "Effect of pre-, pro-, and synbiotics on biomarkers of systemic inflammation in children: a scoping review. *Nutrients*. 2024; 16:336.
48. Phavichitr N, Wang S, Chomto S, et al.. COLOR study group wongteerasut anundorn 1 ben-amor kaouther 2 martin rocio 2 ting steven 3 suteerojntrakool orapa 4 visuthranukul chonikarn 4 piriyanon punnapatch 5, guus roeselers, and jan knol. "impact of synbiotics on gut microbiota during early life: a randomized, double-blind study. *Sci Rep*. 2021;11(1):3534. doi:10.1038/s41598-021-83009-2
49. Desai V, Kozyrskyj AL, Lau S, et al.. "Effectiveness of probiotic, prebiotic, and synbiotic supplementation to improve perinatal mental health in mothers: a systematic review and meta-analysis. *Frontiers in Psychiatry.* 2021;12:622181. doi:10.3389/fpsyt.2021.622181
50. Freijy TM, Cribb L, Oliver G, et al.. "Effects of a high-prebiotic diet versus probiotic supplements versus synbiotics on adult mental health: the "Gut Feelings randomised controlled trial. *Front Neurosci*. 2023;16:1097278. doi:10.3389/fnins.2022.1097278
51. Xiong R-G, Jiahui L, Cheng J, et al.. "The role of gut microbiota in anxiety, depression, and other mental disorders as well as the protective effects of dietary components. *Nutrients*. 2023;15(14):3258. doi:10.3390/nu15143258
52. Ribera C, Vicent Sánchez-Ortí J, Clarke G, Marx W, Mörkl S, Balanzá-Martínez V. "Probiotic, prebiotic, synbiotic and fermented food supplementation in psychiatric disorders: a systematic review of clinical trials. *Neurosci Biobehav Rev*. 2024;158:105561. doi:10.1016/j.neubiorev.2024.105561
53. Wenzl HH. "Diarrhea in chronic inflammatory bowel diseases. *Gastroenterol Clin North Am*. 2012;41(3):651–675. doi:10.1016/j.gtc.2012.06.006
54. Gupte N, Puliyel JM. "4 CPAP technology: where affordability meets utility. *Recent Adv Pediatr.* 2009; 21:49.
55. Nemeth V, Pfleghaar N. Diarrhea 2022. PMID: 28846339.
56. Diarrhea & Gastroenteriti. Overview of Gastroenteritis. *The Merck Manual*. 2020. Available from: https://www.merckmanuals.com/professional/gastrointestinal. Accessed February 11, 2025.
57. Pearce AP, Naumann DN, O'Reilly D. Mission command: applying principles of military leadership to the SARS-CoV-2 (COVID-19) crisis. *BMJ Mil Health*. 2020;167(1):3–4. PMID: 32303574. doi:10.1136/bmjmilitary-2020-001485
58. Principi N, Gnocchi M, Gagliardi M, Argentiero A, Neglia C, Esposito S. "Prevention of clostridium difficile infection and associated diarrhea: an unsolved problem. *Microorganisms*. 2020;8(11):1640. doi:10.3390/microorganisms8111640
59. Hung Y-P, Lee J-C, Tsai B-Y, et al.. "Risk factors of Clostridium difficile-associated diarrhea in hospitalized adults: vary by hospitalized duration. *J Microbiol Immunol Infect*. 2021;54(2):276–283. doi:10.1016/j.jmii.2019.07.004
60. Abbasi E, Mondanizadeh M, Van Belkum A, et al.. Multi-drug-resistant diarrheagenic *Escherichia coli* pathotypes in pediatric patients with gastroenteritis from central Iran. *Infect Drug Resist*. 2020;13:1387–1396. PMID: 32523359; PMCID: PMC7234969. doi:10.2147/IDR.S247732
61. Uddin MS, Mijanur Rahman M, Omar Faruk M, et al.. "Bacterial gastroenteritis in children below five years of age: a cross-sectional study focused on etiology and drug resistance of Escherichia coli O157, Salmonella spp. and Shigella spp. *Bull Natl Res Cent*. 2021; 45: 1–7.
62. Areeba A, Tunio N, Sameer T, Zafar MR, Bajwa N. "Salmonella urinary tract infection and bacteremia following non-typhoidal Salmonella gastroenteritis: an unusual presentation. *Cureus*. 2020;12.

