ISSN: 3066-8115
Review Article

Science Set Journal of Medical and Clinical Case Studies

The Role of Probiotics in the Vaginal and Intestinal Microbiota

Ferro M*, **Graubard H and Perez R**

FG Scientifica and Science Department at Happy V/Nutrition Formulators Inc., Miramar, Fl. 3260 Executive Way, Miramar, Fl 33025, USA

***Corresponding author:** Ferro M, FG Scientifica and Science Department at Happy V/Nutrition Formulators Inc., Miramar, Fl. 3260 Executive Way, Miramar, Fl 33025, USA.

Submitted: 07 September 2023 **Accepted:** 14 September 2023 **Published:** 17 October 2023

https://doi.org/10.63620/MKSSJMCCS.2023.1021

***Citation:** Ferro, M., Graubard, H., & Perez, R. (2023). The Role of Probiotics in the Vaginal and Intestinal Microbiota. Sci Set J of Med Cli Case Stu 2(4), 01-12.*

Abstract

Probiotics are live bacteria beneficial to the body, especially for the digestive system. Researchers are still trying to uncover in detail how probiotics work. So far, there is evidence that probiotics help to keep the microbiota in mucous membranes healthy by helping in several aspects, mainly in the immune system. Probiotics can be used in a diversity of treatments, including irritable bowel syndrome, inflammatory bowel disease (IBD), infectious diarrhea (caused by viruses, bacteria, or parasites), diarrhea caused by antibiotics, eczema, and others. Emerging evidence highlights their use in addressing issues related to other parts of the body, such as urinary and vaginal health, prevention of allergies and colds, and oral health. Therefore, this review aims to analyze the role of these microorganisms in the human body, the differences between probiotics, prebiotics, and postbiotics, as well as the mechanisms of action of some strains and their benefits to the host.

Keywords: Prebiotics, Probiotics, Postbiotics, Bacterial Vaginosis, Microbiota

Introduction

The human body is a habitat of trillions of microbial cells whose coordinated actions are considered essential for human life. These populations of microbial cells can be found in greater numbers in the intestines, mouth, and vaginal canal, with the first having the highest density. This process is known as microbiota which develops throughout the host's childhood to eventually reach its adult form [1-5].

Members of this microbiota encompass the three domains of life: Archaea, Bacteria, Eukarya, and viruses [6, 7]. They are known to establish complex trophic relationships with one another and with their human host, ranging from symbiosis to parasitism [7]. There are a relatively small number of pathogens considered members of the microbiota, mainly in the intestines, residing undisturbed in the enteric microbiota of the host [1]. These pathogens threaten the host's health when there is a disturbance in the ecosystem, altering the homeostasis of the microbiota [8].

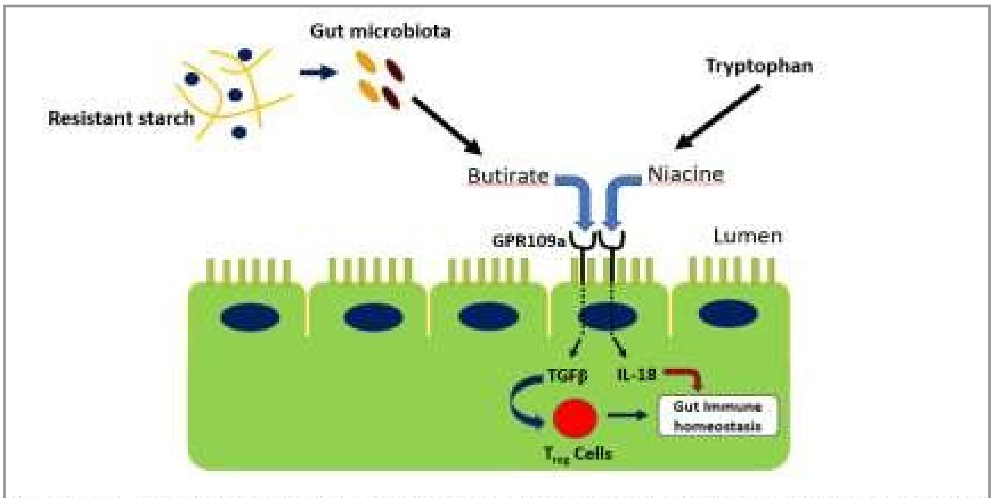
The composition of gastrointestinal, mouth, and vaginal microbiota can be affected by several environmental parameters, such as pH, reactive oxygen levels, nutrient availability, and temperature. Depending on how the environment interacts with these microorganisms they can thrive and perform different activities on the host [9]. The human intestinal microbiota plays critical roles in maintaining health, helping to break down food substances, such as resistant starches, and forming essential nutrients for the host, as in short-chain fatty acids [10]. This brings benefits to host cells, protecting them from colonization by pathogens and modulating the immune system [11].

Short-chain fatty acids, mainly butyrate, promote metabolism benefits not only to colonocytes but also to the liver [12]. Formed in the large intestine by the action of intestinal bacteria through resistant starch, this fatty acid interacts with the G protein-coupled receptor 109A (GPR109A) in intestinal epithelia [13]. Butyrate has a synergistic interaction with niacin in the same receptor, modulating the action of macrophages in immunoinflammatory processes [14] (figure 1). Other short-chain fatty acids such as acetate and propionate, also produced by intestinal bacteria, interact with G protein-coupled receptors 41 and 43 (GPR41/43), keeping interleukin 10 (IL-10) in control of the inflammation [12].

Several epidemiological studies have already established a correlation between changes in the microbiota in childhood and metabolic disorders in adult life [15-18]. Thus, research has been supporting nutritional strategies to maintain intestinal microbiota homeostasis through functional foods, prebiotics, and probiotics [15].

The consumption of some drinks with probiotics, such as Kombucha, has already demonstrated positive effects on the human microbiota [19]. Kombucha is a fermented tea drink with an acidic and effervescent flavor, composed of several species in a microbial ecosystem with complex interactions characterized by cooperation and conflict [20]. In kombucha, a complex community of bacteria and yeasts starts the fermentation of an initial tea, which can be green tea with sugar, producing a biofilm that covers the liquid for several weeks [21]. This happens through several fermentative phases that are characterized by cooperation and competition between microbes in the kombucha solution [21]. The bacteria produce a surface biofilm that can act as a public good, providing protection against invaders, storage of resources, and greater access to oxygen for microbes embedded in it [22]. Ethanol and acid produced during the fermentation process (by yeast and bacteria, respectively) can also help protect the system from invasions by microbial competitors in the environment [21].

Therefore, in this review, we investigate the role of these microorganisms in the human body, the differences between probiotics, prebiotics, and postbiotics, as well as the mechanisms of action of some strains and their benefits to the host.



IL-18: Interleukin-18; **TGFβ**: Transforming growth factor beta; **GPR109a**: G protein-coupled receptor 109 A

Figure 1: Adapted Nature Chemical Biology 10(6):416-24.

Prebiotics

Prebiotics were first defined in 1995 by Gibson and Roberfroid as non-digestible starch [23]. In this category of foods, the resistant starches act for the benefit of the host, stimulating the growth and activity of beneficial bacteria present in the colon [24]. Updated methods regarding prebiotics occurred in 2004 when three distinct criteria were used: 1) resistance to gastric acidity and hydrolysis by mammalian enzymes and gastrointestinal absorption; 2) fermentation by intestinal microbiota; and 3) selectively stimulate the growth and/or activity of intestinal bacteria associated with health and well-being [25-27].

While Probiotics are living organisms that live in the mucous membranes, such as the intestine, mouth and vagina to protect the host system against invaders, especially harmful bacteria, prebiotics, in turn, are carbohydrates not digestible to the system, which serve as food for probiotics [28-31]. For the maintenance of intestinal and vaginal microbes, it is necessary to constantly and homogeneously consume prebiotics [30, 31]. However, the concept of prebiotics is a bit complex. Not all fibers can be classified as prebiotics. On the other hand, most prebiotics can be classified as dietary fiber [32].

Prebiotics have also been associated with stimulating the specific groups of beneficial bacteria, Bifidobacterium, and Lactobacillus [33]. These two strains are two types that are extremely important in gut health [34]. The relationship between the increase in these bacteria and healthy intestinal microbiota has been substantially investigated by the scientific community, although this relationship has not yet been fully proven [35]. The production of acetate and lactate by Bifidobacterium and Lactobacillus is already well elucidated in the scientific literature [36, 37]. These studies also state that the production of acetate and lactate can stimulate several species of beneficial bacteria, which benefit in the presence of the prebiotic.

Postbiotics

The concept of postbiotics may be related to the observation of the beneficial effects of the microbiota mediated by the secretion of certain metabolites [38]. However, its definition remains under discussion. Unlike prebiotics and probiotics, the scientific community does not consider postbiotics to be symbiotic [39]. On the other hand, some authors such as Klemashevich et al., state that postbiotics can also strengthen the intestinal microbiome, noting that the term "symbiotics" should be revised and postbiotics should be incorporated into its definition [40]. Although postbiotics do not contain live microorganisms, they have a beneficial effect on health through mechanisms like probiotics, minimizing the risks associated with their ingestion [39]. Due to the high heterogeneity of substances classified as postbiotics, we can cite some examples, such as Bacterial Lysates (BLs), Bacterial Lipoteichoic Acid (LTA), antioxidant enzymes, such as glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase, and NADH-oxidase, Cell-free Supernatants, Exopolysaccharides (EPSs), Bacterial Lysates (BLs), and Short-chain Fatty Acids (SCFAs) [41-50].

