Egypt. J. Chem. Vol. 67, SI: M. R. Mahran, pp. **2227 - 2244** (2024)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Correlation between Probiotic and Prebiotic: A Systematic review

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Abstract

Human health and nutrition are profoundly influenced by the combined effects of prebiotics and probiotics, which play essential roles in promoting digestive health and preventing disease. Prebiotics are non-digestible compounds that selectively stimulate the growth of beneficial gut bacteria, serving as a fuel source for probiotics. Probiotics, live microorganisms that confer health benefits, have demonstrated therapeutic potential in managing conditions such as irritable bowel syndrome, inflammatory bowel disease, and infections in the gut, respiratory system, and urogenital tract. Additionally, probiotics and the gut microbiota influence drug metabolism, affecting drug activation, toxicity, and efficacy. Examples include the sulfation of acetaminophen, dehydroxylation of caffeine, and glucuronidation, a process that enhances drug solubility and reduces toxicity. These interactions underscore the microbiota's role in modulating metabolic and therapeutic processes. Despite their recognized benefits, systematic reviews on the types, mechanisms, and relationship of prebiotics and probiotics remain limited. This review provides a comprehensive analysis of their classifications, functional pathways, and synergistic effects in promoting gut health and optimizing metabolic processes. We offer insights into innovative applications and propose directions for future research to maximize their potential in health management.

Keywords: Probiotics; Prebiotics; Microbiome; Drug metabolism; Intestinal flora.

1. Introduction

The state of the gut microbiome has captured the attention of many scientists since the early 21st century. The intestinal flora is more numerous and complex than the symbiotic flora found in other areas of the human body. In the colon, there are roughly 3.9×10^{13} adult intestinal flora, which is slightly greater than the total number of human cells [1]. The human gut hosts 300 to 500 various bacterial species. The microorganism living in the gut aids in the digestion of nutrients consumed by the host and participates in systemic physiological processes that are directly linked to human health. We categorized the gut flora into three functional groups based on their effect on individual health: probiotics, neutral microorganisms, and pathogenic bacteria [2]. The digestive system is crucial for good health; the human gut is often referred to as the body's "second brain.". Our body and gut microorganisms interact to give functional substances, such as vitamins, amino acids, short-chain fatty acids (SCFAs), and many essential substances required for a healthy life, as well as to aid our body metabolize toxic substances produced in the gut and help in the digestion and absorption of nutrients from food [3, 4]. Preserving the equivalence of gut microorganisms is important because disruptions can have a negative impact on human health and can lead to conditions such as obesity, diabetes, irritable bowel syndrome, and colon cancer [5-7]. Therefore, outside factors are required to control the ratio of harmful bacteria to probiotics to maintain a healthy state of the gut flora. When consumed in adequate quantities, probiotic living microorganisms benefit host health by colonizing the body. Probiotics can alter the components of human gut bacteria and inhibit harmful bacteria from colonizing the intestine. Furthermore, probiotics improve the development of a strong intestinal mucosa layer, support the role of the intestinal barrier, and improve immunity [8, 9]. Probiotics have certain characteristics that demand deep understanding to improve their development and reproduction within the human body. The promotion of prebiotics is necessary for the growth and replication of probiotics. Prebiotics are substances, mostly polysaccharides, which the body is unable to process and absorb. They can aid the development or propagation of live microorganisms within the host [10]. Prebiotics influence metabolism, strengthen immunity control, resist various infections, improve absorption of minerals, and generally improve health [11]. Prebiotics can be found in many sources and are naturally referred to as polysaccharides, oligosaccharides, microalgae, and natural plants. Algae, fruit juice, peels, seeds, traditional Chinese medicine, and microorganisms containing polysaccharides, polyphenols, and polypeptide polymers are basic resources for arising prebiotics. previous research has concentrated on the advantages of probiotics and prebiotics for health [12, 13]. There are only some comprehensive studies on the different kinds of prebiotics and probiotics, their processes, and how they interact. As

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Receive Date: 12 October 2024, Revise Date: 28 December 2024, Accept Date: 22 January 2025

DOI: 10.21608/ejchem.2025.327475.10617

a result, this work offers a thorough explanation of the widespread prebiotic types, the functional roots of the newly discovered ones, and how prebiotics function in the gut. Furthermore, probiotic types, roles, and uses are discussed, along with an explanation of the mechanism of essential probiotic impacts on the human body. Additionally, the mechanism of promotion between both prebiotics and probiotics is the focus of this article. This article will help in recognizing the relationship between probiotics and prebiotics and offer suggestions for improving human health, particularly the equilibrium of gut flora.

What are the prebiotics

In 1995, the term "prebiotic" was initially used to refer to an indigestible component of the body. This is a substance that our body cannot metabolize, as it is resistant to gastric acid and is not broken down by enzymes found in mammals or absorbed by the gastrointestinal system. Prebiotics selectively activate some bacteria in the colon and change their development and activity to benefit the host by being fermented by the intestinal flora [14]. Under the assumption that they are beneficial to host health, In 2016, the International Scientific Association for Probiotics and Prebiotics defined prebiotics as substances that are selectively utilized and modified by the host's intestinal flora to promote gut health. Prebiotics are now defined to include non-carbohydrates, and their mode of action is no longer restricted to the gastrointestinal system or specific foods [15].

Prebiotic types

Based on previous findings, prebiotics are oligosaccharide carbohydrates, primarily xylooligosaccharides (XOS), galacto-oligosaccharides (GOS), lactulose, inulin, and the fructose-oligosaccharides (FOS) that are generated from them [16-19]. However, recent research indicates that prebiotics are not just carbs; they can also be other non-carbohydrate substances that fit the prebiotic profile, such as polyphenols that are separated from fruits such as blueberries and black raspberries [20]. New prebiotic species are constantly being generated as a result of ongoing process optimization for prebiotic synthesis, mostly consisting of polyphenols, polysaccharides, and polypeptide polymers, all have promising future research directions.

Galacto-oligosaccharides

GOS are novel functional materials with natural characteristics that the body finds difficult to absorb and metabolize. GOS is composed of two to eight sugar units, one of which is terminal glucose; the remaining units are galactose and disaccharides, which have two galactose units each [21]. The distinct glycosidic connections between glucose and galactose or between the degree of polymerization (DP) and galactose molecules demonstrate the hybrid structure of GOS, which is an essential characteristic [22] A schematic model of lactose hydrolysis for GOS production from glucose and galactose by enzymes is shown in Figure 1. GOS is a very safe food additive, according to numerous studies that have assessed its toxicity and genotoxicity [22-26]. Several countries, such as America, Japan, and the European Union, have officially approved the GOS as safe [27]. One of the most popular and extensively utilized prebiotics, GOS, has a variety of beneficial qualities, including balancing the bacteria in the human intestines and supporting the growth of Bifidobacterium in the gut [27-28]. Currently, GOS is mostly found in newborn milk powder and formulas. When human milk is unavailable, a formula enhanced with GOS or a mixture with FOS can effectively substitute human milk and change the intestinal flora of newborns [10, 29]. After being given a newborn formula fortified with GOS, an investigation including 35 healthy full-term babies demonstrated a large improvement in Bifidobacterium abundance; however, there was a noticeable drop in microbial alpha diversity (OM55N). Furthermore, their patterns of fecal pH and SCFAs matched those of control infants, indicating that GOS promotes the proliferation of native Bifidobacterium and creates a microbiota resembling that of breastfed children [30]. The results of that experiment were in line with the findings of Fanaro et al.[31], who reported several studies including more than 400 term and preterm newborns in which prebiotic mixes (long-chain FOS and short-chain GOS) effectively improve the development of lactic acid bacteria (LAB) and Bifidobacterium, reduced the growth of pathogens and improved the stool characteristics of the experimental individuals who drank infant formula containing GOS in line with those of breastfed babies.

Effects of galacto-oligosaccharides on skin

Prebiotic consumption helps treat allergic skin conditions in addition to the stomach [32]. Research has demonstrated that oral Lactobacillus treatment maintains immunological homeostasis in the skin during UV exposure and improves atopic dermatitis in clinical studies [33]. In hairless mice, phenols given by intestinal microbes gather in the skin through circulation and impair keratinocyte development [34]. GOS has been claimed to improve skin health by lowering phenol synthesis in the gut microbiota. GOS consumption prevents women from losing keratin and water owing to phenolic compounds [35]. Prebiotic use decreases the severity of allergic skin conditions. Although atopic dermatitis (AD) in healthy newborns was avoided by a combination of GOS in a randomized controlled study [36]. GOS also stimulates the synthesis of IL-10 and suppresses the production of IL-17, which helps in preventing atopic dermatitis in mice [37]. Moreover, GOS supplementation decreased total immunoglobulin activity, regulated allergic reactions, and reduced IgE levels in high-risk newborns [38].

Galacto-oligosaccharides and calcium absorption

GOS has been found to positively affect bone constitution and configuration in both human body and animal body studies [39]. Numerous processes have been suggested: (1) bacterial fermentation of acidic metabolites in the colon lowers the intestine's local pH, which increases calcium ion concentration in the luminal phase and increases passive calcium absorption; (2) SCFAs alter calcium's charge, activate calcium channels, and improve calcium absorption [40]. Postmenopausal women have also been shown to benefit from GOS's favourable effects of GOS on calcium absorption and bone mineralization [41].

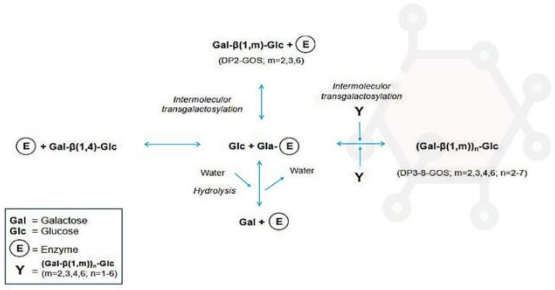

Figure 1: Schematic model of lactose hydrolysis and GOS synthesis.

Relieve lactose intolerance and prevent constipation

Protecting the structure of the intestinal barrier, GOS is crucial in reducing the symptoms of lactose intolerance and minimizing constipation. According to a clinical trial study, using GOS for three weeks helped constipate women's symptoms dramatically become better [42]. Prebiotics encourage the capability of the gut to bind water. Stools become softer as a result of these motions, which also increase stool weight and frequency and shorten transit times. The frequency of stools increases with varying amounts of GOS in baby formulas [43]. Children taking prebiotic supplements had softer feces and consistency similar to that of breastfed children when compared to those receiving regular formula [44-45].

Reduce the risk of cancer

A study found that administering 10% GOS to a colon cancer mouse model, following a 20-week examination of the mouse colon tissue significantly reduced colon tumors. Metagenomic sequencing revealed an increase in advantageous bacteria and a reduction in pro-inflammatory ones [46]. GOS supplementation also increased IL-10 and IL-1β in older individuals compared to placebo [47]. GOS consumption can help reduce cholesterol levels, indicating potential benefits for managing hypercholesterolemia [48].

Inulin-type fructan

Prebiotics can also include common carbohydrates such as inulin-type fructans, in addition to GOS. Polymers known as inulin-type fructans are formed when fructose is bound to the terminal α-linked glucose through a β-2,1 bond. With a DP of 2–60, inulin is the longer chain, and oligofructose/FOS is the shorter chain with a DP of 2–8 [49]. Numerous studies have demonstrated the ability of inulin-type fructans to stimulate the growth of LAB, cyanobacteria, and bifidobacteria [50]. Inulin, a water-soluble storage polysaccharide, is a non-digestible carbohydrate (fructan-type) [51-52]. For generations, humans have included inulin in their daily diets. It is present in approximately 36,000 plant species, with chicory plant roots as the most common source [53-54]. A linear chain of β-2,1-linked d-fructofuranose molecules makes up inulin, and at the reducing end, a glucose residue forms a sucrose-type connection, which makes it difficult to absorb and metabolize inulin because of the existence of β-()-D-frutosyl fructose bonds between the fructose unit and the isomeric carbon. The gut microbe of the human large intestine may ferment inulin [55-56]. Although it only provides about one-third of the energy and is much less sweet than sucrose, inulin is a multipurpose ingredient that is widely used in food processing for the following main purposes: (i) to replace fats or carbohydrates to give food a good flavor [57-58]; (ii) to promote the absorption of minerals (e.g., calcium, magnesium, and iron [59-60]; (iii) to relieve constipation, prevent gastrointestinal diseases, and stimulate the immune system [61]; and (iv) as a prebiotic with a bifidogenic effect, it proficiently encourages the development and metabolism of Lactobacillus and Bifidobacterium in the colon while also boosting the activity of gut microbes [53, 60]. Furthermore, following inulin administration, the relative abundances of Anaerostipes, Faecalibacterium, and Lactobacillus increased, whereas that of Bacteroides decreased [61]. Many common plants, including wheat, onions, bananas, and garlic, contain fructans of the other well-known inulin-type fructans of sulfur (FOS). They are indigestible, with low-calorie carbohydrates with a DP of less than 10, and the food industry frequently uses them as prebiotics [62-65]. The numerous positive physiological effects of fructooligosaccharides (FOS) include reduced carcinogenicity, enhanced intestinal mineral absorption, and decreased levels of triacylglycerols, phospholipids, and serum fat [66]. Our attention was on the prebiotic activity of fructo-oligosaccharides (FOS) in gastrointestinal digestion. FOS helps the body's intestinal flora, eases constipation, lowers the risk of heart disease and some malignancies, improves cholesterol levels in hyperlipidemia, prevents the synthesis of putrefactive chemicals in the gut, and promotes healthier digestive system function [66-69].