63. Oppong TB, Yang H, Amponsem-Boateng C, et al.. “Enteric pathogens associated with gastroenteritis among children under 5 years in sub-Saharan Africa: a syste matic review and meta-analysis. *Epidemiol Infect*. 2020;148:e64. doi:10.1017/S0950268820000618
64. Minetti C, Chalmers RM, Beeching NJ, Probert C, Lamden K. Giardiasis. *BMJ*. 2016;355:i5369. doi:10.1136/bmj.i5369
65. Moraitis I, Guiu J, Rubert J. “Gut microbiota controlling radiation-induced enteritis and intestinal regeneration. *Trends Endocrinol Metab*. 2023;34 (8):489–501. doi:10.1016/j.tem.2023.05.006
66. Çelebi D, Çelebi Ö. “In pediatric gastroenteritis: the presence of helicobacter pylori prevalence of entamoeba histolytica, giardia intestinalis and cryptosporidium spp. *Dicle Tip Dergisi*. 2021; 48:425–430.
67. Markowiak P, Śliżewska K, Kao C-Y, Fang TJ. “The role of probiotics, prebiotics and synbiotics in animal nutrition. *Gut Pathog*. 2018;10:1–20. doi:10.1186/s13099-018-0228-y
68. Liang W, Gao Y, Zhao Y, et al.. “Lactiplantibacillus plantarum ELF051 alleviates antibiotic-associated diarrhea by regulating intestinal inflammation and gut microbiota. *Probiotics Antimicrob Proteins*. 2023;16: 1–11.
69. Barbosa MLL, Oliveira Albano M, da Silva Martins C, Alcantara Warren C, Castro Brito GAD. “Role of probiotics in preventing Clostridioides difficile infection in older adults: an integrative review. *Front Med*. 2023; 10:219225.
70. Yan M, Yu Yang J, Peng X, Yi Xiao K, Qing X, Wang C. “Which probiotic has the best effect on preventing Clostridium difficile-associated diarrhea? A systematic review and network meta-analysis. *J Diges Dis*. 2020;21(2):69–80. doi:10.1111/1751-2980.12839
71. Ahn S-I, Seong Kim M, Gun Park D, Kyung Han B, Jun Kim Y. “Effects of probiotics administration on lactose intolerance in adulthood: a meta-analysis. *Journal of Dairy Science*. 2023;106(7):4489–4501. doi:10.3168/jds.2022-22762
72. Oak SJ, Jha R. “The effects of probiotics in lactose intolerance: a systematic review. *Crit. Rev. Food Sci. Nutr.* 2019;59(11):1675–1683. doi:10.1080/10408398.2018.1425977
73. Ibrahim SA, Gyawali R, Awaisheh SS, et al.. “Fermented foods and probiotics: an approach to lactose intolerance. *J Dairy Res*. 2021;88 (3):357–365. doi:10.1017/S0022029921000625
74. Zacharof M-P, Lovitt RW. “Bacteriocins produced by lactic acid bacteria a review article. *Apcbee Procedia*. 2012;2:50–56. doi:10.1016/j.apcbee.2012.06.010
75. Yang S-C, Lin C-H, Sung CT, Fang J-Y. “Antibacterial activities of bacteriocins: application in foods and pharmaceuticals. *Front Microbiol*. 2014;5:241. doi:10.3389/fmicb.2014.00241
76. Indira M, Venkateswarulu TC, Abraham Peele K, Nazneen Bobby M, Krupanidhi S. “Bioactive molecules of probiotic bacteria and their mechanism of action: a review. *Biotech*. 2019;3:306.
77. Chugh B, Kamal-Eldin A. “Bioactive compounds produced by probiotics in food products. *Curr. Opin. Food Sci.* 2020;32:76–82. doi:10.1016/j.cofs.2020.02.003
78. Şanlier N, Başar Gökcen B, Ceyhun Sezgin A. “Health benefits of fermented foods. *Crit. Rev. Food Sci. Nutr.* 2019;59(3):506–527. doi:10.1080/10408398.2017.1383355
79. Azad MAK, Sarker M, Wan D. “Immunomodulatory effects of probiotics on cytokine profiles. *Biomed Res. Int.* 2018;2018:8063647. doi:10.1155/2018/8063647
80. Delgado S, Sánchez B, Margolles A, Ruas-Madiedo P, Ruiz L. “Molecules produced by probiotics and intestinal microorganisms with immunomodulatory activity. *Nutrients*. 2020;12(2):391. doi:10.3390/nu12020391
81. Sredkova P, Batsalova T, Moten D, Dzhambazov B. “Prebiotics can change immunomodulatory properties of probiotics. *Cent Eur J Immunol*. 2020;45(3):248–255. doi:10.5114/ceji.2020.101237