Short-chain fatty acids (SCFAs), acetate, propionate, and butyrate are the main end products of bacterial fermentation of complex carbohydrates, being an important indicator of bacterial fermentation in the colon considered postbiotic [51]. The concentration of SCFAs changes throughout the gastrointestinal tract, with the highest concentrations in the proximal colon and the lowest concentrations in the distal colon, the region of the gastrointestinal tract with the highest density of microbes [52].

Although the balance between SCFAs is fundamental, butyrate is the key energy source for colonocytes and enterocytes [12]. Alternatively, propionate can also be functional in the intestines by intestinal gluconeogenesis or even diffused into the portal vein to be used as a substrate for gluconeogenesis (figure 2). Although 90 to 99% of SCFAs are absorbed by the intestine or even harnessed by the microbiota, a small amount of propionate and acetate are found in the peripheral circulation [52, 53].

Recently, several studies have been affirming the relationship between gut-brain pertaining to neurodegenerative diseases [54]. Interestingly, acetate, in addition to being the most abundant SCFA found in the bloodstream, this SCFA has been shown to easily cross the blood-brain barrier, interacting with the Central Nervous System [55]. However, the function of these postbiotics is to maintain glucose homeostasis, maintain cellular integrity in the gastrointestinal epithelium, control immunoinflammatory processes, and regulate lipid metabolism as well as appetite modulation [38, 56].

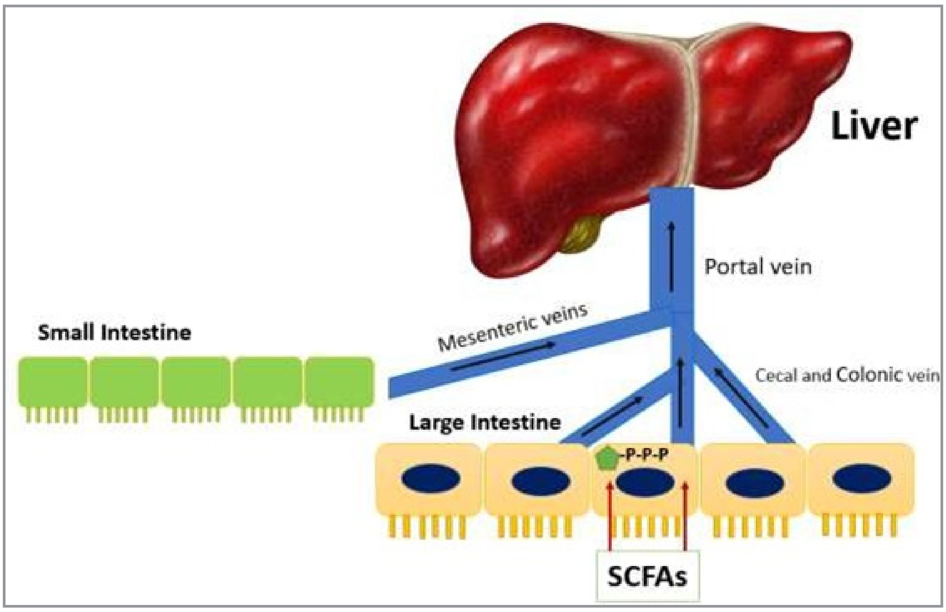


Figure 2: Adapted International Journal of Molecular Sciences 19(6), 2018.

Probiotics

The term probiotic is derived from the Latin preposition "pro," which means "for" and the Greek word "biotic" meaning "life" [57]. Probiotics are live bacteria beneficial to the body, especially for your digestive system [58]. Researchers are still trying to find out exactly how probiotics work. So far, evidence indicates that probiotics help to keep the microbiota in mucous membranes healthy by helping in several.

aspects, mainly in the immune system [59]. Probiotics help to send food through the intestine, affecting the nerves that control movement called intestinal peristalsis [60].

Probiotics can be used in various types of treatments, including irritable bowel syndrome, inflammatory bowel disease (IBD), infectious diarrhea (caused by viruses, bacteria, or parasites), diarrhea caused by antibiotics, eczema, and others. Furthermore, additional research establishes their usefulness in problems related to other parts of your body, such as urinary and vaginal health, prevention of allergies and colds, and oral health [61-68]. While research has not yet determined exactly how probiotics work, some of the ways these strains can keep you healthy would be in extreme cases when beneficial bacteria are lost, such as after taking antibiotics or after diarrhea caused by food poisoning. In these cases, probiotics can help by re-establishing these beneficial bacteria helping to keep the body functioning in a healthy way [63, 64]. Some studies suggest that administering a probiotic alongside antibiotic treatment helps in cases of diarrhea caused by the antibiotic [64]. However, probiotics are commonly used to reduce gastrointestinal symptoms that are not caused by acute illnesses, such as gas, bloating, and constipation [69].

In women, some strains of Lactobacillus have been shown to help prevent and treat bacterial vaginosis and vulvovaginal candidiasis [70]. However, studies have demonstrated the antibacterial efficacy of Bifidobacterium, a type of probiotic, to aid vaginal health [71]. Bifidobacterium is a genus of gram-positive anaerobic bacteria [72]. They are ubiquitous inhabitants of the gastrointestinal tract, vagina, and mouth of mammals, including humans [73]. Alternatively, it is viable for women to prevent digestive and vaginal infections by taking probiotic supplements aimed at restoring pH balance [74].

Bacterial vaginosis (BV) is one of the most common diseases in women of reproductive age [74]. Considering the contrast identified in the microbiome profile between women of different races, in the work of Wang et al., (2019) the lactobacillus showed satisfactory results in BV [75]. Compared to Caucasian women, black women tend to have a more diverse vaginal microbial profile, with a higher prevalence of BV and Nugent scores and a considerably stronger immune response related to BV-associated bacteria [76]. Contrastingly, the vaginal flora of Caucasian women was mainly dominated by Lactobacillus [76]. Thus, the exclusive use of probiotics in therapy showed a better benefit in the treatment of BV compared to a placebo [77]. Therefore, using probiotics for vaginal health has been an interesting strategy for women.

A healthy lower female reproductive system is dominated by several Lactobacillus spp., with L. crispatus, L. gasseri, L. jensenii, L. iners and L. vaginalis the most frequent and abundant organisms present in American women [78, 79]. Several studies have shown that the predominant bacterial species that colonize the female genital tract differ by geography and ethnicity [80, 81]. Depletion of Lactobacillus spp. is directly associated with an overgrowth of pathogenic bacteria leading to the development of bacterial vaginosis [82]. Despite a wide diversity of opinions regarding probiotics in the treatment of bacterial vaginosis, promising studies have been found with acidophilus lactobacillus and rhamnoses lactobacillus. Oral or intravaginal administration of these lactobacilli significantly inhibited the breakdown of epithelial cells induced by Gardnerella vaginalis [83, 84].

Lactobacillus Acidophilus

Lactobacillus acidophilus is a gram-positive bacillus of the Lactobacillus genus of the Lactobacillaceae family [85]. Most strains of L. acidophilus are microaerobic bacteria and grow more efficiently in anaerobic rather than aerobic environments [86]. Their optimum growing temperature ranges from 35 to 38°C, and they basically do not grow at temperatures below 20°C [87]. L. acidophilus has low heat resistance, and its pH optimum is between 5.5~6.0 [88]. Due to its eosinophilic nature, this strain has good acid and bile resistance and can maintain itself in different environments than other strains [89]. L. acidophilus still has distinct characteristics, such as the use of mono and disaccharides such as glucose, fructose, lactose, and sucrose respectively to carry out homotypic fermentation, producing DL-lactic through fermentation [90].

The nature of L. acidophilus is one of the kinds of beneficial microbial flora. Recent studies have stated that L. acidophilus participates in the intestinal tract of the host mainly through the production of metabolites and regulation of the intestinal microbiota, regulating the balance of the intestinal flora, reducing the intestinal pH, and producing beneficial metabolites to the host [91].

L. acidophilus can lower the pH of the environment and inhibit the growth and reproduction of pathogenic bacteria, which produce enzymes able to catalyze the conversion of carcinogenic precursors to carcinogens, such as azo reductase, nitro reductase and β-glucosidase [91]. L. acidophilus can inhibit the enzymatic activity of these pathogens as well as compete for adhesion sites, thus inhibiting cell invasion [92].

As a cholesterol modulator in the host, L. acidophilus possesses the capacity to aid in several diseases associated with dyslipidemia [93, 94]. Among the various biological functions of L. acidophilus is risk reduction of cardiovascular disease, improvement of gastrointestinal disease outcomes, improvement of lactose intolerance, prevention and treatment of cancer, and regulation of immune capacity, among others [94-98].