Emerging prebiotics

Improvements in machinery have led to advanced prebiotic preparation techniques. Furthermore, a number of novel prebiotic species have been created, the most notable of which are polysaccharides, polyphenols, and polypeptide polymers [70]. Algae, fruit juices, fruits and their waste, herbal remedies, and various microorganisms are the main sources of emerging prebiotics. Although we don't have a comprehensive knowledge of these prebiotics as advanced as that of FOS and GOS, their effects permit further investigation and appear to have a

bright future. Table 1 summarizes the benefits of polyphenols, polysaccharides, and peptide chains in prebiotics in recent years.

Table 1: summarizes the benefits of polyphenols, polysaccharides, and peptide chains in prebiotics in recent years.

Prebiotic	Component	Source	Function	References
Polyphenol	Blueberry polyphenol extract	Blueberry	Reduce weight and normalize lipid metabolism	[71]
	Wine grape seed flour	Grape seed	Gut permeability is enhanced, and adipocyte gene expression is altered to inhibit high-fat-induced obesity and inflammation.	[72]
	Orange albedo	Orange	Stimulates the growth, reproduction, and metabolism of Lactobacillus acidophilus and Lactobacillus animalis	[73]
	Catechin and punicalagin	Fermented pomegranate juice	Increases antioxidant capacity and improves the survival of lactic acid bacteria	[74]
Polypeptide polymers	Poly-gamma-glutamate (PGA)	Bacillus fermentation	Increases the abundance of Lactobacillus and reduces the abundance of Clostridium, helping to regulate the intestinal microbiota.	[75]
Polysaccharides	Algae polysaccharides	Algae	Improves the activity of some beneficial flora and stimulates the production of functional metabolites in the intestinal microbiota.	[76]
	Lotus seed-resistant starch (LRS3-20%)	Lotus seed	Shows high probiotic activity against Bifidobacterium and Lactobacillus acidophilus.	[77]
	Longan pulp polysaccharides	Logan	Promotes the growth of Lactobacillus plantarum, Lactobacillus bulgaricus and	[78]
			Lactobacillus fermentum	

Mechanism of action of prebiotics

Prebiotics can generally withstand digestion in the small intestine by remaining in the gastrointestinal system due to the absence of enzymes in the human gut that break down their polymer bonds. Prebiotics are subsequently carried by the human body intact to the large intestine, where the gut flora metabolizes them down and selectively ferments them to produce specific secondary metabolites. These substances are then absorbed by the gut epithelium or transferred to the liver through the portal vein. These metabolites can have positive effects on host physiological processes, including immune regulation, pathogen resistance, improved gut barrier structure, improved mineral gut absorption, and decreased blood lipid levels [27,79,80]. Beneficial bacteria in the colon metabolize the most prevalent SCFAs, such as acetate, and propionate, butyrate, which are beneficial for preserving systemic and intestinal health [81]. Additionally, one particular benefit of prebiotics is that they support the growth of target bacteria. By protecting or encouraging the creation of advantageous fermentation products, they can encourage the proliferation of beneficial flora to compete with other species following the consumption of particular prebiotics (e.g., inulin, FOS, and GOS) [82,83]. Furthermore, prebiotics provide defence to different parts of the body, Figure 2 demonstrates the prebiotic effect on the human body.

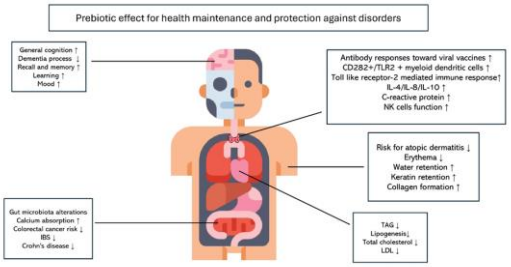

Figure 2: prebiotics offer protection to different body organs.

The role of probiotics

Because they directly carry cytokines to target locations within the host, lactic acid bacteria (LAB) and Escherichia coli are commonly utilized to treat constipation, cancer of the colon, and inflammatory bowel disease [84-86]. Researchers have found that non-pathogen apoptosis induction within carcinoma cells significantly inhibits cancer of the colon (HGC-27) and colon cancerous cells (Caco-2, DLD-1, and HT-29). This protective effect is mediated by the actions of the Lactobacillus rhamnosus, Bifidobacterium latis, and Escherichia coli K-12 strains [87]. Through the interaction of lactic acid bacteria with human immune-competent cells, which alters the production of cytokines and subsequent impacts on the immune system, probiotics indirectly increase and improve immunity [88]. When probiotics lactobacilli are administered to treat minor gingival inflammation, the quantity of Interleukin-8

produced in the gingival crevicular fluid decreases significantly [89]. Lactobacillus species immunomodulate the host immune system. The decreased expression of osteoclastogenic factors (IL-6, IL-17, TNF-α, and RANKL) and a higher level of anti-osteoclastogenic factors are caused by Lactobacillus acidophilus. By modifying the balance of Treg-Th17 cells, Lactobacillus acidophilus also exerts therapeutic and osteoprotective impacts on bone wellness in postmenopausal osteoporosis and prevents diabetes mellitus [90]. Prebiotics can influence not only the gastrointestinal tract but also organs in other parts of the body. [91] Figure 3 demonstrates how probiotics such as Lactobacillus rhamnoses, Bifidobacterium, and Bacteroides dorei work to combat various forms of diabetes mellitus. Hypercalcemia can cause significant impairments to kidney function and is an elevated risk for the development of renal stones. The main procedure was oxalate production. Lactobacilli are supplemented to treat this condition, perhaps by lowering the risk of urolithiasis and preventing the production of stones. Lactobacillus casei HY2743 and L. casei HY7201 may stop oxalate formation [92]. The mechanism by which Lactobacillus species work against oxalate stones is illustrated in Figure 4.

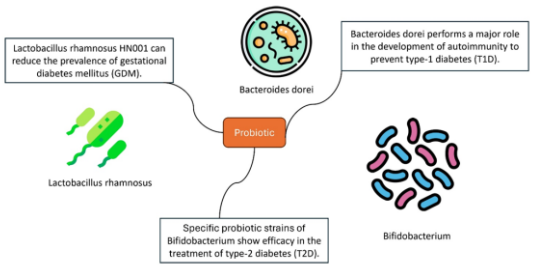

Figure 3: demonstrates how probiotics such as Lactobacillus rhamnoses, Bifidobacterium, and Bacteroides dorei work to combat various forms of diabetes mellitus.

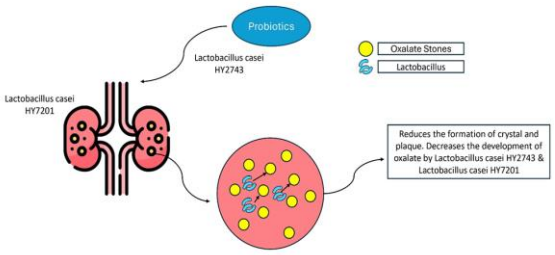

Figure 4: The mechanism by which Lactobacillus species work against oxalate stones.

Summary of the various probiotics

The idea of conventional probiotics originated with studies carried out in 1907 by Elie Metchnikoff, who found that older Bulgarians who regularly consumed fermented dairy products high in lactobacilli (LAB), like yogurt, lived longer and were healthier. According to Metchnikoff, natural gut microbiota may benefit from the presence of bacteria. Since then, probiotics have come to be associated with microorganisms that enhance host health. The meaning of probiotics has changed significantly throughout time [93]. Probiotics are defined by the World Health Organization and the Food and Agriculture Organization of the United Nations as live bacterial strains that have undergone rigorous screening. and can have positive effects on a person's health when consumed in the right way [94]. Probiotics offer a wide range of beneficial impacts on human health that have been shown., such as improved blood lipid and blood sugar metabolism, improved food digestion and absorption, immune system regulation, preservation of microflora balance, treatment and alleviation of lactose intolerance, and regulation of intestinal health [95–97]. For probiotics to be useful to health, they need to be able to multiply and survive in food products in large enough quantities. until they arrive at their final location, the gut. Thus, when selecting probiotics, it's crucial to take into account their capacity to stick to intestinal mucosa and intestinal epithelial cells [98]. Probiotics benefit

the body through four main mechanisms of action: They strengthen the gut barrier and stop any infections from spreading, regulate the immune system, and create neurotransmitters that have the ability to alter the host body [99]. Oelschlaeger [100], discovered that probiotics have the ability to directly influence or interact wi**th** other microbial products, host products, or dietary items by altering the host immune system. The inclusion of probiotic bacteria is necessary for the health benefits of probiotics to occur, and the components that a probiotic secretes and its metabolic characteristics determine how well it behaves. or its surface. Furthermore, whole substances like DNA and peptidoglycan may be essential to probiotic efficacy. It should be emphasized that no single probiotic strain can provide any of the benefits mentioned above. Probiotics can boost host immunity in a number of ways, which directly impact immune cells and other host cells, as shown by the mechanisms of action of probiotics in Figure 5.

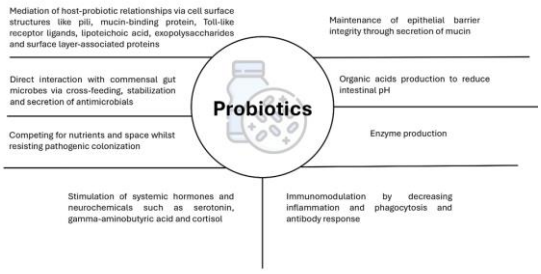

Figure 5: shows the mechanism of action of probiotics.

Types of probiotics

Probiotics come in an extensive variety of species and can be generically categorized into three primary groups: Bifidobacteria, Lactobacilli, and others. Since the LAB group is the most represented probiotic, This category is the subject of current studies on probiotic organisms. In the study of human intestinal microorganisms, which are directly linked to human health, lactobacillus is a crucial probiotic. It helps enhance intestinal microecology by preventing the growth of pathogenic microorganisms

while also synthesizing vital vitamins and amino acids and facilitating the absorption of minerals [101]. Furthermore, SCFAs, a significant Lactobacillus metabolite, support Lactobacillus growth and reproduction, which lowers the amount of Escherichia coli in the intestine by maintaining the colon's normal physiological function and the structure of the colonic epithelium [102]. Lactobacillus has a significant beneficial impact on host development, especially by enhancing body weight and size. For example, Lactobacillus plantarum (which is termed as Lactiplantibacillus plantarum based on recent microbial taxonomy) ZJUFT17 (T17), which was extracted from traditional Chinese sour dough, has the potential to function as a probiotic with anti-obesity or weight-loss characteristics. It may also enhance insulin resistance and systemic inflammation, which are mediated by gut microbiota [103]. More specifically, when mice were given 24 x 10^8 CFU of T17 for 10 weeks, the weight development, calorie consumption, and blood lipid levels of mice fed a high-fat diet were suppressed. Researchers investigated the use of soymilk fermented with Lactobacillus plantarum HFY01 for weight reduction and lipid lowering in HFD-induced obese mice, and the results were similar [104]. In obese mice, Lactobacillus plantarum HFY01 fermented soymilk dramatically inhibited obesity generated by a high-fat diet and reduced body fat percentage and liver index, suggesting that it had good utilization potential. In order to prevent pathogen invasion and preserve or enhance the microbial balance in the host environment, lactobacillus affects microbial interventions. Synergistic interactions between LAB and endogenous intestinal flora are vital for maintaining microbial balance [105]. For example, the LAB in sour dough can be combined with animal or plant-based ingredients. The combination has good flavor and nutritional value, and its functional qualities can be improved due to its various methods of action and perfect symbiotic activities [106]. LAB generate chemicals having antimicrobial properties in the defense against pathogens by improving the function of the intestine's epithelial barrier, in addition to their synergistic action with intestinal flora [107,108]. The name "bifidobacterium" comes from this species of gram-positive, specialized anaerobic bacteria, which is frequently bifurcated at the end [109]. It is a kind of physiological bacteria that is essential to human health and is present in the body. In order to maintain intestinal health, In the center and terminal parts of the small and large intestines, bifidobacterium can multiply and metabolize, adapt to anaerobic intestinal life, and exude bifidogenic substances that have probiotic benefits [110,111]. There are now 32 types and 9 subtypes of Bifidobacterium; 14 of them were isolated from human tissue in the past [112]. The physiological functions of Bifidobacterium are as follows: (i) Like other LAB, Bifidobacterium has the ability to inhibit the growth of harmful bacteria., thus maintaining the balance of normal intestinal bacterial flora and inhibiting pro-inflammatory cytokines [113,114]. Moreover, related studies have shown that Bifidobacterium can guard against intestinal barrier disruption in vivo as well as in vitro. This protective impact is linked to improved intestinal tight junction integrity, vimentin release, and suppression of pro-inflammatory cytokine secretion [115]. (ii) Bifidobacterium bifidum synthesizes vitamins and amino acids in the intestine, increases calcium bioavailability, and is thought to improve bone health [116,117]. (iii) Bifidobacterium bifidum has antitumor effects. Researchers successfully produced a strain of Bifidobacterium longum that secretes C-CPE-PE23 and grows and localizes specifically in malignancies. Without causing major side effects like weight loss or damage to the liver or kidneys, the isolated Bifidobacteria were specifically found in the tumors of mice with breast cancer. The experimental results also suggested that Bifidobacteria may be unique carriers of anti-cancer proteins against malignant tumors [118].