82. Nwobodo DC, Chigozie Ugwu M. “Immunomodulatory potentials of probiotics: a review. 2020.
83. Begum J, Buyamayum B, Lingaraju MC, Dev K, Biswas A. “Probiotics: role in immunomodulation and consequent effects: probiotics and immunity. *Letters in Animal Biol*. 2021;1(1):01–06. doi:10.62310/liab.v1i1.53
84. Hassan AA-M, Essam Elenany Y, Nassrallah A, Cheng W, Abd El-Maksoud AA. “Royal jelly improves the physicochemical properties and biological activities of fermented milk with enhanced probiotic viability. *Lwt*. 2022;155:112912. doi:10.1016/j.lwt.2021.112912
85. Fathy HM, Abd El-Maksoud AA, Cheng W, Elshaghabee FMF. “Value-added utilization of citrus peels in improving functional properties and probiotic viability of Acidophilus-bifidus-thermophilus (ABT)-type synbiotic yoghurt during cold storage. *Foods*. 2022;11(17):2677. doi:10.3390/foods11172677
86. Arab, Radia M, Lamine Freidja B, Oomah D, Benali S, Madani K, Boulekbache-Makhlouf L. “Quality parameters, probiotic viability and sensory properties of probiotic stirred sesame yogurt. *Ann Univ Dunarea de Jos of Galati Fascicle VI-Food Technology*. 2023;44:9–25.
87. Afzaal M, Saeed F, Ateeq H, et al.. Probiotics encapsulated gastroprotective cross-linked microgels: enhanced viability under stressed conditions with dried apple carrier. *Food sci nutr*. 2023;11(2):817–827. PMID: 36789050; PMCID: PMC9922151. doi:10.1002/fsn3.3116
88. Yang S, Wei S, Yan W, et al.. “Encapsulation techniques, action mechanisms, and evaluation models of probiotics: recent advances and future prospects. *Food Front*. 2024;5(3):1212–1239. doi:10.1002/fft2.374
89. Gogineni VK, Morrow LE, Malesker MA. “Probiotics: mechanisms of action and clinical applications. *J Prob Health*. 2013;1: 2.
90. Sanders ME, Merenstein D, Merrifield CA, Hutkins R. “Probiotics for human use. *Nutr Bull*. 2018;43(3):212–225. doi:10.1111/nbu.12334
91. Daisley BA, Pitek AP, Chmiel JA, et al.. Novel probiotic approach to counter *Paenibacillus larvae* infection in honey bees, *The*. *Isme J*. 2020;14 (2):476–491. doi:10.1038/s41396-019-0541-6
92. Peghaire E, Moné A, Delbac F, Debroas D, Chaucheyras-Durand F, El Alaoui H. Frédérique chaucheyras-durand, hicham el alaoui, a pediococcus strain to rescue honeybees by decreasing Nosema ceranae- and pesticide-induced adverse effects. *Pest Biochem Physiol*. 2020;163:138–146. ISSN 0048-3575. doi:10.1016/j.pestbp.2019.11.006
93. Abouelela ME, Helmy YA. Next-generation probiotics as novel therapeutics for improving human health: current trends and future perspectives. *Microorganisms*. 2024;12(no. 3):430. doi:10.3390/microorganisms12030430
94. Papadopoulou OS, Doulgeraki A, Panagou E, Argyri AA. “Recent advances and future perspective in probiotics isolated from fermented foods: from quality assessment to novel products. *Front Microbiol*. 2023;14:1150175. doi:10.3389/fmicb.2023.1150175
95. Jan T, Negi R, Sharma B, et al. “Probiotic formulations for human health: current research and future perspective. *J Appl Biol Biotechnol*. 2024;12 (no. 2024):14–29.
96. Guarino MPL, Altomare A, Emerenziani S, et al.. Mechanisms of action of prebiotics and their effects on gastro-intestinal disorders in adults. *Nutrients*. 2020;12(4):1037. PMID: 32283802; PMCID: PMC7231265. doi:10.3390/nu12041037