Bifidobacterium Lactis

Bifidobacterium is a genus of gram-positive, immobile, often branching anaerobic bacteria [99]. Although predominantly present in the gastrointestinal tract, these strains can also be encountered in the vagina and mouth of mammals, including humans [100, 101]. Similar to Lactobacillus, Bifidobacterium species are abundant in the gastrointestinal tract [101]. Bifidobacterium breve, Bifidobacterium lactis, B. infantile are some of the probiotic strains of Bifidobacterium with multiple health benefits ranging from colorectal cancer and enterocolitis, inflammatory bowel disease to competitive elimination of pathogens [102].

Clinical studies already demonstrate that the subspecies of Bifidobacterium animalis lactis 420 (B420) positively impact metabolic syndrome by limiting weight gain, improving glucose metabolism, and reducing low-grade inflammation [103]. Studies established that the addition of Bifidobacterium lactis as a probiotic to conventional treatment of ulcerative colitis had not only improved remission rates but also improved maintenance of remission [104]. Different species and/or strains of Bifidobacterium have been proven to exert a number of beneficial health effects, including regulation of intestinal microbial homeostasis, inhibition of harmful pathogens and bacteria that colonize and/or infect the intestinal mucosa, modulation of local immune responses and systemic effects, the repression of pro-carcinogenic enzymatic activities within the microbiota, the production of vitamins and the bioconversion of various dietary compounds into bioactive molecules [105]. Bifidobacterium also improves the barrier of the intestinal mucosa and reduces the levels of lipopolysaccharides in the intestine, which are responsible for an alteration in the gut-brain axis in diseases of the Central Nervous System [106].

Lactobacillus Rhamnosus

Lactobacillus rhamnosus, more recently named Lacticaseibacillus rhamnosus, is a gram-positive homofermentative facultative anaerobic non-spore-forming lactobacillus often appearing in chains [107]. Some strains of this bacteria are being used as probiotics, mainly in the treatment of female urogenital tract infections [108]. Studies have shown promising results with L. rhamnosus, especially in more complicated cases to treat bacterial vaginosis [108, 109]. L. rhamnosus is commonly found in the healthy female genitourinary tract and is useful for maintaining control of dysbiotic bacterial overgrowth during an active infection [110]. Despite being considered a beneficial organism, L. rhamnosus may rarely show some changes in certain subsets of the population, especially those mainly involving weakened immune systems or infants, and may cause endocarditis [111]. Although infections caused by L. rhamnosus are rare, it is important to note that the L. rhamnosus strains isolated from blood cultures are distinct from the specific strain known as L. rhamnosus GG. The probiotic L. rhamnosus GG is considered safe for use in healthy individuals with a properly functioning immune system [112].

The ability to create co-aggregates with pathogenic microorganisms can modulate the fate of pathologies such as vulvovaginal candidiasis [113]. Some strains showed greater capacity for adhesion and self-aggregation, with L. rhamnosus AD3 being the most efficient to form co-aggregates with all three Candida species, especially C. tropicalis [114]. Although the coaggregation capacity of L. rhamnosus GG is greater, L. rhamnosus AD3 has demonstrated the capacity of binding to Candida cells more consistently [108, 115].

Studies by Stivala et al., (2021) indicated that among all strains of vaginal lactobacilli tested, L. rhamnosus AD3 revealed the necessary properties as a potential probiotic strain, addressing all safety features, showing the highest levels of resistance in relation to the gastrointestinal tract, in the production of active biotic powders, action against pathogenic fungi and bacteria, ability to adhere to epithelial mucosa, and ability to form strong aggregates as well as co-aggregating with Candida [108].

Lactobacillus Crispatus

Lactobacillus crispatus is a common rod-shaped species of the genus Lactobacillus [116]. This strain is used as a probiotic for premenopausal and postmenopausal women who have recurrent urinary tract infections [117]. Clinical studies have specifically pointed to the administration of L. crispatus in the prevention and treatment of bacterial vaginosis, characterized by the absence of the Lactobacillus flora necessary to protect the host from infection [116].

The role of L. crispatus in maintaining vaginal health is correlated with hormonal factors, including testosterone as well as a strong interdependence between the intestinal and vaginal microbiota [118]. On the other hand, L. crispatus appeared more abundant in the fecal microbiome of patients with atherosclerotic cardiovascular disease [119]. Several studies have already indicated that L. crispatus is critical in preserving fertility and preventing vaginal infections, in Bacterial Vaginosis as well as Vulvovaginal Atrophy (VVA), which can cause irritation and a foul-smelling vaginal discharge [116]. We know that if the population of L. crispatus is low, there is a favorable environment for bacterial vaginosis [119]. Therefore, one of the characteristics of L. crispatus is keeping a low pH, preventing infections, and preserving the balance of microbe populations [116]. This occurs due to the production of lactic acids from sugars, using homofermentative metabolism, helping to slow down epithelial cells [120].

Lactobacillus Gasseri

Lactobacillus gasseri is a species of the genus Lactobacillus identified in 1980 by François Gasser [121]. It occurs in the vaginal and intestinal flora alike and is a normal inhabitant of the lower reproductive tract in healthy women [122]. One of the characteristics of L. gasseri was associated with stress control [123]. Studies have shown that daily intake of L. gasseri for four weeks improved symptoms associated with stress in medical students who participated in a cadaver dissection course and improved clinical symptoms in patients with irritable bowel syndrome (IBS) [124].

As a lactic bacteria, L.gasseri has shown interesting results in controlling stress, as well as improving sleep quality and bowel function [125]. Previous studies have shown that ingesting fermented milk with pasteurized L.gasseri improved bowel habits and the intestinal environment compared to the effects of a placebo prepared with artificially acidified sour milk, indicating that pasteurized L.gasseri bacterial cells promote these improvements [126].

Several studies have already proven some probiotics alter the production of SCFAs by the intestinal microbiota [50]. Stimulating endocrine epithelial cells in colonocytes, as well as gut hormones, modulating the gut-brain axis [12]. In studies by Nishida et al., (2019) L.gasseri significantly increased n- valeric acid concentrations compared to the placebo [125]. In another study, Yuille et al., (2018) established that n-valeric acid is a potent inhibitor of class I histone deacetylase (HDAC) [127]. This study used HT-29 human colon cancer cells suggesting an increase in the concentration of n-valeric acid in comparison to the one found in feces in the study by Nishida et al., (approximately 10–15 mM). However, the physiological significance of n-valeric acid in stool is still not completely understood, requiring further research on the topic.

Lactobacillus Reuteri

Lactobacillus reuteri DSM 17938 (L. reuteri) recently renamed Limosilactobacillus reuteri (L. reuteri) is a probiotic present in different parts of the human body, including the gastrointestinal and urinary tract, skin, and breast milk [128]. L. reuteri has the ability to adhere to the intestinal epithelium forming proteins that bind to mucus, making it difficult for pathogenic microorganisms to enter [129]. Hou et al., (2015) demonstrated that L. Reuteri remodeled the intestinal microbiota of swine-producing antimicrobial molecules, improving the functionality of regulatory T cells, and strengthening the intestinal barrier [130]. This study also demonstrated that in humans the translocation of pathogenic bacteria from the lumen to tissues was reduced in the presence of L. reuteri [130].

Several studies have already shown that L. reuteri has several beneficial effects on gastrointestinal symptoms, including diarrhea due to intestinal infections [128], antibiotic-associated diarrhea, inflammatory bowel disease (IBD), and colorectal cancer [131-133]. Likewise, L. reuteri can reduce abdominal pain in infantile colic as well as abdominal discomfort due to necrotizing enterocolitis in premature neonates [134]. Other studies have also reported that L. reuteri may improve intestinal motility and chronic constipation in infants [128].

In a randomized clinical trial by Shornikova et al., (1997), L. reuteri showed promoting results in acute watery diarrhea in children and in rotavirus gastroenteritis [135]. In this study, the authors randomized children to receive 1010 or 107 colony-forming units (CFU) of L. reuteri or a placebo once daily for 5 days.

The results showed that the use of L. reuteri shortened the duration of acute watery diarrhea with a dose-related effect, being 1.5 days in the group taking a large dose of L. reuteri, 1.9 days in the group taking a small dose and 2.5 days in the placebo group [135]. The results also denoted that on the second day of treatment with L. reuteri, acute watery diarrhea persisted in 48% of patients taking the high dose, 70% of those taking the low dose, and 80% of those taking the placebo. Several other studies have shown the positive effects of L. reuteri supplementation [136-138].

This can be seen in a meta- analysis by Patro-Golab et al., (2019), where a reduction in the duration of diarrhea was observed, as well as the volume of feces in children [139]. The results of this work led the authors to conclude that L. reuteri together with other probiotics can be useful and safe for the treatment and prevention of diarrhea, reducing both its duration and the intensity of symptoms.

Table 1.