Additional species of bacteria

In addition to Lactobacillus and Bifidobacterium, gram-positive parthenococci such as Enterococcus are frequently used in the food industry. One of the main benefits of probiotics is the capacity of Enterococcus strains to coexist, compete, and adhere to the surrounding cells in the intestine. In addition, Enterococcus is highly resistant to a wide range of pH and temperature, which is attributed to its strong bacteriocin production capacity and can be used as a natural antibacterial substance used in the food sector [119]. For instance, its probiotic function has been well investigated, and it is frequently used as a supplement to antibiotic therapy to treat gastrointestinal conditions such as diarrhea symptoms. Moreover, Saccharomyces boulardii has a greater capacity for survival during digestion than other probiotics, which aids in preserving the harmony of the natural flora in human intestines. It also has immunomodulatory effects that fine-tune immunological pathways during pathogenic infections or chronic diseases [120-122]. Probiotics like Bacillus spp., Streptococcus spp., and E. coli are widespread, with their functions summarized in Table 2.

Mechanism of action of probiotics

Increasing the gut mucosa's barrier efficacy: Human health is greatly dependent on the gut, which is the body's largest immune organ. The lamina propria of the intestinal epithelium, extracellular substances such as mucus, and cellular components make up the heterogeneous body known as the intestinal barrier [125]. Intestinal bacteria may be physically blocked by the distinct cell types found in the layer of mucus and intestinal epithelium. Enterocytes, for instance, take up chemicals through the intestinal lumen. In response to intestinal bacteria, paneth cells can synthesis and exude antimicrobial peptides. Mucus is secreted by

Saccharomyces cerevisiae cells. Intestinal endocrine cells make up the intestinal epithelium [96, 132, 133]. The intestinal epithelium mucus layer's primary functions are to assist food transit, prevent pathogen adherence into the lamina propria, and provide a protective shield between you and the threatening luminal environment [134]. Probiotics interact with intestinal microbes after they get to the colon. The intestinal mucosa is the initial physical barrier that protects the intestine from toxic compounds in the intestinal lumen. Once in the colon, probiotics interact with bacteria to strengthen their chemical, mechanical,

biological, and immunological defenses [135]. Probiotics collaborate with intestinal cells to maintain the structural integrity of the mucosal lining when they enter the intestine and the regular operation of the intestinal mechanical barrier, in addition to encouraging mucous production, restoring intestinal permeability, and promoting mucosal regeneration [136].

Table 2: the functions and applications of some common probiotics.

Strain	Function	Application	References
Bifidobacteria	The exopolysaccharides produced have antioxidant, anticancer, antibacterial, and immunological activities	Used as a starter culture for fermented foods	[123]
Lactobacillus casei	Prevention or treatment of diseases that disrupt the intestinal microbiota	Dairy fermentation	[124]
Bifidobacterium adolescentis	It modifies the microbiota of the colon and cecum and decreases inflammation in the brain and spleen.	Medicine and clinic	[125]
Lactobacillus acidophilus	Reduces cytokines to relieve inflammatory bowel disease, alleviate cancer, modulate immunity, lower cholesterol and relieve diarrhea	Medicine and clinic	[126]
Bacillus coagulans	It can control the balance of bacteria in the intestines, promote the metabolism and utilization of nutrients, improve immunity, and has the characteristics of high temperature resistance, acid resistance, and bile resistance	Medicine and animal husbandry	[127,128]
Bacillus subtilis	Improved growth, nutrition, immunity and disease resistance of aquatic species	Aquaculture	[129]
Lactobacillus rhamnosus	Has the ability to fight against pathogenic bacteria and fungi in the genitourinary tract, preventing the recurrence of urinary tract infections in postmenopausal women	Fermentation of milk, millet, fruit juice and Medicine	[130]
Lactococcus lactis	Aid in developing the consistency and flavor profile of fermented products, and breaks down metabolic amino acids to produce volatile flavor substances	Cheese fermentation	[131]

Antibiotics, for instance, have been shown in certain studies to disturb the usual flora in the gut and to cause damage to the intestinal barrier. However, by raising intestinal secretory IgA (SIgA) secretion and reducing inflammation, the water-soluble polysaccharide from Fagopyrum esculentum Moench bee pollen can mitigate antibiotic-induced microbiota dysbiosis and enhance intestinal barrier integrity [137]. Boosting the immune system: The function of many immune cells in the body, including as monocytes, macrophages, T cells, B cells, and natural killer (NK) cells, can be impacted either directly or indirectly by some probiotics in the gut. These cells serve as immune regulators and control inflammation; some of these cells are of the immunostimulatory type [9,138,139]. By attacking cancer cells, stimulating the synthesis of IL-12, which activates NK cells and develops Th1 cells, and secret various cytokines in a dose-dependent and strain-specific way, these probiotics improve non-specific cellular immune responses. Additionally, they combat allergies by maintaining the proper ratio of Th1 to Th2 [140]. Yogurt, for instance, can be used to supply the necessary probiotics to boost the immune response of the system and enhance the amount of IgA+ cells and cells that produce cytokine in the intestinal effector sites, thus improving the intestinal mucosal immune system [141]. When taken for a brief period, probiotic supplements boost the immune system. In one investigation, probiotics were found to increase the body's polymorphonuclear NK cells' ability to phagocytose and destroy tumors, as well as enhance cellular immunity in elderly individuals who take the recommended dosages of probiotic supplements [142]. Through direct or indirect stimulation, probiotics can generally enhance the immune cells' ability to function in the gut. By modifying microbial metabolism, certain probiotics (i.e., immunomodulatory probiotics) can also control the activity of enzymes [143]. When the host comes into contact with any foreign antigen, the intestinal mucosa's immune system starts an immunological response, partially through an adaptive immune response and partially by generating inflammation to preserve homeostasis in the body. The generation of IL-10 and Treg cells is a characteristic of immunomodulatory probiotics, which reduce symptoms including inflammation and allergies [144, 145]. It's also been demonstrated that short-term probiotic consumption can improve the body's cellular immunological function. It has been demonstrated that probiotics enhance the function of the intestinal barrier via activating B cells and altering cytokine production, thus triggering an adaptive response in the host body. In the presence of probiotics,

monocytes and NK cells collaborate to reduce and regulate the secretion of inflammatory cytokines by secreting IL-10, which causes stem cells to become regulatory differentiated and resistant to the cytotoxicity of NK cells [146].

The impact of probiotics on certain clinical illnesses

Pouchitis

In order to treat ulcerative colitis surgically and familial adenomatous polyposis, proctocolectomy The most effective option is to use ileal pouch-anal anastomosis (IPAA), which removes nearly all of the colorectal mucosa while preserving intestinal consistency and sphincter activity. Permanent ileostomy following a proctocolectomy is not advised. Pouchitis, either chronic or acute inflammation of the ileal reservoir, is the most commonly documented long-term side effect of IPAA. Pouchitis is indicated by higher episodes of hematochezia, pain in the abdomen, fever, and extraintestinal signs associated with inflammatory bowel diseases. Less than 1% of patients undergoing colectomies to cure familial polyposis experience pouchitis; however, 20% of patients with ulcerative colitis experience it in the year after IPAA development, while 50% of patients do so five years later. Numerous investigations on the microbiota of individuals with pouchitis have revealed distinct patterns, such as an increase in enteric and Fusobacteria species, a decrease in Faecalibacterium and Streptococcus species, and an increase in Clostridium perfringens in the inflamed pouch [147–150]. These findings imply that bacteria play a significant role in the pathophysiology of pouchitis, as does the high rate of response to several medicines. This supports the current treatment trials that aim to utilize probiotics to alter the microbiome.

Ulcerative colitis

Probiotic supplementation is not well-supported in ulcerative colitis patients [151–156]. Although some bacterial species have shown promising for the management of ulcerative colitis, Systematic reviews have yielded inconsistent results on the use of probiotics for remission induction and maintenance [157-160]. These findings may be influenced by publication bias because to the small number of patients included in these studies and the possible risks of probiotics. The gram-positive, anaerobic bacterium Bifidobacterium lactis is present in the majority of animal intestines. B. lactis attaches heavily to the epithelial mucosa and is a fundamental component of optimal gut microbiota [161]. In terms of B. lactis's effectiveness against ulcerative colitis (UC), mice treated with B. lactis strains A6, BB12, and 5,764 for colitis brought on by DSS or TNBS shown notable improvements in immunomodulation and intestinal barrier function [162-164].

Crohn disease

The idea of treating Crohn's disease with a symbiotic approach originated from a study that demonstrated better clinical outcomes if a probiotic (B. longum) and prebiotic were combined [165]. However, preliminary results with other medicines are not encouraging. Probiotics are generally thought to be benign, however toxicity could occur if immunodeficiency and enhanced mucosal permeability are present. This was demonstrated by the sepsis brought on by lactobacillus that developed in an HIV-positive Crohn's disease patient following the consumption of homemade yogurt [166].

Infectious diarrhea

Probiotic use is not advised for children who may develop an acute infectious diarrheal disease. For people suffering from acute infectious gastroenteritis, probiotics may or may not be beneficial. Despite the prevalence of study heterogeneity, previous systematic reviews have shown that probiotic use can shorten the duration of infectious diarrhea [158,167–172]. When administered in conjunction with rehydration therapy, probiotics appear to be safe and help reduce the incidence and duration of acute infectious diarrhea. Further research is required to guide the usage of specific probiotic regimens in specific patient populations [171].

Constipation

Probiotics, either alone or in combination, are not recommended for children or adults with functional constipation as there is a lack of evidence [173,174]. Numerous small, randomized, placebo-controlled trials have shown that probiotics, such as Bifidobacterium lactis DN-173 010, Bifidobacterium lactis BB12, Lactobacillus casei Shirota, L. reuteri DSM 19738, and E. coli Nissle 1917, improve intestinal transit time, frequency, and consistency for those with chronic constipation lacking IBS and in healthy individuals who typically have infrequent stools [175–179].

Irritable bowel syndrome

The beneficial effects of probiotics for treating irritable bowel syndrome (IBS) are still not adequately supported by evidence because IBS is a pretty varied condition and the agents investigated ranged substantially. [151] Nonviable Bifidobacterium bifidum HI-MIMBb75 was given daily to 443 IBS patients for eight weeks. Of the participants, 34 percent reported at least a 30% reduction in stomach pain and a decrease in activity in relation to other symptoms of IBS in at least four of the eight weeks of treatment, compared to 19% of those who received a placebo (risk ratio 1.7, 95% CI 1.3-2.4). This is what a multicenter controlled trial carried out in Germany found [180].

Lactose intolerance

Patients with intolerance to lactose may benefit from probiotics that contain lactase-producing microbes because they help break down lactose. Numerous studies have assessed the advantages of different probiotics for lactose intolerant people [181,97]. Although the effects of the various strains varied, a comprehensive examination of 15 controlled studies revealed that probiotics were typically advantageous. Nonetheless, more research may be necessary on a few strains that appeared to be very beneficial [97]. After an in vivo lactose challenge, a trial of a lactose-fermenting strain of Lactobacillus acidophilus

revealed fewer symptoms, setting the stage for more in-depth investigation [182].

Pancreatitis

A multispecies probiotic mixture was used in a multicenter, double-blind, placebo-controlled randomized experiment that indicated probiotics increased mortality from mesenteric ischemia in pancreatitis patients but did not lower the risk of infection complications [183]. For this reason, probiotics are not advised in cases of a severe case of acute pancreatitis.

Hypersensitivity reaction

Atopic dermatitis (AD) is a persistent inflammatory skin condition marked by flare-ups of itchy eczema and recurrent allergic and immunological reactions. The harmless and advantageous effects of consuming a probiotic preparation containing a combination of Lactobacillus rhamnosus ŁOCK 0900, Lactobacillus rhamnosus ŁOCK 0908, and Lactobacillus casei ŁOCK 0918 strains are demonstrated by a multicenter randomized, double-blind, placebo-controlled investigation involving children with AD and cow's milk protein (CMP) allergy, which included children who were less than two years old. As determined by the assessment of atopic dermatitis (SCORAD index), the probiotic combination introduced to the children's nutrition for three months considerably decreased the severity of AD symptoms [184].

The Antiviral Potential of Bacterial Levan Against COVID-19

This study is a new attempt to test how different types of levan, extracted from certain bacteria, can stop the hCoV-19/Egypt/NRC-03/2020 strain. The results showed that levan is a strong antiviral and protective agent against COVID-19. The research also looked at the link between the probiotic effects of two bacterial honey isolates and the antiviral abilities of their levan products [185].

Probiotic impact on drug function

The gut microbiota may have direct or indirect effects on drug metabolism, which could have an impact on toxicity and efficacy [186]. This demonstrated that the microbiota may operate as a mediator in the drug activation process [187]. The sulfation of acetaminophen, a dehydroxylation of caffeine, as well as L-dopa, the demethylation of methamphetamine, the dehalogenation of salicylic acid to form aspirin, and the acetylation/diacylation of salicylic acid, Other noteworthy medication metabolisms that have been linked to microbiota include Cid. One well-known example of how the microbiota might help reduce the toxicity of drugs is glucuronidation, a conjugate hydrolysis reaction in which UDP-glucuronosyltransferase attaches glucuronic acid to a substrate to form hydrophilic and negatively charged glucuronides [188]. The enzyme β-glucuronidase, which may deconjugate endogenous chemicals and xenobiotics which have already been detoxified via the glucuronidation pathway, is produced by a wide variety of anaerobic bacteria [189]. In addition to the enterohepatic recirculation of hormones, other drugs, and toxins, this deconjugation can stimulate the formation of local carcinogens. Consequently, an excess of β-glucuronidases may increase the risk of colon cancer. β-glucuronidase activity, on the other hand, requires a certain amount to ensure enterohepatic recirculation of vital substances, such as estrogen, thyroid hormone, or vitamin D. Probiotics may lessen the efficacy of medicinal products, thereby compromising the safety of patients. The field of pharmacomicrobiomics, or toxicity-microbiomics, is a relatively new field of research that looks at how xenobiotic medications interact with microorganisms [190]. The researchers' examples indicate that understanding the connections between diet, drug metabolism and response, and microbiome diversity and how these may affect customized treatment in the future may be crucial [191].

Conclusion

Prebiotics and probiotics have shown remarkable potential in positively impacting human health, particularly in maintaining the balance of the gut microbiota. By modulating gut microbiota composition, they contribute to disease prevention, support immune function, and promote overall well-being. Prebiotics stimulate the growth of beneficial gut bacteria, while probiotics introduce live microorganisms that offer therapeutic benefits, such as preventing gastrointestinal disorders, managing inflammatory diseases, and improving digestion. These substances also play a role in the production of beneficial compounds like short-chain fatty acids (SCFAs) and antimicrobial peptides, which further contribute to health. Their applications extend beyond healthcare, with potential uses in the food, pharmaceutical, and cosmetic industries. However, despite their promising effects, the efficacy of probiotics remains difficult to assess conclusively. This is due to several factors, including small sample sizes, inconsistent probiotic formulations, and variations in experimental design across studies. For instance, while some probiotic strains have been linked to positive health outcomes, others have shown no significant benefit, largely due to differences in their preparation and delivery methods. Compared to pharmaceutical drugs, which undergo rigorous clinical testing for efficacy, the scientific validation of probiotics is still developing. Therefore, more large-scale, well-designed clinical trials are essential to confirm the therapeutic potential of probiotics and to determine their effectiveness in specific conditions. To fully harness the benefits of prebiotics and probiotics, it is crucial to better understand the mechanisms by which prebiotics selectively promote the growth and activity of probiotics. For example, the concentration of prebiotics, the method of preparation (e.g., fermentation or extraction processes), and the structure of glycosidic bonds within prebiotic molecules may all influence how effectively probiotics utilize them. Investigating these factors will enable the development of more efficient and targeted prebiotic interventions in clinical settings. Moreover, many studies have demonstrated a positive relationship between probiotics and medicinal products, highlighting the potential of probiotics to mitigate adverse drug effects or enhance drug bioavailability. For instance, certain probiotic strains have been shown to influence the metabolism of medications like acetaminophen and

antidepressants, potentially reducing toxicity or improving therapeutic outcomes. As the understanding of these interactions grows, future research may offer novel strategies to incorporate probiotics into drug regimens to decrease side effects and improve drug efficacy. In addition to these advancements, there is considerable room for growth in both theoretical knowledge and experimental techniques in this field. One of the most exciting and underexplored areas is the gut-brain axis, where emerging studies suggest that the gut microbiota, influenced by probiotics, may play a role in mood regulation, cognitive function, and mental health disorders such as anxiety and depression. Understanding how probiotics affect this pathway could lead to new therapeutic approaches for neurological and psychological conditions. This area represents a critical focus for future research, as it holds the potential to bridge the gap between gastrointestinal health and mental well-being.

2. **Author Contributions**: Conceptualization, M.O.A, A.A.A., Y.M.A., I.A.A., R.A.A., T.A.A., A.M.L., M.A.A., and M.A.R.; software, M.O.A, A.A.A., Y.M.A., I.A.A., R.A.A., T.A.A., A.M.L., and M.A.A.; validation, M.O.A, A.A.A., Y.M.A., I.A.A., R.A.A., T.A.A., A.M.L., and M.A.A.; writing— original draft preparation, M.O.A, A.A.A., Y.M.A., I.A.A., R.A.A., T.A.A., A.M.L., and M.A.A.; writing—review and editing, M.O.A.; project administration, M.A.R.; and funding acquisition, M.A.R. Each author has reviewed the published version of the manuscript and provided their consent.

3. **Fund**: The authors have no funds.

4. **Conflict of interest**
There is no conflict of interest for the authors.

5. **Acknowledgment**
The authors are grateful to acknowledge flaticon.com many figures have been designed using resources from flaticon.com

6. **References**

[1]. Sender, R., Fuchs, S., & Milo, R. (2016). Are We Really Vastly Outnumbered? Revisiting the Ratio of Bacterial to Host Cells in Humans. *Cell*, 164(3), 337–340. https://doi.org/10.1016/j.cell.2016.01.013

[2]. Jones, J. L., & Foxx-Orenstein, A. E. (2007). The role of probiotics in inflammatory bowel disease. *Digestive diseases and sciences,* 52(3), 607–611. https://doi.org/10.1007/s10620-006-9225-y

[3]. Dai, L., Gu, Y., Xu, J., Guo, J., Jiang, K., Zhou, X., et al. (2022). Toward green production of xylooligosaccharides and glucose from sorghum straw biowaste by sequential acidic and enzymatic hydrolysis. *Industrial Crops and Products*, 179, 114662. https://doi.org/10.1016/j.indcrop.2022.114662

[4]. Lian, Z., Zhang, Q., Xu, Y., Zhou, X., & Jiang, K. (2022). Biorefinery cascade processing for converting corncob to xylooligosaccharides and glucose by maleic acid pretreatment. *Applied Biochemistry and Biotechnology.* https://doi.org/10.1007/s12010-022-03985-7

[5]. Yan, B., Huang, C., Lai, C., Ling, Z., & Yong, Q. (2022). Production of prebiotic xylooligosaccharides from industrial-derived xylan residue by organic acid treatment. *Carbohydrate Polymers*, 292, 119641. https://doi.org/10.1016/j.carbpol.2022.119641

[6]. Gao, X., Jia, R., Xie, L., Kuang, L., Feng, L., & Wan, C. (2018). A study of the correlation between obesity and intestinal flora in school-age children. *Scientific Reports*, 8, 1. https://doi.org/10.1038/s41598-018-32730-6

[7]. Huang, C., Yu, Y., Li, Z., Yan, B., Pei, W., & Wu, H. (2022). The preparation technology and application of xylo-oligosaccharide as prebiotics in different fields: A review. *Frontiers in Nutrition*, 9, 996811. https://doi.org/10.3389/fnut.2022.996811

[8]. Wang, X., Zhang, P., & Zhang, X. (2021). Probiotics regulate gut microbiota: An effective method to improve immunity. *Molecules*, 26, 6076. https://doi.org/10.3390/molecules26196076

[9]. Johansson, M. A., Björkander, S., Mata Forsberg, M., Qazi, K. R., Salvany Celades, M., Bittmann, J., et al. (2016). Probiotic lactobacilli modulate Staphylococcus aureus-induced activation of conventional and unconventional T cells and NK cells. *Frontiers in Immunology*, 7, 273. https://doi.org/10.3389/fimmu.2016.00273

[10]. Li, X., Zhang, Q., Wang, W., & Yang, S. T. (2021). A novel inulin-mediated ethanol precipitation method for separating endo-inulinase from inulinases for inulooligosaccharides production from inulin. *Frontiers in Bioengineering and Biotechnology*, 9, 679720. https://doi.org/10.3389/fbioe.2021.679720

[11]. Peredo-Lovillo, A., Romero-Luna, H. E., & Jiménez-Fernández, M. (2020). Health-promoting microbial metabolites produced by gut microbiota after prebiotics metabolism. *Food Research International*, 136, 109473. https://doi.org/10.1016/j.foodres.2020.109473

[12]. Liu, R. T., Walsh, R. F., & Sheehan, A. E. (2019). Prebiotics and probiotics for depression and anxiety: A systematic review and meta-analysis of controlled clinical trials. *Neuroscience and Biobehavioral Reviews*, 102, 13–23. https://doi.org/10.1016/j.neubiorev.2019.03.023

[13]. Quigley, E. M. (2019). Prebiotics and probiotics in digestive health. *Clinical Gastroenterology and Hepatology*, 17, 333–344. https://doi.org/10.1016/j.cgh.2018.09.028

[14]. Gibson, G. R., & Roberfroid, M. B. (1995). Dietary modulation of the human colonic microbiota: Introducing the concept of prebiotics. *Journal of Nutrition*, 125, 1401–1412. https://doi.org/10.1093/jn/125.6.1401

[15]. Gibson, G. R., Hutkins, R., Sanders, M. E., Prescott, S. L., Reimer, R. A., Salminen, S. J., et al. (2017). Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nature Reviews Gastroenterology & Hepatology*, 14, 491–502. https://doi.org/10.1038/nrgastro.2017.75

[16]. Yin, X., Cai, T., Liu, C., Ma, Y., Hu, J., Jiang, J., et al. (2022). A novel solvothermal biorefinery for production of lignocellulosic xylooligosaccharides, fermentable sugars, and lignin nanoparticles in a biphasic system. *Carbohydrate Polymers*, 295, 119901. https://doi.org/10.1016/j.carbpol.2022.119901

[17]. xylooligosaccharides by xylan hydrolysis using a novel recyclable and separable furoic acid. *Frontiers in*

Bioengineering and Biotechnology, 9, 660266. https://doi.org/10.3389/fbioe.2021.660266

[18]. Ashwini, A., Ramya, H. N., Ramkumar, C., Reddy, K. R., Kulkarni, R. V., Abinaya, V., et al. (2019). Reactive mechanism and the applications of bioactive prebiotics for human health. *Journal of Microbiological Methods*, 159, 128–137. https://doi.org/10.1016/j.mimet.2019.02.019

[19]. Khangwal, I., & Shukla, P. (2019). Potential prebiotics and their transmission mechanisms: Recent approaches. *Journal of Food and Drug Analysis*, 27, 649–656. https://doi.org/10.1016/j.jfda.2019.02.003

[20]. Gu, J., Thomas-Ahner, J. M., Riedl, K. M., Bailey, M. T., Vodovotz, Y., Schwartz, S. J., et al. (2019). Dietary black raspberries impact the colonic microbiome and phytochemical metabolites in mice. *Molecular Nutrition & Food Research*, 63, 1800636. https://doi.org/10.1002/mnfr.201800636

[21]. Delgado-Fernandez, P., de Las Rivas, B., Munoz, R., Jimeno, M. L., Doyaguez, E. G., Corzo, N., et al. (2021). Biosynthesis of nondigestible galactose-containing hetero-oligosaccharides by Lactobacillus plantarum WCFS1 MelA α-Galactosidase. *Journal of Agricultural and Food Chemistry*, 69, 955–965. https://doi.org/10.1021/acs.jafc.0c06417

[22]. Torres, D., Gonçalves, M. P., & Teixeira, J. A. (2010). Galacto-oligosaccharides: Production, properties, applications, and significance as prebiotics. *Comprehensive Reviews in Food Science and Food Safety*, 9, 438–454. https://doi.org/10.1111/j.1541-4337.2010.00119.x

[23]. Baek, Y., Ahn, Y., Shin, J., Suh, H. J., & Jo, K. (2021). Evaluation of safety through acute and subacute tests of galacto-oligosaccharide (GOS). *Preventive Nutrition and Food Science*, 26, 315. https://doi.org/10.3746/pnf.2021.26.3.315

[24]. Kobayashi, T., Ishida, S., Kaneko, K., & Onoue, M. (2014). A 6-week oral gavage toxicity study of a novel galacto-oligosaccharide in juvenile rats. *Human & Experimental Toxicology*, 33, 722–728. https://doi.org/10.1177/0960327113506239

[25]. Kobayashi, T., Yasutake, N., Uchida, K., Ohyama, W., Kaneko, K., & Onoue, M. (2009). Safety of a novel galacto-oligosaccharide: Genotoxicity and repeated oral dose studies. *Human & Experimental Toxicology*, 28, 619–630. https://doi.org/10.1177/0960327109346789

[26]. Zhou, Y., Kruger, C., Ravi, G. S., Kumar, D. S., Vijayasarathi, S. K., Lavingia, M., et al. (2017). Safety evaluation of galacto-oligosaccharides: Subchronic oral toxicity study in Sprague-Dawley rats. *Toxicology Research & Application*, 1, 2397847317715864. https://doi.org/10.1177/2397847317715864

[27]. Slavin, J. (2013). Fiber and prebiotics: Mechanisms and health benefits. *Nutrients*, 5, 1417–1435. https://doi.org/10.3390/nu5041417

[28]. Ambrogi, V., Bottacini, F., O'Callaghan, J., Casey, E., Van Breen, J., Schoemaker, B., et al. (2021). Infant-associated Bifidobacteria β-galactosidases and their ability to synthesize galacto-oligosaccharides. *Frontiers in Microbiology*, 12, 662959. https://doi.org/10.3389/fmicb.2021.662959

[29]. Van Hoffen, E., Ruiter, B., Faber, J., M'Rabet, L., Knol, E. F., Stahl, B., et al. (2009). A specific mixture of short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides induces a beneficial immunoglobulin profile in infants at high risk for allergy. *Allergy*, 64, 484–487. https://doi.org/10.1111/j.1398-9995.2008.01765.x