S.no	Name of Probiotic	Illnesses Treated	References
1	Lactobacillus acidophilus	Dyslipidemia and cardiovascular disease	Reamtong, et al. (2021) Anderson and Gilliland (1999)
2	Bifidobacterium lactis	Ulcerative colitis	Lapez-pier, et al. (2021)
3	Lactobacillus crispatus	Vaginal infection	Wright, et al. (2021)
4	Lactobacillus gasseri	Gut-brain axis modulation	Blaak, et al. (2020)
5	Lactobacillus reuteri	Diarrhea and colorectal cancer	Saviano et al. (2021) kim, et al. (2022)
6	Bacillus subtilis	Antimicrobial drug	Li, et al. (2022)
7	Lactobacillus rhamnosus	Urogenital tract infection	Stivala et al. (2021)

Bacillus Subtilis

Bacillus subtilis is a gram-positive, catalase-positive bacterium found predominantly in the gastrointestinal tract of humans [140]. As a member of the Bacillus genus, B. subtilis is rod-shaped and is able to develop a tough, protective endospore, allowing it to tolerate extreme environmental conditions [141]. Despite being dominant in soil, B. subtilis has been identified in water, air, human and animal intestines, vegetables, fermented food, raw and pasteurized milk, and dairy products [142]. Due to their ubiquity in diverse environments, B. subtilis also holds potential value in food products, primarily in the microflora of milk [143]. Resembling the mitochondrial genome, the genomic sequence of B. subtilis is formed by a single double-stranded DNA molecule in a circular shape [144]. A circular chromosome is typical of bacteria, mitochondria, and plant chloroplasts.

Due to increased resistance to antibiotics by humans, B. subtilis has been studied as an alternative antimicrobial drug [145]. The capacity of B. subtilis to produce bacteriocins, specifically, peptides exhibiting antimicrobial activity, has drawn the scientific community's attention indicating a promising potential in treatments against bacterial infection [146]. This is due to the fact that these bacteriocins withstand large temperature fluctuations as well as retard the growth and/or destroy many types of harmful bacteria [147]. Types of B. subtilis bacteriocins include the lanthionine-containing peptide antibiotic, also called subtilin, and an antibiotic called subtilisin [148]. Subtilisin has both antimicrobial activity against gram-negative and gram-positive bacteria as well as anaerobic and aerobic microorganisms, including Enterococcus faecalis, Enterobacter aerogenes, Streptococcus pyogenes, and Shigella sonnei. Subtilin, on the other hand, tends to demonstrate enhanced efficacy against gram-negative bacteria and fungi [149].

Discussion

There are a few hundred trillion bacteria per gram of feces in the human gut, which together form a complex gut microbiome [150]. However, this organ seems to be interconnected not only with the digestion and absorption of nutrients. Several studies have already reported a close relationship between the intestine and the brain, demonstrating that some neurodegenerative diseases began several decades in the past primarily in the intestine [151]. This relationship does not solely occur between the gut and the brain. The immune system is also directly linked to the gut as well as obesity and diabetes [11, 15, 55, 56, 59]. Recent studies have established that metabolic syndrome may be attributed to an imbalance in the intestinal microbiota [15, 152]. Despite some controversies, the use of beneficial bacteria present in the human microbiome has been a target of alternative therapies in the treatment of several diseases that are associated with the intestine and/or vagina. Uusitupa et al...., (2020) had already stated that Bifidobacterium animalis lactis 420 (B420) positively impacts metabolic syndrome by limiting weight gain, improving glucose metabolism, and reducing low-grade inflammation [152]. Similarly, Dong et al...., (2022) revealed that Bifidobacterium improves the barrier of the intestinal mucosa and reduces the levels of lipopolysaccharides in the intestine, protecting the host from one of the developmental causes of dementia, especially "Lewy body dementia" (figure 3) [106]. Some other strains may also interact positively with other types of diseases, such as colon and liver tumor growth [153]. According to El-Deeb et al...., (2022) the synthesis of polysaccharides carried out by L. acidophilus has demonstrated health benefits by stimulating the immune response related to tumor cells [154]. Contrastingly, one of the most important factors that must be considered in terms of the effectiveness of probiotics in the body is the hydrophobicity of the cell surface, autoaggregation, and adhesion of epithelial cells [155].

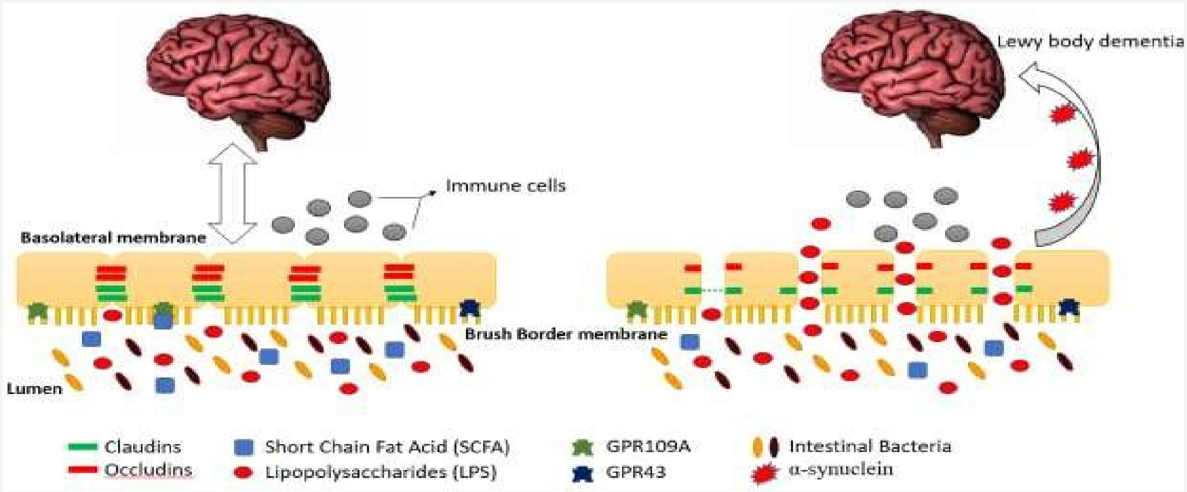


Figure 3: Adapted Nutrients. 2021 Jan; 13(1): 28.

According to Plaza-Diaz et al...., (2029) it becomes necessary for adhesion to target sites in the gastrointestinal tract of the host in the extracellular matrix of tissues as well as the ability for bacteria to attach to one another. This autoaggregation prevents the organism from eliminating the bacteria and maintains the ability to interact with other types of bacteria in the host [156]. In the same way that autoaggregation refers to the adhesion of genetically identical strains between bacteria and bacteria, the adhesion of distinct strains or different species is known as coaggregation [156]. Understanding both autoaggregation and coaggregation mechanisms is important since probiotics often protect against infections by these mechanisms antagonistic towards pathogens [157]. While autoaggregation allows for competitive exclusion and displacement of pathogens coaggregation enhances the proximity of type VI secretion systems of coaggregating probiotic bacteria releasing the antimicrobial substance to the target pathogen [156, 158].

Another no less important factor about probiotics is their interaction with mitochondria [159, 160]. Recent evidence shows that there is a bidirectional interaction between mitochondria and microbiota that can affect both mitochondrial biogenesis and the regulation of the intestinal microbiota itself [161]. Through the intestinal microbiota, it is possible to regulate the main transcriptional coactivators involved in mitochondrial biogenesis, among them the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), sirtuin 1 (SIRT1) and 5' adenosine monophosphate- activated protein kinase (AMPK) genes [159]. SCFAs produced by the gut microbiota are also directly associated with both energy production in gut mitochondria as well as modulation of ROS and inflammation which attenuate TNF-α-mediated immune responses [162]. In contrast, the production of ROS by mitochondria plays a crucial role in the regulation of the intestinal microbiota by modulating the function of the intestinal barrier and mucosal immune responses. The mitochondrial genome has also been shown to have a crucial influence on the gut microbiota by altering its composition and activity [163-165].

Conclusion

Given that the human body harbors bacteria at a magnitude tenfold greater than that of its own cells, the study of probiotics is becoming increasingly necessary in the scientific community. However, the exact understanding of how these microorganisms work concerning the host still needs further investigation. We know that some strains really bring benefits to the host, but the treatment time and the ideal dosage are still not well established. The fact that probiotics engage in a bidirectional interaction with mitochondria further increases the demand to understand the optimal approach to maintain homeostasis both regarding the intestinal and vaginal microbiota.

Several studies have already revealed that mitochondria are directly linked to the maintenance of cell health, and the influence of probiotics on mitochondrial biogenesis is crucial. Moreover, the metabolites generated by this organelle for the maintenance of the microbiota of the host are correspondingly fundamental. Therefore, this discussion about probiotics and mitochondria should be further investigated, as it is a promising way to enhance the comprehension of this symbiosis between the microorganism and the human body.