[30]. Matsuki, T., Tajima, S., Hara, T., Yahagi, K., Ogawa, E., & Kodama, H. (2016). Infant formula with galacto-oligosaccharides (OM55N) stimulates the growth of indigenous Bifidobacteria in healthy term infants. *Beneficial Microbes*, 7, 453–461. https://doi.org/10.3920/BM2015.0168

[31]. Fanaro, S., Boehm, G., Garssen, J., Knol, J., Mosca, F., Stahl, B., et al. (2005). Galacto-oligosaccharides and long-chain fructo-oligosaccharides as prebiotics in infant formulas: A review. *Acta Paediatrica*, 94, 22–26. https://doi.org/10.1111/j.1651-2227.2005.tb02150.x

[32]. Hong, K. B., Jeong, M., Han, K. S., Kim, J. H., Park, Y., & Suh, H. J. (2015). Photoprotective effects of galacto-oligosaccharide and/or Bifidobacterium longum supplementation against skin damage induced by ultraviolet irradiation in hairless mice. *International Journal of Food Science & Nutrition*, 66, 923–930. https://doi.org/10.3109/09637486.2015.1088823

[33]. Peguet-Navarro, J., Dezutter-Dambuyant, C., Buetler, T., Leclaire, J., Smola, H., Blum, S., et al. (2008). Supplementation with oral probiotic bacteria protects human cutaneous immune homeostasis after UV exposure—Double blind, randomized, placebo-controlled clinical trial. *European Journal of Dermatology*, 18, 504–511. https://doi.org/10.1684/ejd.2008.0496

[34]. Kalliomäki, M., Salminen, S., Poussa, T., Arvilommi, H., & Isolauri, E. (2003). Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet*, 361, 1869–1871. https://doi.org/10.1016/s0140-6736(03)13490-3

[35]. Kano, M., Masuoka, N., Kaga, C., Sugimoto, S., Iizuka, R., Manabe, K., et al. (2013). Consecutive intake of fermented milk containing Bifidobacterium breve strain Yakult and galacto-oligosaccharides benefits skin condition in healthy adult women. *Bioscience, Microbiota, Food, and Health*, 32(1), 33–39. https://doi.org/10.12938/bmfh.2012-003

[36]. Moro, G., Arslanoglu, S., Stahl, B., Jelinek, J., Wahn, U., & Boehm, G. (2006). A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. *Archives of Disease in Childhood*, 91, 814–819. https://doi.org/10.1136/adc.2006.098251

[37]. Tanabe, S., & Hochi, S. (2010). Oral administration of a galactooligosaccharide preparation inhibits development of atopic dermatitis-like skin lesions in NC/Nga mice. *International Journal of Molecular Medicine*, 25, 331–336. https://doi.org/10.3892/ijmm_00000349

[38]. Van Hoffen, E., Ruiter, B., Faber, J., M'Rabet, L., Knol, E. F., Stahl, B., et al. (2009). A specific mixture of short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides induces a beneficial immunoglobulin profile in infants at high risk for allergy. *Allergy*, 64, 484–487. https://doi.org/10.1111/j.1398-9995.2008.01765.x

[39]. Weaver, C. M., Martin, B. R., Nakatsu, C. H., Armstrong, A. P., Clavijo, A., McCabe, L. D., McCabe, G. P., Duignan, S., Schoterman, M. H., & van den Heuvel, E. G. (2011). Galactooligosaccharides improve mineral absorption and bone properties in growing rats through gut fermentation.

Journal of Agricultural and Food Chemistry, 59(12), 6501–6510. https://doi.org/10.1021/jf2009777

[40]. Griffin, I. J., Davila, P. M., & Abrams, S. A. (2002). Non-digestible oligosaccharides and calcium absorption in girls with adequate calcium intakes. *The British Journal of Nutrition*, 87(Suppl 2), S187–S191. https://doi.org/10.1079/BJNBJN/2002536

[41]. Abrams, S. A., Griffin, I. J., Hawthorne, K. M., Liang, L., Gunn, S. K., Darlington, G., & Ellis, K. J. (2005). A combination of prebiotic short- and long-chain inulin-type fructans enhances calcium absorption and bone mineralization in young adolescents. *The American Journal of Clinical Nutrition*, 82(2), 471–476. https://doi.org/10.1093/ajcn.82.2.471

[42]. Teuri, U., & Korpela, R. (1998). Galacto-oligosaccharides relieve constipation in elderly people. *Annals of Nutrition & Metabolism*, 42(6), 319–327. https://doi.org/10.1159/000012751

[43]. Ben, X. M., Li, J., Feng, Z. T., Shi, S. Y., Lu, Y. D., Chen, R., & Zhou, X. Y. (2008). Low level of galacto-oligosaccharide in infant formula stimulates growth of intestinal Bifidobacteria and Lactobacilli. *World Journal of Gastroenterology*, 14(42), 6564–6568. https://doi.org/10.3748/wjg.14.6564

[44]. Schmelzle, H., Wirth, S., Skopnik, H., Radke, M., Knol, J., Böckler, H. M., Brönstrup, A., Wells, J., & Fusch, C. (2003). Randomized double-blind study of the nutritional efficacy and bifidogenicity of a new infant formula containing partially hydrolyzed protein, a high beta-palmitic acid level, and nondigestible oligosaccharides. *Journal of Pediatric Gastroenterology and Nutrition*, 36(3), 343–351. https://doi.org/10.1097/00005176-200303000-00008

[45]. Fedorak, R. N., & Madsen, K. L. (2004). Probiotics and the management of inflammatory bowel disease. *Inflammatory Bowel Diseases*, 10(3), 286–299. https://doi.org/10.1097/00054725-200405000-00018

[46]. Fernández, J., Moreno, F. J., Olano, A., Clemente, A., Villar, C. J., & Lombó, F. (2018). A galacto-oligosaccharides preparation derived from lactulose protects against colorectal cancer development in an animal model. *Frontiers in Microbiology*, 9, 2004. https://doi.org/10.3389/fmicb.2018.02004

[47]. Vulevic, J., Juric, A., Walton, G. E., Claus, S. P., Tzortzis, G., Toward, R. E., et al. (2015). Influence of galacto-oligosaccharide mixture (B-GOS) on gut microbiota, immune parameters and metabonomics in elderly persons. *British Journal of Nutrition*, 114, 586–595. https://doi.org/10.1017/s0007114515001889

[48]. Hashmi, A., Naeem, N., Farooq, Z., Masood, S., Iqbal, S., & Naseer, R. (2016). Effect of prebiotic galacto-oligosaccharides on serum lipid profile of hypercholesterolemics. *Probiotics and Antimicrobial Proteins*, 8(1), 19–30. https://doi.org/10.1007/s12602-016-9206-1

[49]. Wilson, B., & Whelan, K. (2017). Prebiotic inulin-type fructans and galacto-oligosaccharides: Definition, specificity, function, and application in gastrointestinal disorders. *Journal of Gastroenterology and Hepatology*, 32(1), 64–68. https://doi.org/10.1111/jgh.13700

[50]. Moens, F., Verce, M., & De Vuyst, L. (2017). Lactate- and acetate-based cross-feeding interactions between selected strains of lactobacilli, bifidobacteria, and colon bacteria in the presence of inulin-type fructans. *International Journal of Food Microbiology*, 241, 225–236. https://doi.org/10.1016/j.ijfoodmicro.2016.10.019

[51]. Martínez-Tomé, M., Cedeño-Pinos, C., Bañón, S., & Jiménez-Monreal, A. M. (2022). Rosemary extracts improved the antioxidant status of low-fat yoghurt sauces enriched with inulin. *Antioxidants*, 11(4), 789. https://doi.org/10.3390/antiox11040789

[52]. Illippangama, A. U., Jayasena, D. D., Jo, C., & Mudannayake, D. C. (2022). Inulin as a functional ingredient and their applications in meat products. *Carbohydrate Polymers*, 275, 118706. https://doi.org/10.1016/j.carbpol.2021.118706

[53]. Shoaib, M., Shehzad, A., Omar, M., Rakha, A., Raza, H., Sharif, H. R., et al. (2016). Inulin: Properties, health benefits and food applications. *Carbohydrate Polymers*, 147, 444–454. https://doi.org/10.1016/j.carbpol.2016.04.020

[54]. Giri, S., Dutta, P., & Giri, T. K. (2021). Inulin-based carriers for colon drug targeting. *Journal of Drug Delivery Science and Technology*, 64, 102595. https://doi.org/10.1016/j.jddst.2021.102595

[55]. Apolinário, A. C., de Lima Damasceno, B. P. G., de Macêdo Beltrão, N. E., Pessoa, A., Converti, A., & da Silva, J. A. (2014). Inulin-type fructans: A review on different aspects of biochemical and pharmaceutical technology. *Carbohydrate Polymers*, 101, 368–378. https://doi.org/10.1016/j.carbpol.2013.09.081

[56]. Chi, Z. M., Zhang, T., Cao, T. S., Liu, X. Y., Cui, W., & Zhao, C. H. (2011). Biotechnological potential of inulin for bioprocesses. *Bioresource Technology*, 102(7), 4295–4303. https://doi.org/10.1016/j.biortech.2010.12.086

[57]. Ahmed, W., & Rashid, S. (2019). Functional and therapeutic potential of inulin: A comprehensive review. *Critical Reviews in Food Science and Nutrition*, 59(1), 1–13. https://doi.org/10.1080/10408398.2017.1355775

[58]. Lightowler, H., Thondre, S., Holz, A., & Theis, S. (2018). Replacement of glycaemic carbohydrates by inulin-type fructans from chicory (oligofructose, inulin) reduces the postprandial blood glucose and insulin response to foods: Report of two double-blind, randomized, controlled trials. *European Journal of Nutrition*, 57(4), 1259–1268. https://doi.org/10.1007/s00394-017-1409-z

[59]. Wan, X., Guo, H., Liang, Y., Zhou, C., Liu, Z., Li, K., et al. (2020). The physiological functions and pharmaceutical applications of inulin: A review. *Carbohydrate Polymers*, 246, 116589. https://doi.org/10.1016/j.carbpol.2020.116589

[60]. Lin, H., Wang, Q., Yuan, M., Liu, L., Chen, Z., Zhao, Y., et al. (2020). The prolonged disruption of a single-course amoxicillin on mice gut microbiota and resistome, and recovery by inulin, Bifidobacterium longum and fecal microbiota transplantation. *Environmental Pollution*, 265, 114651. https://doi.org/10.1016/j.envpol.2020.114651

[61]. Bastard, Q. L., Chapelet, G., Javaudin, F., Lepelletier, D., & Montassier, E. (2020). The effects of inulin on gut microbial composition: A systematic review of evidence from human studies. *European Journal of Clinical Microbiology & Infectious Diseases*, 39, 403–413. https://doi.org/10.1007/s10096-019-03721-w

[62]. Agopian, R., Soares, C. A., Purgatto, E., Cordenunsi, B. R., & Lajolo, F. M. (2008). Identification of fructooligosaccharides in different banana cultivars.

Journal of Agricultural and Food Chemistry, 56(8), 3305–3310. https://doi.org/10.1021/jf0730111

[63]. Kumar, V. P., Prashanth, K., & Venkatesh, Y. P. (2015). Structural analyses and immunomodulatory properties of fructo-oligosaccharides from onion (Allium cepa). *Carbohydrate Polymers*, 117, 115–122. https://doi.org/10.1016/j.carbpol.2014.09.039

[64]. Pinto-Sanchez, M. I., & Verdu, E. F. (2018). Non-celiac gluten or wheat sensitivity: it's complicated!. *Neurogastroenterology & Motility*, 30(9), e13392. https://doi.org/10.1111/nmo.13392

[65]. Sunu, P., Sunarti, D., Mahfudz, L. D., & Yunianto, V. D. (2019). Prebiotic activity of garlic (Allium sativum) extract on Lactobacillus acidophilus. *Veterinary World*, 12(12), 2046–2051. https://doi.org/10.14202/vetworld.2019.2046-2051

[66]. Hussain, M., Anjum, F. M., Rahim, M. A., Saeed, F., & Khalid, W. (2021). Functional and nutraceutical properties of fructo-oligosaccharides derivatives: A review. *International Journal of Food Properties*, 24(1), 1588602. https://doi.org/10.1080/10942912.2021.1986520

[67]. Nie, Y., & Luo, F. (2021). Dietary fiber: An opportunity for a global control of hyperlipidemia. *Oxidative Medicine and Cellular Longevity*, 2021, 5542342. https://doi.org/10.1155/2021/5542342

[68]. Pinna, C., Vecchiato, C. G., Bolduan, C., Grandi, M., Stefanelli, C., Windisch, W., & et al. (2018). Influence of dietary protein and fructooligosaccharides on fecal fermentative end-products, fecal bacterial populations and apparent total tract digestibility in dogs. *BMC Veterinary Research*, 14, 1–10. https://doi.org/10.1186/s12917-018-1436-x

[69]. Zheng, Z., Tao, L. A., Ym, A., Miao, H., Lun, S., Hj, A., & et al. (2021). FOS/GOS attenuates high-fat diet induced bone loss via reversing microbiota dysbiosis, high intestinal permeability and systemic inflammation in mice. *Metabolism*, 119, 154767. https://doi.org/10.1016/j.metabol.2021.154767

[70]. Rezende, E. S. V., Lima, G. C., & Naves, M. M. (2021). Dietary fibers as beneficial microbiota modulators: A proposed classification by prebiotic categories. *Nutrition*, 89, 111217. https://doi.org/10.1016/j.nut.2021.111217

[71]. Jiao, X., Wang, Y., Lin, Y., Lang, Y., Li, E., Zhang, X., et al. (2019). Blueberry polyphenols extract as a potential prebiotic with anti-obesity effects on C57BL/6 J mice by modulating the gut microbiota. *Journal of Nutritional Biochemistry*, 64, 88–100. https://doi.org/10.1016/j.jnutbio.2018.07.008

[72]. Cho, Y. H., Lee, H. G., Seo, K. H., Yokoyama, W., & Kim, H. (2018). Antiobesity effect of prebiotic polyphenol-rich grape seed flour supplemented with probiotic kefir-derived lactic acid bacteria. *Journal of Agricultural and Food Chemistry*, 66(49), 12498–12511. https://doi.org/10.1021/acs.jafc.8b03720

[73]. Rezende, E. S. V., Lima, G. C., dos Santos Lima, M., Coelho, A. S. G., & Naves, M. M. (2022). Prebiotic potential of isolated commercial dietary fibres compared to orange albedo in Lactobacillus and Bifidobacterium species. *Bioactive Carbohydrates and Dietary Fibre*, 28, 100316. https://doi.org/10.1016/j.bcdf.2022.100316

[74]. Valero-Cases, E., Nuncio-Jáuregui, N., & Frutos, M. J. (2017). Influence of fermentation with different lactic acid bacteria and in vitro digestion on the biotransformation of phenolic compounds in fermented pomegranate juices. *Journal of Agricultural and Food Chemistry*, 65(29), 6488. https://doi.org/10.1021/acs.jafc.6b04854

[75]. Jin, H. E., Choi, J. C., Lim, Y. T., & Sung, M. H. (2017). Prebiotic effects of poly-gamma-glutamate on bacterial flora in murine gut. *Journal of Microbiology and Biotechnology*, 27(3), 412–415. https://doi.org/10.4014/jmb.1611.11023

[76]. Zheng, L. X., Chen, X. Q., & Cheong, K. L. (2020). Current trends in marine algae polysaccharides: The digestive tract, microbial catabolism, and prebiotic potential. *International Journal of Biological Macromolecules*, 151, 344–354. https://doi.org/10.1016/j.ijbiomac.2020.02.168

[77]. Zeng, H., Chen, P., Chen, C., Huang, C., Lin, S., Zheng, B., et al. (2018). Structural properties and prebiotic activities of fractionated lotus seed resistant starches. *Food Chemistry*, 251, 33–40. https://doi.org/10.1016/j.foodchem.2018.01.057

[78]. Huang, F., Liu, H., Zhang, R., Dong, L., Liu, L., Ma, Y., et al. (2019). Physicochemical properties and prebiotic activities of polysaccharides from longan pulp based on different extraction techniques. *Carbohydrate Polymers*, 206, 344–351. https://doi.org/10.1016/j.carbpol.2018.11.012

[79]. Cockburn, D. W., & Koropatkin, N. M. (2016). Polysaccharide degradation by the intestinal microbiota and its influence on human health and disease. *Journal of Molecular Biology*, 428(16), 3230–3252. https://doi.org/10.1016/j.jmb.2016.06.021

[80]. Guarino, M. P. L., Altomare, A., Emerenziani, S., Di Rosa, C., Ribolsi, M., Balestrieri, P., et al. (2020). Mechanisms of action of prebiotics and their effects on gastrointestinal disorders in adults. *Nutrients*, 12(4), 1037. https://doi.org/10.3390/nu12041037

[81]. David, R., Patricia, R. M., Abelardo, M., Miguel, G., de los Reyes Gavilán, C. G., & Nuria, S. (2016). Intestinal short chain fatty acids and their link with diet and human health. *Frontiers in Microbiology*, 7, 185. https://doi.org/10.3389/fmicb.2016.00185

[82]. Ashaolu, T. J. (2020). Immune boosting functional foods and their mechanisms: A critical evaluation of probiotics and prebiotics. *Biomedicine & Pharmacotherapy*, 130, 110625. https://doi.org/10.1016/j.biopha.2020.110625

[83]. Carlson, J. L., Erickson, J. M., Hess, J. M., Gould, T. J., & Slavin, J. L. (2017). Prebiotic dietary fiber and gut health: Comparing the in vitro fermentations of beta-glucan, inulin, and xylooligosaccharide. *Nutrients*, 9(12), 1361. https://doi.org/10.3390/nu9121361

[84]. Neffe-Skocinska, K., Rzepkowska, A., Szydlowska, A., & Kotozyn-Krajewska, D. (2018). Trends and possibilities of the use of probiotics in food production. *Alternative and replacement foods* (pp. 33–49). Academic Press. https://doi.org/10.1016/B978-0-12-811446-9.00003-4

[85]. Behnsen, J., Deriu, E., Sassone-Corsi, M., & Raffatellu, M. (2013). Probiotics: Properties, examples, and specific applications. *Cold Spring Harbor Perspectives in Medicine*, 3, a010074. https://doi.org/10.1101/cshperspect.a010074

[86]. Slizewska, K., Markowiak-Kopec, P., & Slizewska, W. (2020). The role of probiotics in cancer prevention. *Cancers*, 13(1), 20. https://doi.org/10.3390/cancers13010020

[87]. Altonsy, M. O., Andrews, S. C., & Tuohy, K. M. (2010). Differential induction of apoptosis in human colonic carcinoma cells (Caco-2) by Atopobium, and commensal, probiotic and enteropathogenic bacteria: mediation by the mitochondrial pathway. *International journal of food microbiology*, 137(2-3), 190–203. https://doi.org/10.1016/j.ijfoodmicro.2009.11.015

[88]. Hashemi, A., Villa, C. R., & Comelli, E. M. (2016). Probiotics in early life: a preventative and treatment approach. *Food & function*, *7*(4), 1752–1768. https://doi.org/10.1039/c5fo01148e

[89Lefevre, M., Racedo, S. M., Denayrolles, M., Ripert, G., Desfougères, T., Lobach, A. R., Simon, R., Pélerin, F., Jüsten, P., & Urdaci, M. C. (2017). Safety assessment of Bacillus subtilis CU1 for use as a probiotic in humans. *Regulatory Toxicology and Pharmacology*: RTP, 83, 54–65. https://doi.org/10.1016/j.yrtph.2016.11.010

[90]. Cerdó, T., García-Santos, J. A., G Bermúdez, M., & Campoy, C. (2019). The Role of Probiotics and Prebiotics in the Prevention and Treatment of Obesity. *Nutrients*, 11(3), 635. https://doi.org/10.3390/nu11030635

[91]. Davani-Davari, D., Negahdaripour, M., Karimzadeh, I., Seifan, M., Mohkam, M., Masoumi, S. J., et al. (2019). Prebiotics: Definition, types, sources, mechanisms, and clinical applications. *Foods, 8*(3), 92. https://doi.org/10.3390/foods8030092

[92]. Lieske, J. C. (2017). Probiotics for prevention of urinary stones. *Annals of Translational Medicine*, 5(2), 29. https://doi.org/10.21037/atm.2016.11.86

[93]. Martín, R., & Langella, P. (2019). Emerging health concepts in the probiotics field: Streamlining the definitions. Frontiers in Microbiology, 10, 1047. https://doi.org/10.3389/fmicb.2019.01047

[94]. Markowiak, P., & Slizewska, K. (2018). The role of probiotics, prebiotics, and synbiotics in animal nutrition. *Gut Pathogens*, 10, 1–20. https://doi.org/10.1186/s13099-018-0250-0

[95]. Cho, Y. A., & Kim, J. (2015). Effect of probiotics on blood lipid concentrations: A meta-analysis of randomized controlled trials. *Medicine*, 94(47), e1714. https://doi.org/10.1097/MD.0000000000001714

[96]. La Fata, G., Weber, P., & Mohajeri, M. H. (2018). Probiotics and the gut immune system: Indirect regulation. *Probiotics and Antimicrobial Proteins*, 10(1), 11–21. https://doi.org/10.1007/s12602-017-9322-6

[97]. Oak, S. J., & Jha, R. (2019). The effects of probiotics in lactose intolerance: A systematic review. *Critical Reviews in Food Science and Nutrition*, 59(10), 1675–1683. https://doi.org/10.1080/10408398.2018.1425977

[98]. Shewale, R. N., Sawale, P. D., Khedkar, C. D., & Singh, A. (2014). Selection criteria for probiotics: A review. *International Journal of Probiotics & Prebiotics*, 9(1/2), 17–22.

[99]. Sánchez, B., Delgado, S., Blanco-Míguez, A., Lourenço, A., Gueimonde, M., & Margolles, A. (2017). Probiotics, gut microbiota, and their influence on host health and disease. *Molecular Nutrition & Food Research*, 61(1), 1600240. https://doi.org/10.1002/mnfr.201600240

[100]. Oelschlaeger, T. A. (2010). Mechanisms of probiotic actions—a review. *International Journal of Medical Microbiology*, 300(1), 57–62. https://doi.org/10.1016/j.ijmm.2009.08.005

[101]. Milani, C., Duranti, S., Bottacini, F., Casey, E., Turroni, F., Mahony, J., … & van Sinderen, D. (2017). The first microbial colonizers of the human gut: Composition, activities, and health implications of the infant gut microbiota. *Microbiology and Molecular Biology Reviews*, 81(4), e00036–17. https://doi.org/10.1128/MMBR.00036-17

[102]. Ding, S., Wang, Y., Yan, W., Li, A., Jiang, H., & Fang, J. (2019). Effects of Lactobacillus plantarum 15-1 and fructooligosaccharides on the response of broilers to pathogenic Escherichia coli 78 challenge. *PLOS ONE*, 14(3), e0212079. https://doi.org/10.1371/journal.pone.0212079

[103]. Liu, T., Li, Y., Zhao, M., Mo, Q., & Feng, F. (2020). Weight-reducing effect of Lactobacillus plantarum ZJUFT17 isolated from sourdough ecosystem. *Nutrients*, 12(4), 977. https://doi.org/10.3390/nu12040977

[104]. Li, C., Liu, H., Yang, J., Mu, J., Wang, R., & Zhao, X. (2020). Effect of soybean milk fermented with Lactobacillus plantarum HFY01 isolated from yak yogurt on weight loss and lipid reduction in mice with obesity induced by a high-fat diet. *RSC Advances*, 10(34), 34276–34289. https://doi.org/10.1039/D0RA06977A

[105]. Zhang, Z., Lv, J., Pan, L., & Zhang, Y. (2018). Roles and applications of probiotic Lactobacillus strains. *Applied Microbiology and Biotechnology*, 102(18), 8135–8143. https://doi.org/10.1007/s00253-018-9217-9

[106]. Bartkiene, E., Özogul, F., & Rocha, J. M. (2022). Bread sourdough lactic acid bacteria—technological, antimicrobial, toxin-degrading, immune system, and faecal microbiota-modelling biological agents for the preparation of food, nutraceuticals and feed. *Foods*, 11(3), 452. https://doi.org/10.3390/foods11030452

[107]. Rajoka, M. S. R., Mehwish, H. M., Zhang, H., Ashraf, M., Fang, H., Zeng, X., et al. (2020). Antibacterial and antioxidant activity of exopolysaccharide mediated silver nanoparticle synthesized by Lactobacillus brevis isolated from Chinese koumiss. *Colloids and Surfaces B: Biointerfaces*, 186, 110734. https://doi.org/10.1016/j.colsurfb.2019.110734

[108]. Zhang, W., Ji, H., Zhang, D., Liu, H., Wang, S., Wang, J., et al. (2018). Complete genome sequencing of Lactobacillus plantarum ZLP001, a potential probiotic that enhances intestinal epithelial barrier function and defense against pathogens in pigs. *Frontiers in Physiology*, 9, 1689. https://doi.org/10.3389/fphys.2018.01689

[109]. Henrick, B. M., Hutton, A. A., Palumbo, M. C., Casaburi, G., Mitchell, R. D., Underwood, M. A., et al. (2018). Elevated fecal pH indicates a profound change in the breastfed infant gut microbiome due to reduction of Bifidobacterium over the past century. *mSphere*, 3(2), e00041–18. https://doi.org/10.1128/mSphere.00041-18

[110]. Bested, A. C., Logan, A. C., & Selhub, E. M. (2013). Intestinal microbiota, probiotics and mental health: From Metchnikoff to modern advances: Part III–convergence toward clinical trials. *Gut Pathogens*, 5, 1–13. https://doi.org/10.1186/1757-4749-5-4

[111]. Valdemiro, C. S. (2011). The importance of prebiotics in functional foods and clinical practice. *Food and Nutrition Sciences*, 2(2), 4536. https://doi.org/10.4236/fns.2011.22019153

[112]. Klaassens, E. S., Boesten, R. J., Haarman, M., Knol, J., Schuren, F. H., Vaughan, E. E., & de Vos, W. M. (2009).