References

1. Milani, C., Duranti, S., Bottacini, F., Casey, E., Turroni, F., et al. (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
2. Lozupone, C. A., Stombaugh, J. I., Gordon, J. I., Jansson, J. K., & Knight, R. (2012). Diversity, stability and resilience of the human gut microbiota. Nature, 489, 220–230. https://doi.org/10.1038/nature11550
3. Sedghi, L., DiMassa, V., Harrington, A., Lynch, S. V., & Kapila, Y. L. (2021). The oral microbiome: Role of key organisms and complex networks in oral health and disease. Periodontology 2000, 87(1), 107–131. https://doi.org/10.1111/prd.12343
4. Chen, X., Lu, Y., Chen, T., & Li, R. (2021). The female vaginal microbiome in health and bacterial vaginosis. Frontiers in Cellular and Infection Microbiology, 11, 631972. https://doi.org/10.3389/fcimb.2021.631972
5. Putignani, L., Del Chierico, F., Petrucca, A., Vernocchi, P., & Dallapiccola, B. (2014). The human gut microbiota: A dynamic interplay with the host from birth to senescence settled during childhood. Pediatric Research, 76(1), 2–10. https://doi.org/10.1038/pr.2014.40
6. Bassetti, M., Bandera, A., & Gori, A. (2020). Therapeutic potential of the gut microbiota in the management of sepsis. Critical Care, 24, 105. https://doi.org/10.1186/s13054-020-2784-z
7. Libertucci, J., & Young, V. B. (2019). The role of the microbiota in infectious diseases. Nature Microbiology, 4, 35–45. https://doi.org/10.1038/s41564-018-0278-4
8. Vonaesch, P., Anderson, M., & Sansonetti, P. J. (2018). Pathogens, microbiome and the host: Emergence of the ecological Koch's postulates. FEMS Microbiology Reviews, 42(3), 273–292. https://doi.org/10.1093/femsre/fuy002
9. Hasan, N., & Yang, H. (2019). Factors affecting the composition of the gut microbiota, and its modulation. PeerJ, 7, e7502. https://doi.org/10.7717/peerj.7502
10. Mohajeri, M. H., Brummer, R. J. M., Rastall, R. A., Weersma, R. K., Harmsen, H. J. M., Faas, M., & Eggersdorfer, M. (2018). The role of the microbiome for human health: From basic science to clinical applications. European Journal of Nutrition,

57(Suppl 1), 1–14. https://doi.org/10.1007/s00394-018-1740-2
11. Zheng, D., Liwinski, T., & Elinav, E. (2020). Interaction between microbiota and immunity in health and disease. Cell Research, 30, 492–506. https://doi.org/10.1038/s41422-020-0332-7
12. Blaak, E. E., Canfora, E. E., Theis, S., Frost, G., Groen, A. K., Mithieux, G., ... & Cani, P. D. (2020). Short chain fatty acids in human gut and metabolic health. Beneficial Microbes, 11(5), 411–455. https://doi.org/10.3920/BM2020.0055
13. Silva, Y. P., Bernardi, A., & Frozza, R. L. (2020). The role of short-chain fatty acids from gut microbiota in gut-brain communication. Frontiers in Endocrinology, 11, 25. https://doi.org/10.3389/fendo.2020.00025
14. Lee, W., & Hase, K. (2014). Gut microbiota-generated metabolites in animal health and disease. Nature Chemical Biology, 10(6), 416–424. https://doi.org/10.1038/nchembio.1535
15. Fan, Y., & Pedersen, O. (2021). Gut microbiota in human metabolic health and disease. Nature Reviews Microbiology, 19(1), 55–71. https://doi.org/10.1038/s41579-020-0433-9
16. Durack, J., & Lynch, S. V. (2019). The gut microbiome: Relationships with disease and opportunities for therapy. The Journal of Experimental Medicine, 216(1), 20–40. https://doi.org/10.1084/jem.20180448
17. Tamburini, S., Shen, N., Wu, H. C., & Clemente, J. C. (2016). The microbiome in early life: Implications for health outcomes. Nature Medicine, 22, 713–722. https://doi.org/10.1038/nm.4142
18. Oliveira, G. L. V., Oliveira, C. N. S., Pinzan, C. F., de Salis, L. V. V., & Cardoso, C. R. B. (2021). Microbiota modulation of the gut-lung axis in COVID-19. Frontiers in Immunology, 12, 635471. https://doi.org/10.3389/fimmu.2021.635471
19. Kapp, J. M., & Sumner, W. (2019). Kombucha: A systematic review of the empirical evidence of human health benefit. Annals of Epidemiology, 30, 66–70. https://doi.org/10.1016/j.annepidem.2018.11.001
20. Greenwalt, C. J., Steinkraus, K. H., & Ledford, R. A. (2000). Kombucha, the fermented tea: Microbiology, composition, and claimed health effects. Journal of Food Protection, 63(7), 976–981. https://doi.org/10.4315/0362-028X-63.7.976
21. Antolak, H., Piechota, D., & Kucharska, A. Z. (2021). Kombucha tea—A double power of bioactive compounds from tea and symbiotic culture of bacteria and yeasts (SCOBY). Antioxidants, 10(10), 1541. https://doi.org/10.3390/antiox10101541
22. Morales, D. (2020). Biological activities of kombucha beverages: The need of clinical evidence. Trends in Food Science & Technology, 105, 323–333. https://doi.org/10.1016/j.tifs.2020.09.002
23. Younis, K., Ahmad, S., & Jahan, K. (2015). Health benefits and application of prebiotics in foods. Journal of Food Processing & Technology, 6(4), 1–6. https://doi.org/10.4172/2157-7110.1000435
24. Zaman, S. A., & Sarbini, S. R. (2016). The potential of resistant starch as a prebiotic. Critical Reviews in Biotechnology, 36(3), 578–584. https://doi.org/10.3109/07388551.2014.993591
25. Bedu-Ferrari, C., Biscarrat, P., Langella, P., & Cherbuy, C. (2022). Prebiotics and the human gut microbiota: From breakdown mechanisms to the impact on metabolic health. Nutrients, 14(10), 2096. https://doi.org/10.3390/nu14102096
26. Davani-Davari, D., Negahdaripour, M., Karimzadeh, I., Seifan, M., Mohkam, M., Masoumi, S. J., ... & Ghasemi, Y. (2019). Prebiotics: Definition, types, sources, mechanisms, and clinical applications. Foods, 8(3), 92. https://doi.org/10.3390/foods8030092
27. Guarino, M. P. L., Altomare, A., Emerenziani, S., Di Rosa, C., Ribolsi, M., Balestrieri, P., ... & Cicala, M. (2020). Mechanisms of action of prebiotics and their effects on gastrointestinal disorders in adults. Nutrients, 12(4), 1037. https://doi.org/10.3390/nu12041037
28. Liu, Y., Alookaran, J. J., & Rhoads, J. M. (2018). Probiotics in autoimmune and inflammatory disorders. Nutrients, 10(10), 1537. https://doi.org/10.3390/nu10101537
29. Lin, T., Lin, C., & Pan, T. (2018). The implication of probiotics in the prevention of dental caries. Applied Microbiology and Biotechnology, 102(2), 577–586. https://doi.org/10.1007/s00253-017-8650-9
30. Mei, Z., & Li, D. (2022). The role of probiotics in vaginal health. Frontiers in Cellular and Infection Microbiology, 12, 963868. https://doi.org/10.3389/fcimb.2022.963868
31. Markowiak, P., & Śliżewska, K. (2017). Effects of probiotics, prebiotics, and synbiotics on human health. Nutrients, 9(9), 1021. https://doi.org/10.3390/nu9091021
32. lavin, J. (2013). Fiber and prebiotics: Mechanisms and health benefits. Nutrients, 5(4), 1417–1435. https://doi.org/10.3390/nu5041417
33. Lordan, C., Thapa, D., Ross, R. P., & Cotter, P. D. (2020). Potential for enriching next-generation health-promoting gut bacteria through prebiotics and other dietary components. Gut Microbes, 11(1), 1–20. https://doi.org/10.1080/19490976.2019.1638727
34. Xiao, Y., Zhai, Q., Zhang, H., Chen, W., & Hill, C. (2021). Gut colonization mechanisms of Lactobacillus and Bifidobacterium: An argument for personalized designs. Annual Review of Food Science and Technology, 12, 213–233. https://doi.org/10.1146/annurev-food-062520-013231
35. Malard, F., Dore, J., Gaugler, B., & Mohty, M. (2021). Introduction to host microbiome symbiosis in health and disease. Mucosal Immunology, 14, 547–554. https://doi.org/10.1038/s41385-020-00370-7
36. O'Callaghan, A., & van Sinderen, D. (2016). Bifidobacteria and their role as members of the human gut microbiota. Frontiers in Microbiology, 7, 925. https://doi.org/10.3389/fmicb.2016.00925
37. Alcon-Giner, C., Dalby, M. J., Caim, S., Ketskemety, J., Shaw, A., Sim, K., ... & Hall, L. J. (2020). Microbiota supplementation with Bifidobacterium and Lactobacillus modifies the preterm infant gut microbiota and metabolome: An observational study. Cell Reports Medicine, 1(5), 100077. https://doi.org/10.1016/j.xcrm.2020.100077
38. Vinderola, G., Sanders, M. E., & Salminen, S. (2022). The concept of postbiotics. Foods, 11(8), 1077. https://doi.org/10.3390/foods11081077
39. Żółkiewicz, J., Marzec, A., Ruszczyński, M., & Feleszko, W. (2020). Postbiotics—A step beyond pre- and probiotics. Nutrients, 12(8), 2189. https://doi.org/10.3390/nu12082189
40. Żółkiewicz, J., Marzec, A., Ruszczyński, M., & Feleszko, W. (2020). Postbiotics—A step beyond pre- and probiotics. Nutrients, 12, 2189. https://doi.org/10.3390/nu12082189
41. Kim, M. Y., Hyun, I. K., An, S., Kim, D., Kim, K. H., & Kang, S. (2022). In vitro anti-inflammatory and antibiofilm activities of bacterial lysates from lactobacilli against oral pathogenic bacteria. Food & Function, 13(24), 12755–12765. https://doi.org/10.1039/D2FO02456D
42. Pradhan, D., Gulati, G., Avadhani, R., Rashmi, H. M., Soumya, K., Kumari, A., ... & Kumar, A. (2023). Postbiotic lipoteichoic acid of probiotic Lactobacillus origin ameliorates inflammation in HT-29 cells and colitis mice. International Journal of Biological Macromolecules, 236, 123962. https://doi.org/10.1016/j.ijbiomac.2023.123962
43. Bai, W., Zhang, F. J., He, T. J., Su, P. W., Ying, X. Z., Zhang, L. L., ... & Wang, T. (2016). Dietary probiotic Bacillus subtilis strain FMBJ increases antioxidant capacity and oxidative stability of chicken breast meat during storage. PLoS ONE, 11, e0167339. https://doi.org/10.1371/journal.pone.0167339
44. Nantapong, N., Murata, R., Trakulnaleamsai, S., Kataoka, N., Yakushi, T., & Matsushita, K. (2019). The effect of reactive oxygen species (ROS) and ROS-scavenging enzymes, superoxide dismutase and catalase, on the thermotolerant ability of Corynebacterium glutamicum. Applied Microbiology and Biotechnology, 103, 5355–5366. https://doi.org/10.1007/s00253-019-09862-5