Mixed-species genomic microarray analysis of fecal samples reveals differential transcriptional responses of Bifidobacteria in breast and formula-fed infants. *Applied and Environmental Microbiology*, 75(9), 2668–2676. https://doi.org/10.1128/AEM.02492-08

[113]. Makras, L., & De Vuyst, L. (2006). The in vitro inhibition of Gram-negative pathogenic bacteria by Bifidobacteria is caused by the production of organic acids. *International Dairy Journal*, 16(9), 1049–1057. https://doi.org/10.1016/j.idairyj.2005.09.006

[114]. Meng, H., Ba, Z., Lee, Y., Peng, J., Lin, J., Fleming, J. A., et al. (2017). Consumption of Bifidobacterium animalis subsp. lactis BB-12 in yogurt reduced expression of TLR-2 on peripheral blood-derived monocytes and pro-inflammatory cytokine secretion in young adults. *European Journal of Nutrition*, 56(2), 649–661. https://doi.org/10.1007/s00394-015-1109-5

[115]. Krumbeck, J. A., Rasmussen, H. E., Hutkins, R. W., Clarke, J., Shawron, K., Keshavarzian, A., et al. (2018). Probiotic Bifidobacterium strains and galactooligosaccharides improve intestinal barrier function in obese adults but show no synergism when used together as synbiotics. *Microbiome*, 6(1), 1–16. https://doi.org/10.1186/s40168-018-0494-4

[116]. Dubey, M. R., & Patel, V. P. (2018). Probiotics: A promising tool for calcium absorption. *Open Nutrition Journal*, 12, 10. https://doi.org/10.2174/1874288201812010059

[117]. Sadiq, F. A., Wenwei, L., Wei, C., Jianxin, Z., & Zhang, H. (2021). Transcriptional changes in Bifidobacterium bifidum involved in synergistic multispecies biofilms. *Microbial Ecology*. https://doi.org/10.1007/s00248-021-01904-7

[118]. Shimizu, Y., Isoda, K., Taira, Y., Taira, I., Kondoh, M., & Ishida, I. (2020). Anti-tumor effect of a recombinant Bifidobacterium strain secreting a claudin-targeting molecule in a mouse breast cancer model. *European Journal of Pharmacology*, 887, 173596. https://doi.org/10.1016/j.ejphar.2020.173596

[119]. Hanchi, H., Mottawea, W., Sebei, K., & Hammami, R. (2018). The genus Enterococcus: Between probiotic potential and safety concerns—An update. *Frontiers in Microbiology*, 9, 1791. https://doi.org/10.3389/fmicb.2018.01791

[120]. Czerucka, D., & Rampal, P. (2019). Diversity of Saccharomyces boulardii CNCM I-745 mechanisms of action against intestinal infections. *World Journal of Gastroenterology*, 25(18), 2188. https://doi.org/10.3748/wjg.v25.i18.2188

[121]. Pais, P., Almeida, V., Yilmaz, M., & Teixeira, M. C. (2020). Saccharomyces boulardii: What makes it tick as a successful probiotic?. *Journal of Fungi*, 6(2), 78. https://doi.org/10.3390/jof6020078

[122]. Szajewska, H., & Kołodziej, M. (2020). Systematic review with meta-analysis: Saccharomyces boulardii for treating acute gastroenteritis in children—a 2020 update. *Alimentary Pharmacology & Therapeutics*, 51(7), 678–688. https://doi.org/10.1111/apt.15659

[123]. Xu, Y., Cui, Y., Yue, F., Liu, L., Shan, Y., Liu, B., et al. (2019). Exopolysaccharides produced by lactic acid bacteria and Bifidobacteria: Structures, physiochemical functions and applications in the food industry. *Food Hydrocolloids*, 94, 475–499. https://doi.org/10.1016/j.foodhyd.2019.03.032

[124]. Hill, D., Sugrue, I., Tobin, C., Hill, C., Stanton, C., & Ross, R. P. (2018). The Lactobacillus casei group: History and health-related applications. *Frontiers in Microbiology*, 9, 2107. https://doi.org/10.3389/fmicb.2018.02107

[125]. Wang, B., Kong, Q., Cui, S., Li, X., Gu, Z., Zhao, J., et al. (2021). Bifidobacterium adolescentis isolated from different hosts modifies the intestinal microbiota and displays differential metabolic and immunomodulatory properties in mice fed a high-fat diet. *Nutrients*, 13(3), 1017. https://doi.org/10.3390/nu13031017

[126]. Huang, Z., Zhou, X., Stanton, C., Ross, R. P., Zhao, J., Zhang, H., et al. (2021). Comparative genomics and specific functional characteristics analysis of Lactobacillus acidophilus. *Microorganisms*, 9(9), 1992. https://doi.org/10.3390/microorganisms9091992

[127]. Mu, Y., & Cong, Y. (2019). Bacillus coagulans and its applications in medicine. *Beneficial Microbes*, 10(6), 679–688. https://doi.org/10.3920/BM2019.0016

[128]. Zhou, Y., Zeng, Z., Xu, Y., Ying, J., Wang, B., Majeed, M., et al. (2020). Application of Bacillus coagulans in animal husbandry and its underlying mechanisms. *Animals*, 10(3), 454. https://doi.org/10.3390/ani10030454

[129]. Nayak, S. K. (2021). Multifaceted applications of probiotic Bacillus species in aquaculture with special reference to Bacillus subtilis. *Reviews in Aquaculture*, 13(3), 862–906. https://doi.org/10.1111/raq.12503

[130]. Westerik, N., Kort, R., Sybesma, W., & Reid, G. (2018). Lactobacillus rhamnosus probiotic food as a tool for empowerment across the value chain in Africa. *Frontiers in Microbiology*, 9, 1501. https://doi.org/10.3389/fmicb.2018.01501

[131]. Kleerebezem, M., Bachmann, H., van Pelt-KleinJan, E., Douwenga, S., Smid, E. J., Teusink, B., & others. (2020). Lifestyle, metabolism and environmental adaptation in Lactococcus lactis. FEMS *Microbiology Reviews*, 44(6), 804–820. https://doi.org/10.1093/femsre/fuaa033

[132]. Burgueño, J. F., & Abreu, M. T. (2020). Epithelial Toll-like receptors and their role in gut homeostasis and disease. Nature *Reviews Gastroenterology & Hepatology*, 17(5), 263. https://doi.org/10.1038/s41575-019-0261-4

[133]. Wu, Y., Tang, L., Wang, B., Sun, Q., Zhao, P., Li, W., et al. (2019). The role of autophagy in maintaining intestinal mucosal barrier. *Journal of Cellular Physiology*, 234(12), 19406–19419. https://doi.org/10.1002/jcp.28722

[134]. Patel, S., & McCormick, B. A. (2014). Mucosal inflammatory response to Salmonella typhimurium infection. *Frontiers in Immunology*, 5, 311. https://doi.org/10.3389/fimmu.2014.00311

[135]. Cheng, F. S., Pan, D., Chang, B., Jiang, M., & Sang, L. X. (2020). Probiotic mixture VSL#3: An overview of basic and clinical studies in chronic diseases. *World Journal of Clinical Cases*, 8(8), 1361. https://doi.org/10.12998/wjcc.v8.i8.1361

[136]. Toumi, R., Abdelouhab, K., Rafa, H., Soufli, I., Raissi-Kerboua, D., Djeraba, Z., & et al. (2013). Beneficial role of the probiotic mixture Ultrabiotique on maintaining the integrity of intestinal mucosal barrier in DSS-induced experimental colitis. *Immunopharmacology and Immunotoxicology*, 35(4), 403–409. https://doi.org/10.3109/08923973.2013.790413

[137]. Zhu, L., Li, J., Wei, C., Luo, T., Deng, Z., Fan, Y., & et al. (2020). A polysaccharide from Fagopyrum esculentum Moench bee pollen alleviates microbiota dysbiosis to improve intestinal barrier function in antibiotic-treated mice. *Food Function*, 11(11), 10519–10533. https://doi.org/10.1039/D0FO01948H

[138]. Scharek-Tedin, L., Filter, M., Taras, D., Wrede, P., & Schmidt, M. F. (2009). Influence of an Enterococcus faecium probiotic on the development of Peyer's patches B cells in piglets. *Archives of Animal Nutrition*, 63(5), 343–355. https://doi.org/10.1080/17450390903052771

[139]. Shida, K., Nanno, M., & Nagata, S. (2011). Flexible cytokine production by macrophages and T cells in response to probiotic bacteria: A possible mechanism by which probiotics exert multifunctional immune regulatory activities. *Gut Microbes*, 2(2), 109–114. https://doi.org/10.4161/gmic.2.2.15661

[140]. Azad, M., Kalam, A., Sarker, M., & Wan, D. (2018). Immunomodulatory effects of probiotics on cytokine profiles. *Biomed Research International*, 2018, 8063647. https://doi.org/10.1155/2018/8063647

[141]. Ashraf, R., & Shah, N. P. (2014). Immune system stimulation by probiotic microorganisms. *Critical Reviews in Food Science and Nutrition*, 54(7), 938–956. https://doi.org/10.1080/10408398.2011.619671

[142]. Miller, L. E., Lehtoranta, L., & Lehtinen, M. J. (2019). Short-term probiotic supplementation enhances cellular immune function in healthy elderly: Systematic review and meta-analysis of controlled studies. *Nutrition Research*, 64, 1–8. https://doi.org/10.1016/j.nutres.2018.12.011

[143]. Duary, R. K., Bhausaheb, M. A., Batish, V. K., & Grover, S. (2012). Anti-inflammatory and immunomodulatory efficacy of indigenous probiotic Lactobacillus plantarum Lp91 in colitis mouse model. *Molecular Biology Reports*, 39(5), 4765–4775. https://doi.org/10.1007/s11033-011-1269-1

[144]. Dargahi, N., Johnson, J., Donkor, O., Vasiljevic, T., & Apostolopoulos, V. (2019). Immunomodulatory effects of probiotics: Can they be used to treat allergies and autoimmune diseases?. *Maturitas*, 119, 25–38. https://doi.org/10.1016/j.maturitas.2018.11.002

[145]. Chiba, Y., Shida, K., Nagata, S., Wada, M., Bian, L., Wang, C., & et al. (2010). Well-controlled proinflammatory cytokine responses of Peyer's patch cells to probiotic Lactobacillus casei. *Immunology*, 130(3), 352–362. https://doi.org/10.1111/j.1365-2567.2009.03204.x

[146]. Bui, V. T., Tseng, H. C., Kozlowska, A., Maung, P. O., Kaur, K., Topchyan, P., & et al. (2015). Augmented IFN-γ and TNF-α induced by probiotic bacteria in NK cells mediate differentiation of stem-like tumors leading to inhibition of tumor growth and reduction in inflammatory cytokine release; regulation by IL-10. *Frontiers in Immunology*, 6, 576. https://doi.org/10.3389/fimmu.2015.00576

[147]. Komanduri, S., Gillevet, P. M., Sikaroodi, M., Mutlu, E., & Keshavarzian, A. (2007). Dysbiosis in pouchitis: Evidence of unique microfloral patterns in pouch inflammation. *Clinical Gastroenterology and Hepatology*, 5(3), 352–360. https://doi.org/10.1016/j.cgh.2007.01.001

[148]. Sokol, H., Lay, C., Seksik, P., & Tannock, G. W. (2008). Analysis of bacterial bowel communities of IBD patients: What has it revealed?. *Inflammatory Bowel Diseases*, 14(6), 858–867. https://doi.org/10.1002/ibd.20392

[149]. Reshef, L., Kovacs, A., Ofer, A., Yahav, L., Maharshak, N., Keren, N., Konikoff, F. M., Tulchinsky, H., Gophna, U., & Dotan, I. (2015). Pouch inflammation is associated with a decrease in specific bacterial taxa. *Gastroenterology*, 149(3), 718–727. https://doi.org/10.1053/j.gastro.2015.05.041

[150]. Dubinsky, V., Reshef, L., Bar, N., Keizer, D., Golan, N., Rabinowitz, K., Godny, L., Yadgar, K., Zonensain, K., Tulchinsky, H., Gophna, U., & Dotan, I. (2020). Predominantly antibiotic-resistant intestinal microbiome persists in patients with pouchitis who respond to antibiotic therapy. *Gastroenterology*, 158(3), 610–624.e13. https://doi.org/10.1053/j.gastro.2019.10.001

[151]. Preidis, G. A., Weizman, A. V., Kashyap, P. C., & Morgan, R. L. (2020). AGA technical review on the role of probiotics in the management of gastrointestinal disorders. *Gastroenterology*, 159(2), 708–738.e4. https://doi.org/10.1053/j.gastro.2020.05.060

[152]. Nguyen, N., Zhang, B., Holubar, S. D., Pardi, D. S., & Singh, S. (2019). Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis. *Cochrane Database of Systematic Reviews*, 2019(11), CD001176. https://doi.org/10.1002/14651858.CD001176.pub5

[153]. Kaur, L., Gordon, M., Baines, P. A., Iheozor-Ejiofor, Z., Sinopoulou, V., & Akobeng, A. K. (2020). Probiotics for induction of remission in ulcerative colitis. Cochrane Database of Systematic Reviews, 2020(3), CD005573. https://doi.org/10.1002/14651858.CD005573.pub3

[154]. Iheozor-Ejiofor, Z., Kaur, L., Gordon, M., Baines, P. A., Sinopoulou, V., & Akobeng, A. K. (2020). Probiotics for maintenance of remission in ulcerative colitis. *Cochrane Database of Systematic Reviews*, 2020(3), CD007443. https://doi.org/10.1002/14651858.CD007443.pub3

[155]. Limketkai, B. N., Akobeng, A. K., Gordon, M., & Adepoju, A. A. (2020). Probiotics for induction of remission in Crohn's disease. *Cochrane Database of Systematic Reviews*, 2020(7), CD006634. https://doi.org/10.1002/14651858.CD006634.pub3

[156]. Tian, C., Huang, Y., Wu, X., Xu, C., Bu, H., & Wang, H. (2020). The efficacy and safety of mesalamine and probiotics in mild-to-moderate ulcerative colitis: A systematic review and meta-analysis. *Evidence-Based Complementary and Alternative Medicine*, 2020, 6923609. https://doi.org/10.1155/2020/6923609

[157]. Derwa, Y., Gracie, D. J., Hamlin, P. J., & Ford, A. C. (2017). Systematic review with meta-analysis: The efficacy of probiotics in inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*, 46(4), 389–400. https://doi.org/10.1111/apt.14203

[158]. Parker, E. A., Roy, T., D'Adamo, C. R., & Wieland, L. S. (2018). Probiotics and gastrointestinal conditions: An overview of evidence from the Cochrane Collaboration. *Nutrition*, 45, 125–134.e11. https://doi.org/10.1016/j.nut.2017.06.024

[159]. Ganji-Arjenaki, M., & Rafieian-Kopaei, M. (2018). Probiotics are a good choice in remission of inflammatory bowel diseases: A meta-analysis and systematic review. *Journal of Cellular Physiology*, 233(3), 2091–2103. https://doi.org/10.1002/jcp.25911

[160]. Dong, J., Teng, G., Wei, T., Gao, W., & Wang, H. (2016). Methodological quality assessment of meta-analyses and systematic reviews of probiotics in inflammatory bowel

disease and pouchitis. *PLOS ONE*, 11(12), e0168785. https://doi.org/10.1371/journal.pone.0168785

[161]. Masco, L., Ventura, M., Zink, R., Huys, G., & Swings, J. (2004). Polyphasic taxonomic analysis of Bifidobacterium animalis and Bifidobacterium lactis reveals relatedness at the subspecies level: Reclassification of Bifidobacterium animalis as Bifidobacterium animalis subsp. animalis subsp. nov. and Bifidobacterium lactis as Bifidobacterium animalis subsp. lactis subsp. nov. *International Journal of Systematic and Evolutionary Microbiology*, 54(Pt 4), 1137–1143. https://doi.org/10.1099/ijs.0.03011-0

[162]. Chae, J. M., Heo, W., Cho, H. T., Lee, D. H., Kim, J. H., Rhee, M. S., et al. (2018). Effects of orally-administered Bifidobacterium animalis subsp. lactis strain BB12 on dextran sodium sulfate-induced colitis in mice. *Journal of Microbiology and Biotechnology*, 28, 1800–1805. https://doi.org/10.4014/jmb.1805.05072

[163]. Hrdý, J., Alard, J., Couturier-Maillard, A., Boulard, O., Boutillier, D., Delacre, M., et al. (2020). Lactobacillus reuteri 5454 and Bifidobacterium animalis ssp. lactis 5764 improve colitis while differentially impacting dendritic cells maturation and antimicrobial responses. *Scientific Reports*, 10, 5345. https://doi.org/10.1038/s41598-020-62161-1

[164]. Wang, H., Fan, C., Zhao, Z., Zhai, Z., & Hao, Y. (2022). Anti-inflammatory effect of Bifidobacterium animalis subsp. lactis A6 on DSS-induced colitis in mice. Journal of Applied Microbiology, 133(5), 2063–2073. https://doi.org/10.1111/jam.15681

[165]. Steed, H., Macfarlane, G. T., Blackett, K. L., Bahrami, B., Reynolds, N., Walsh, S. V., Cummings, J. H., & Macfarlane, S. (2010). Clinical trial: The microbiological and immunological effects of synbiotic consumption—a randomized double-blind placebo-controlled study in active Crohn's disease. *Alimentary Pharmacology & Therapeutics*, 32(7), 872–883. https://doi.org/10.1111/j.1365-2036.2010.04417.x

[166]. Haziri, D., Prechter, F., & Stallmach, A. (2021). Yoghurt induced Lactobacillus bacteremia in a patient with Crohn's disease on therapy with ustekinumab and concomitant HIV-Infection. *Zeitschrift für Gastroenterologie*, 59(4), 317–320. https://doi.org/10.1055/a-1168-7577

[167]. Van Niel, C. W., Feudtner, C., Garrison, M. M., & Christakis, D. A. (2002). Lactobacillus therapy for acute infectious diarrhea in children: A meta-analysis. Pediatrics, 109(4), 678–684. https://doi.org/10.1542/peds.109.4.678

[168]. Szajewska, H., Skórka, A., Ruszczyński, M., & Gieruszczak-Białek, D. (2007). Meta-analysis: Lactobacillus GG for treating acute diarrhoea in children. *Alimentary Pharmacology & Therapeutics*, 25(8), 871–881. https://doi.org/10.1111/j.1365-2036.2007.03282.x

[169]. Britton, R. A., & Versalovic, J. (2008). Probiotics and gastrointestinal infections. *Interdisciplinary Perspectives on Infectious Diseases*, 2008, 290769. https://doi.org/10.1155/2008/290769

[170]. Szajewska, H., & Skórka, A. (2009). Saccharomyces boulardii for treating acute gastroenteritis in children: Updated meta-analysis of randomized controlled trials. *Alimentary Pharmacology & Therapeutics*, 30(9), 960-961. https://doi.org/10.1111/j.1365-2036.2009.04113.x

[171]. Allen, S. J., Martinez, E. G., Gregorio, G. V., & Dans, L. F. (2010). Probiotics for treating acute infectious diarrhoea. Cochrane Database of Systematic Reviews, 2010(11), CD003048. https://doi.org/10.1002/14651858.CD003048.pub3

[172]. Bernaola Aponte, G., Bada Mancilla, C. A., Carreazo, N. Y., & Rojas Galarza, R. A. (2013). Probiotics for treating persistent diarrhoea in children. *Cochrane Database of Systematic Reviews*, 2013(8), CD007401. https://doi.org/10.1002/14651858.CD007401.pub3

[173]. Harris, R. G., Neale, E. P., & Ferreira, I. (2019). When poorly conducted systematic reviews and meta-analyses can mislead: A critical appraisal and update of systematic reviews and meta-analyses examining the effects of probiotics in the treatment of functional constipation in children. *The American Journal of Clinical Nutrition*, 110(1), 177-195. https://doi.org/10.1093/ajcn/nqz071

[174]. Martínez-Martínez, M. I., Calabuig-Tolsá, R., & Cauli, O. (2017). The effect of probiotics as a treatment for constipation in elderly people: A systematic review. *Archives of Gerontology and Geriatrics*, 71, 142-149. https://doi.org/10.1016/j.archger.2017.04.004

[175]. Koebnick, C., Wagner, I., Leitzmann, P., Stern, U., & Zunft, H. J. (2003). Probiotic beverage containing Lactobacillus casei Shirota improves gastrointestinal symptoms in patients with chronic constipation. *Canadian Journal of Gastroenterology*, 17(11), 655-659. https://doi.org/10.1155/2003/654907

[176]. Yang, Y. X., He, M., Hu, G., Wei, J., Pages, P., Yang, X. H., & Bourdu-Naturel, S. (2008). Effect of a fermented milk containing Bifidobacterium lactis DN-173010 on Chinese constipated women. *World Journal of Gastroenterology*, 14(40), 6237-6243. https://doi.org/10.3748/wjg.14.6237

[177]. Chmielewska, A., & Szajewska, H. (2010). Systematic review of randomised controlled trials: Probiotics for functional constipation. *World Journal of Gastroenterology*, 16(1), 69-75. https://doi.org/10.3748/wjg.v16.i1.69

[178]. Sadeghzadeh, M., Rabieefar, A., Khoshnevisasl, P., Mousavinasab, N., & Eftekhari, K. (2014). The effect of probiotics on childhood constipation: A randomized controlled double blind clinical trial. *International Journal of Pediatrics*, 2014, 937212. https://doi.org/10.1155/2014/937212

[179]. Riezzo, G., Orlando, A., D'Attoma, B., Linsalata, M., Martulli, M., & Russo, F. (2018). Randomised double blind placebo controlled trial on Lactobacillus reuteri DSM 17938: Improvement in symptoms and bowel habit in functional constipation. Beneficial Microbes, 9(1), 51-60. https://doi.org/10.3920/BM2017.0049

[180]. Andresen, V., Gschossmann, J., & Layer, P. (2020). Heat-inactivated Bifidobacterium bifidum MIMBb75 (SYN-HI-001) in the treatment of irritable bowel syndrome: A multicentre, randomised, double-blind, placebo-controlled clinical trial. *Lancet Gastroenterology & Hepatology*, 5(7), 658-666. https://doi.org/10.1016/S2468-1253(20)30056-X

[181]. Levri, K. M., Ketvertis, K., Deramo, M., Merenstein, J. H., & D'Amico, F. (2005). Do probiotics reduce adult lactose intolerance? A systematic review. *The Journal of family practice*, 54(7), 613–620.

[182]. Pakdaman, M. N., Udani, J. K., Molina, J. P., & Shahani, M. (2016). The effects of the DDS-1 strain of Lactobacillus on symptomatic relief for lactose intolerance: A randomized, double-blind, placebo-

controlled, crossover clinical trial. *Nutrition Journal*, 15(1), 56. https://doi.org/10.1186/s12937-016-0172-y

[183]. Besselink, M. G., van Santvoort, H. C., Buskens, E., Boermeester, M. A., van Goor, H., Timmerman, H. M., Nieuwenhuijs, V. B., Bollen, T. L., van Ramshorst, B., Witteman, B. J., Rosman, C., Ploeg, R. J., Brink, M. A., Schaapherder, A. F., Dejong, C. H., Wahab, P. J., van Laarhoven, C. J., van der Harst, E., van Eijck, C. H., Cuesta, M. A., Akkermans, L. M., & Gooszen, H. G.; Dutch Acute Pancreatitis Study Group. (2008). Probiotic prophylaxis in predicted severe acute pancreatitis: A randomised, double-blind, placebo-controlled trial. *The Lancet*, 371(9613), 651-659. https://doi.org/10.1016/S0140-6736(08)60207-X

[184]. Cukrowska, B., Ceregra, A., Maciorkowska, E., Surowska, B., Zegadło-Mylik, M. A., Konopka, E., Trojanowska, I., Zakrzewska, M., Bierła, J. B., Zakrzewski, M., Kanarek, E., & Motyl, I. (2021). The effectiveness of probiotic Lactobacillus rhamnosus and Lactobacillus casei strains in children with atopic dermatitis and cow's milk protein allergy: A multicenter, randomized, double-blind, placebo-controlled study. *Nutrients*, 13(4), 1169. https://doi.org/10.3390/nu13041169

[185]. Ezzat, A., Abdelsamad, N. O., Gamal, A. A., Shehata, M., Mahmoud, S. H., Mostafa, A., Ali, M. A., & Esawy, M. A. (2022). Possible correlation between probiotic activity of bacterial honey isolates and severe acute respiratory syndrome coronavirus 2 replication in vitro. *Egyptian Journal of Chemistry*, *65*(9), 467-476. doi: 10.21608/ejchem.2022.115169.5225

[186]. Wilson, I. D., & Nicholson, J. K. (2017). Gut microbiome interactions with drug metabolism, efficacy, and toxicity. Translational Research: *The Journal of Laboratory and Clinical Medicine*, 179, 204–222. https://doi.org/10.1016/j.trsl.2016.08.002

[187]. Chung, J., Kuo, C. J., Crabtree, G. R., & Blenis, J. (1992). Rapamycin-FKBP specifically blocks growth-dependent activation of and signaling by the 70 kd S6 protein kinases. *Cell*, 69(7), 1227–1236. https://doi.org/10.1016/0092-8674(92)90643-q

[188]. Klaassen, C. D., & Cui, J. Y. (2015). Review: Mechanisms of how the intestinal microbiota alters the effects of drugs and bile acids. Drug Metabolism and Disposition: *The Biological Fate of Chemicals*, 43(10), 1505–1521. https://doi.org/10.1124/dmd.115.065698

[189]. Yang, G., Ge, S., Singh, R., Basu, S., Shatzer, K., Zen, M., Liu, J., Tu, Y., Zhang, C., Wei, J., Shi, J., Zhu, L., Liu, Z., Wang, Y., Gao, S., & Hu, M. (2017). Glucuronidation: Driving factors and their impact on glucuronide disposition. *Drug Metabolism Reviews*, 49(2), 105–138. https://doi.org/10.1080/03602532.2017.1293682

[190] . Abdelsalam, N. A., Ramadan, A. T., ElRakaiby, M. T., & Aziz, R. K. (2020). Toxicomicrobiomics: The human microbiome vs. pharmaceutical, dietary, and environmental xenobiotics. *Frontiers in Pharmacology*, 11, 390. https://doi.org/10.3389/fphar.2020.00390

[191]. Dikeocha, I. J., Al-Kabsi, A. M., Miftahussurur, M., & Alshawsh, M. A. (2022). Pharmacomicrobiomics: Influence of gut microbiota on drug and xenobiotic metabolism. *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology*, 36(6), e22350. https://doi.org/10.1096/fj.202101986R