45. Li, N., Wang, Y., Zhu, P., Liu, Z., Guo, B., & Ren, J. (2015). Improvement of exopolysaccharide production in Lactobacillus casei LC2W by overexpression of NADH oxidase gene. Microbiological Research, 171, 73–77. https://doi.org/10.1016/j.micres.2014.11.002
46. Scillato, M., Spitale, A., Mongelli, G., Privitera, G. F., Mangano, K., Cianci, A., ... & Di Marco, R. (2021). Antimicrobial properties of Lactobacillus cell-free supernatants against multidrug-resistant urogenital pathogens. MicrobiologyOpen, 10(2), e1173. https://doi.org/10.1002/mbo3.1173
47. Kawanabe-Matsuda, H., Takeda, K., Nakamura, M., Makino, S., Karasaki, T., Kakimi, K., et al. (2022). Dietary Lactobacillus-derived exopolysaccharide enhances immune-checkpoint blockade therapy. Cancer Discovery, 12(5), 1336–1355. https://doi.org/10.1158/2159-8290.CD-21-1306
48. Sultana, R., McBain, A. J., & O'Neill, C. A. (2013). Strain-dependent augmentation of tight-junction barrier function in human primary epidermal keratinocytes by Lactobacillus and Bifidobacterium lysates. Applied and Environmental Microbiology, 79(16), 4887–4894. https://doi.org/10.1128/AEM.01050-13
49. Hills, R. D., Jr., Pontefract, B. A., Mishcon, H. R., Black, C. A., Sutton, S. C., & Theberge, C. R. (2019). Gut microbiome: Profound implications for diet and disease. Nutrients, 11(7), 1613. https://doi.org/10.3390/nu11071613
50. Markowiak-Kopeć, P., & Śliżewska, K. (2020). The effect of probiotics on the production of short-chain fatty acids by human intestinal microbiome. Nutrients, 12(4), 1107. https://doi.org/10.3390/nu12041107
51. Frolova, M. S., Suvorova, I. A., Iablokov, S. N., Petrov, S. N., & Rodionov, D. A. (2022). Genomic reconstruction of short-chain fatty acid production by the human gut microbiota. Frontiers in Molecular Biosciences, 9, 957835. https://doi.org/10.3389/fmolb.2022.957835
52. Venegas, D. P., De la Fuente, M., Landskron, G., González, M., Quera, R., Dijkstra, G., et al. (2019). Short-chain fatty acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. Frontiers in Immunology, 10, 277. https://doi.org/10.3389/fimmu.2019.00277
53. El Hage, R., Hernandez-Sanabria, E., Arroyo, M., & De Wiele, T. V. (2020). Supplementation of a propionate-producing consortium improves markers of insulin resistance in an in vitro model of gut-liver axis. American Journal of Physiology-Endocrinology and Metabolism, 318(5), E742–E749. https://doi.org/10.1152/ajpendo.00406.2019
54. Sun, P., Su, L., Zhu, H., Li, X., Guo, Y., Du, X., et al. (2021). Gut microbiota regulation and their implication in the development of neurodegenerative disease. Microorganisms, 9(11), 2281. https://doi.org/10.3390/microorganisms9112281
55. Anachad, O., Taouil, A., Taha, W., Bennis, F., & Chegdani, F. (2023). The implication of short-chain fatty acids in obesity and diabetes. Microbiology Insights, 16, 11786361231162720. https://doi.org/10.1177/11786361231162720
56. Sun, S. (2022). The impacts of SCFAs on intestinal homeostasis, and glucose-lipid metabolism. Highlights in Science, Engineering and Technology FBET 2022, 11, 195–198.
57. Jäger, R., Mohr, A. E., Carpenter, K. C., Kerksick, C. M., Purpura, M., Moussa, A., et al. (2019). International Society of Sports Nutrition position stand: Probiotics. Journal of the International Society of Sports Nutrition, 16, 62. https://doi.org/10.1186/s12970-019-0315-1
58. Hill, C., Guarner, F., Reid, G., Gibson, G. R., Merenstein, D. J., Pot, B., et al. (2014). Expert consensus document: The international scientific association for probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nature Reviews Gastroenterology & Hepatology, 11, 506–514. https://doi.org/10.1038/nrgastro.2014.66
59. Wang, X., Zhang, P., & Zhang, X. (2021). Probiotics regulate gut microbiota: An effective method to improve immunity. Molecules, 26(19), 6076. https://doi.org/10.3390/molecules26196076
60. Judkins, T. C., Archer, D. L., Kramer, D. C., & Solch, R. J. (2020). Probiotics, nutrition, and the small intestine. Current Gastroenterology Reports, 22(1), 2. https://doi.org/10.1007/s11894-020-0743-1
61. Dale, H. F., Rasmussen, S. H., Asiller, Ö. O., & Lied, G. A. (2019). Probiotics in irritable bowel syndrome: An up-to-date systematic review. Nutrients, 11(9), 2048. https://doi.org/10.3390/nu11092048
62. Lavelle, A., & Sokol, H. (2020). Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. Nature Reviews Gastroenterology & Hepatology, 17(4), 223–237. https://doi.org/10.1038/s41575-019-0244-7
63. 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
64. Mekonnen, S. A., Merenstein, D., Fraser, C. M., & Marco, M. L. (2020). Molecular mechanisms of probiotic prevention of antibiotic-associated diarrhea. Current Opinion in Biotechnology, 61, 226–234. https://doi.org/10.1016/j.copbio.2019.12.004
65. Sun, S., Chang, G., & Zhang, L. (2022). The prevention effect of probiotics against eczema in children: An updated systematic review and meta-analysis. Journal of Dermatological Treatment, 33(4), 1844–1855. https://doi.org/10.1080/09546634.2020.1868380
66. Borges, S., Silva, J., & Teixeira, P. (2014). The role of lactobacilli and probiotics in maintaining vaginal health. Archives of Gynecology and Obstetrics, 289(3), 479–489. https://doi.org/10.1007/s00404-013-3020-0
67. Fiocchi, A., Cabana, M. D., & Mennini, M. (2022). Current use of probiotics and prebiotics in allergy. The Journal of Allergy and Clinical Immunology: In Practice, 10(9), 2219–2242. https://doi.org/10.1016/j.jaip.2022.04.012
68. Seminario-Amez, M., López-López, J., Estrugo-Devesa, A., Ayuso-Montero, R., & Jané-Salas, E. (2017). Probiotics and oral health: A systematic review. Medicina Oral, Patología Oral y Cirugía Bucal, 22(3), e282–e288. https://doi.org/10.4317/medoral.21360
69. Wilkins, T., & Sequoia, J. (2017). Probiotics for gastrointestinal conditions: A summary of the evidence. American Family Physician, 96(3), 170–178.
70. Abad, C. L., & Safdar, N. (2009). The role of Lactobacillus probiotics in the treatment or prevention of urogenital infections: A systematic review. Journal of Chemotherapy, 21(3), 243–252. https://doi.org/10.1179/joc.2009.21.3.243
71. Giordani, B., Melgoza, L. M., Parolin, C., Foschi, C., Marangoni, A., Abruzzo, A., et al. (2018). Vaginal Bifidobacterium breve for preventing urogenital infections: Development of delayed-release mucoadhesive oral tablets. International Journal of Pharmaceutics, 550(1-2), 455–462. https://doi.org/10.1016/j.ijpharm.2018.09.041
72. Yang, C., Fujita, Y., Ren, Q., Ma, M., Dong, C., & Hashimoto, K. (2017). Bifidobacterium in the gut microbiota confers resilience to chronic social defeat stress in mice. Scientific Reports, 7, 45942. https://doi.org/10.1038/srep45942
73. Rodriguez, C. I., & Martiny, J. B. H. (2020). Evolutionary relationships among bifidobacteria and their hosts and environments. BMC Genomics, 21, 26. https://doi.org/10.1186/s12864-019-6383-1
74. Mizgier, M., Jarząbek-Bielecka, G., Mruczyk, K., & Kędzia, W. (2020). The role of diet and probiotics in prevention and treatment of bacterial vaginosis and vulvovaginal candidiasis in adolescent girls and non-pregnant women. Ginekologia Polska, 91(7), 412–416. https://doi.org/10.5603/GP.2020.0073
75. oosa, Y., Kwon, D., de Oliveira, T., & Wong, E. B. (2020). Determinants of vaginal microbiota composition. Frontiers in Cellular and Infection Microbiology, 10, 467. https://doi.org/10.3389/fcimb.2020.00467
76. Fettweis, J., Brooks, J. P., Serrano, M. G., & Sheth, N. (2014).

Differences in vaginal microbiome in African American women versus women of European ancestry. Microbiology, 160(10), 2272–2282. https://doi.org/10.1099/mic.0.081034-0
77. Chen, R., Li, R., Qing, W., Zhang, Y., Zhou, Z., Hou, Y., et al. (2022). Probiotics are a good choice for the treatment of bacterial vaginosis: A meta-analysis of randomized controlled trials. Reproductive Health, 19, 137. https://doi.org/10.1186/s12978-022-01413-0
78. Chen, X., Lu, Y., Chen, T., & Li, R. (2021). The female vaginal microbiome in health and bacterial vaginosis. Frontiers in Cellular and Infection Microbiology, 11, 631972. https://doi.org/10.3389/fcimb.2021.631972
79. Chee, W. J. Y., Chew, S. Y., & Than, L. T. L. (2020). Vaginal microbiota and the potential of Lactobacillus derivatives in maintaining vaginal health. Microbial Cell Factories, 19, 203. https://doi.org/10.1186/s12934-020-01463-w
80. Gryaznova, M., Lebedeva, O., Kozarenko, O., Smirnova, Y., Burakova, I., Syromyatnikov, M., et al. (2022). Lower genital tract microbiome in early pregnancy in the Eastern European population. Microorganisms, 10(12), 2368. https://doi.org/10.3390/microorganisms10122368
81. Happel, A., Jaumdally, S. Z., Pidwell, T., Cornelius, T., Jaspan, H. B., Froissart, R., et al. (2017). Probiotics for vaginal health in South Africa: What is on retailers' shelves? BMC Women's Health, 17, Article 7. https://doi.org/10.1186/s12905-016-0352-1
82. Łaniewski, P., & Herbst-Kralovetz, M. M. (2021). Bacterial vaginosis and health-associated bacteria modulate the immunometabolic landscape in 3D model of human cervix. NPJ Biofilms and Microbiomes, 7(1), 88. https://doi.org/10.1038/s41522-021-00255-3
83. Falagas, M. E., Betsi, G. I., & Athanasiou, S. (2007). Probiotics for the treatment of women with bacterial vaginosis. Clinical Microbiology and Infection, 13(7), 657–664. https://doi.org/10.1111/j.1469-0691.2007.01797.x
84. Han, Y., & Ren, Q. (2021). Does probiotics work for bacterial vaginosis and vulvovaginal candidiasis? Current Opinion in Pharmacology, 61, 83–90. https://doi.org/10.1016/j.coph.2021.10.001
85. Anjum, N., Maqsood, S., Masud, T., Ahmad, A., Sohail, A., & Momin, A. (2014). Lactobacillus acidophilus: Characterization of the species and application in food production. Critical Reviews in Food Science and Nutrition, 54(9), 1241–1251. https://doi.org/10.1080/10408398.2011.621169
86. Zotta, T., Parente, E., & Ricciardi, A. (2017). Aerobic metabolism in the genus Lactobacillus: Impact on stress response and potential applications in the food industry. Journal of Applied Microbiology, 122(4), 857–869. https://doi.org/10.1111/jam.13385
87. Ahmed, T., Kanwal, R., & Ayub, N. (2006). Influence of temperature on growth pattern of Lactococcus lactis, Streptococcus cremoris and Lactobacillus acidophilus isolated from camel milk. Biotechnology, 5(4), 481–488.
88. Jeon, S., Kim, H., Choi, Y., Cho, S., Seo, M., & Kim, H. (2021). Complete genome sequence of the newly developed Lactobacillus acidophilus strain with improved thermal adaptability. Frontiers in Microbiology, 12, 697351. https://doi.org/10.3389/fmicb.2021.697351
89. Ruiz, L., Margolles, A., & Sánchez, B. (2013). Bile resistance mechanisms in Lactobacillus and Bifidobacterium. Frontiers in Microbiology, 4, 396. https://doi.org/10.3389/fmicb.2013.00396
90. Crawley, A. B., & Barrangou, R. (2018). Conserved genome organization and core transcriptome of the Lactobacillus acidophilus complex. Frontiers in Microbiology, 9, 1834. https://doi.org/10.3389/fmicb.2018.01834
91. Gao, H., Li, X., Chen, X., Hai, D., Wei, C., Zhang, L., & Li, P. (2022). The functional roles of Lactobacillus acidophilus in different physiological and pathological processes. Journal of Microbiology and Biotechnology, 32(10), 1226–1233. https://doi.org/10.4014/jmb.2206.06039
92. Wilson, R. M., Walker, J. M., & Yin, K. (2021). Different concentrations of Lactobacillus acidophilus cell-free filtrate have differing anti-biofilm and immunomodulatory effects. Frontiers in Cellular and Infection Microbiology, 11, 699150. https://doi.org/10.3389/fcimb.2021.699150
93. Reamtong, O., Thiangtrongjit, T., Kosoltanapiwat, N., Panbangred, W., & Prangthip, P. (2021). Potential benefits of L. acidophilus in dyslipidemic rats. Scientific Reports, 11, Article 6115. https://doi.org/10.1038/s41598-021-85473-1
94. Anderson, J. W., & Gilliland, S. E. (1999). Effect of fermented milk (yogurt) containing Lactobacillus acidophilus L1 on serum cholesterol in hypercholesterolemic humans. Journal of the American College of Nutrition, 18(1), 43–50. https://doi.org/10.1080/07315724.1999.10718822
95. Dempsey, E., & Corr, S. C. (2022). Lactobacillus spp. for gastrointestinal health: Current and future perspectives. Frontiers in Immunology, 13, 822940. https://doi.org/10.3389/fimmu.2022.822940
96. Mustapha, A., Jiang, T., & Savaiano, D. A. (1997). Improvement of lactose digestion by humans following ingestion of unfermented acidophilus milk: Influence of bile sensitivity, lactose transport, and acid tolerance of Lactobacillus acidophilus. Journal of Dairy Science, 80(8), 1537–1545. https://doi.org/10.3168/jds.S0022-0302(97)76087-5
97. Mendoza, L. (2019). Potential effect of probiotics in the treatment of breast cancer. Oncology Reviews, 13(2), 422. https://doi.org/10.4081/oncol.2019.422
98. Weiss, G., Rasmussen, S., Zeuthen, L. H., Nielsen, B. N., Jarmer, H., Jespersen, L., et al. (2010). Lactobacillus acidophilus induces virus immune defence genes in murine dendritic cells by a Toll-like receptor-2-dependent mechanism. Immunology, 131(2), 268–281. https://doi.org/10.1111/j.1365-2567.2010.03301.x
99. Magrone, T., & Jirillo, E. (2016). Prebiotics and probiotics in aging population: Effects on the immune-gut microbiota axis. In Molecular Basis of Nutrition and Aging (pp. 693–705). Academic Press. https://doi.org/10.1016/B978-0-12-801816-3.00049-3
100. Turroni, F., Peano, C., Pass, D. A., Foroni, E., Severgnini, M., Claesson, M. J., et al. (2012). Diversity of bifidobacteria within the infant gut microbiota. PLoS One, 7(5), e36957. https://doi.org/10.1371/journal.pone.0036957
101. Freitas, A. C., & Hill, J. E. (2018). Bifidobacteria isolated from vaginal and gut microbiomes are indistinguishable by comparative genomics. PLoS One, 13(4), e0196290. https://doi.org/10.1371/journal.pone.0196290
102. Hidalgo-Cantabrana, C., Delgado, S., Ruiz, L., Ruas-Madiedo, P., Sánchez, B., & Margolles, A. (2017). Bifidobacteria and their health-promoting effects. Microbiology Spectrum, 5(3). https://doi.org/10.1128/microbiolspec.BAD-0010-2016
103. Uusitupa, H., Rasinkangas, P., Lehtinen, M. J., Mäkelä, S. M., Airaksinen, K., Anglenius, H., et al. (2020). Bifidobacterium animalis subsp. lactis 420 for metabolic health: Review of the research. Nutrients, 12(4), 892. https://doi.org/10.3390/nu12040892
104. Lopez-Pier, M. A., Koppinger, M. P., Harris, P. R., Cannon, D. K., Skaria, R. S., Hurwitz, B. L., et al. (2021). An adaptable and non-invasive method for tracking Bifidobacterium animalis subspecies lactis 420 in the mouse gut. Journal of Microbiological Methods, 189, 106302. https://doi.org/10.1016/j.mimet.2021.106302
105. Turroni, F., Duranti, S., Bottacini, F., Guglielmetti, S., Van Sinderen, D., & Ventura, M. (2014). Bifidobacterium bifidum as an example of a specialized human gut commensal. Frontiers in Microbiology, 5, 437. https://doi.org/10.3389/fmicb.2014.00437
106. Dong, J., Ping, L., Cao, T., Sun, L., Liu, D., Wang, S., et al. (2022). Immunomodulatory effects of the Bifidobacterium longum BL-10 on lipopolysaccharide-induced intestinal mu-

cosal immune injury. Frontiers in Immunology, 13, 947755. https://doi.org/10.3389/fimmu.2022.947755
107. Petrova, M. I., Reid, G., & Haar, J. A. T. (2021). Lacticaseibacillus rhamnosus GR-1, a.k.a. Lactobacillus rhamnosus GR-1: Past and future perspectives. Trends in Microbiology, 29(8), 747–761. https://doi.org/10.1016/j.tim.2021.01.004
108. Stivala, A., Carota, G., Fuochi, V., & Furneri, P. M. (2021). Lactobacillus rhamnosus AD3 as a promising alternative for probiotic products. Biomolecules, 11(1), 94. https://doi.org/10.3390/biom11010094
109. Wu, S., Hugerth, L. W., Schuppe-Koistinen, I., & Du, J. (2022). The right bug in the right place: Opportunities for bacterial vaginosis treatment. NPJ Biofilms and Microbiomes, 8, Article 34. https://doi.org/10.1038/s41522-022-00274-7
110. Ceapa, C., Lambert, J., van Limpt, K., Wels, M., Smokvina, T., Knol, J., et al. (2015). Correlation of Lactobacillus rhamnosus genotypes and carbohydrate utilization signatures determined by phenotype profiling. Applied and Environmental Microbiology, 81(16), 5458–5470. https://doi.org/10.1128/AEM.00655-15
111. Harty, D. W., Oakey, H. J., Patrikakis, M., Hume, E. B., & Knox, K. W. (1994). Pathogenic potential of lactobacilli. International Journal of Food Microbiology, 24(1–2), 179–189. https://doi.org/10.1016/0168-1605(94)90219-4
112. Rossi, F., Amadoro, C., & Colavita, G. (2019). Members of the Lactobacillus genus complex (LGC) as opportunistic pathogens: A review. Microorganisms, 7(5), 126. https://doi.org/10.3390/microorganisms7050126
113. Kwok, L., Stapleton, A. E., Stamm, W. E., Hillier, S. L., Wobbe, C. L., & Gupta, K. (2006). Adherence of Lactobacillus crispatus to vaginal epithelial cells from women with or without a history of recurrent urinary tract infection. Journal of Urology, 176(5), 2050–2054.
114. Trunk, T., Khalil, H. S., & Leo, J. C. (2018). Bacterial autoaggregation. AIMS Microbiology, 4(1), 140–164. https://doi.org/10.3934/microbiol.2018.1.140
115. Owens, J. A., Saeedi, B. J., Naudin, C. R., Hunter-Chang, S., Barbian, M. E., & Eboka, R. U. (2021). Lactobacillus rhamnosus GG orchestrates an antitumor immune response. Cellular and Molecular Gastroenterology and Hepatology, 12(4), 1311–1327.
116. Wright, M. L., Fettweis, J. M., Eaves, L. J., Silberg, J. L., Neale, M. C., Serrano, M. G., et al. (2021). Vaginal microbiome Lactobacillus crispatus is heritable among European American women. Communications Biology, 4, 872.
117. Kwok, L., Stapleton, A. E., Stamm, W. E., Hillier, S. L., Wobbe, C. L., & Gupta, K. (2006). Adherence of Lactobacillus crispatus to vaginal epithelial cells from women with or without a history of recurrent urinary tract infection. Journal of Urology, 176(5), 2050–2054.
118. Jia, H. (2022). Epidemiology in the human body. In Investigating Human Diseases with the Microbiome: Metagenomics Bench to Bedside (pp. 83–107).
119. Zhang, Q., Zhang, L., Ross, P., Zhao, J., Zhang, H., & Chen, W. (2020). Comparative genomics of Lactobacillus crispatus from the gut and vagina reveals genetic diversity and lifestyle adaptation. Genes, 11(4), 360.
120. Juturu, V., & Wu, J. C. (2016). Microbial production of lactic acid: The latest development. Critical Reviews in Biotechnology, 36(6), 967–977.
121. Johnson, J. L., Phelps, C. F., Cummins, C. S., London, J., & Gasser, F. (1980). Taxonomy of the Lactobacillus acidophilus group. International Journal of Systematic Bacteriology, 30(1), 53–68.
122. Babu, G., Singaravelu, B. G., Srikumar, R., Reddy, S. V., & Kokan, A. (2017). Comparative study on the vaginal flora and incidence of asymptomatic vaginosis among healthy women and in women with infertility problems of reproductive age. Journal of Clinical and Diagnostic Research, 11(8), DC18–DC22.
123. Carroll, I. M., Andrus, J. M., Bruno-Bárcena, J. M., Klaenhammer, T. R., Hassan, H. M., & Threadgill, D. S. (2007). Anti-inflammatory properties of Lactobacillus gasseri expressing manganese superoxide dismutase using the interleukin 10-deficient mouse model of colitis. American Journal of Physiology-Gastrointestinal and Liver Physiology, 293(3), G729–G738.
124. Abdellah, S. A., Scanzi, J., Gal, C., Martin, M., Beck, M., & Ojetti, V. (2022). Lactobacillus gasseri LA806 supplementation in patients with irritable bowel syndrome: A multicenter study. Journal of Clinical Medicine, 11(24), 7446.
125. Nishida, K., Sawada, D., Kuwano, Y., Tanaka, H., & Rokutan, K. (2019). Health benefits of Lactobacillus gasseri CP2305 tablets in young adults exposed to chronic stress: A randomized, double-blind, placebo-controlled study. Nutrients, 11(8), 1859.
126. Sugawara, T., Sawada, D., Ishida, Y., Aihara, K., Aoki, Y., Takehara, I., et al. (2016). Regulatory effect of paraprobiotic Lactobacillus gasseri CP2305 on gut environment and function. Microbial Ecology in Health and Disease, 27, 30259.
127. Yuille, S., Reichardt, N., Panda, S., Dunbar, H., & Mulder, I. E. (2018). Human gut bacteria as potent class I histone deacetylase inhibitors in vitro through production of butyric acid and valeric acid. PLoS ONE, 13(7), e0201073.
128. Saviano, A., Brigida, M., Migneco, A., Gunawardena, G., Zanza, C., Candelli, M., et al. (2021). Lactobacillus reuteri DSM 17938 (Limosilactobacillus reuteri) in diarrhea and constipation: Two sides of the same coin? Medicina (Kaunas), 57(7), 643.
129. Wu, H., Xie, S., Miao, J., Li, Y., Wang, Z., Wang, M., et al. (2020). Lactobacillus reuteri maintains intestinal epithelial regeneration and repairs damaged intestinal mucosa. Gut Microbes, 11(4), 997–1014.
130. Mu, Q., Tavella, V. J., & Luo, X. M. (2018). Role of Lactobacillus reuteri in human health and diseases. Frontiers in Microbiology, 9, 757.
131. Kołodziej, M., & Szajewska, H. (2019). Lactobacillus reuteri DSM 17938 in the prevention of antibiotic-associated diarrhoea in children: A randomized clinical trial. Clinical Microbiology and Infection, 25(6), 699–704.
132. Wang, H., Zhou, C., Huang, J., Kuai, X., & Shao, X. (2020). The potential therapeutic role of Lactobacillus reuteri for treatment of inflammatory bowel disease. American Journal of Translational Research, 12(5), 1569–1583.
133. Kim, S., Kang, C., Kim, G., & Cho, H. (2022). Anti-tumor effects of heat-killed L. reuteri MG5346 and L. casei MG4584 against human colorectal carcinoma through caspase-9-dependent apoptosis in xenograft model. Microorganisms, 10(3), 533.
134. Mi, G., Zhao, L., Qiao, D., Kang, W., Tang, M., & Xu, J. (2015). Effectiveness of Lactobacillus reuteri in infantile colic and colicky induced maternal depression: A prospective single blind randomized trial. Antonie Van Leeuwenhoek, 107(6), 1547–1553.
135. Shornikova, A. V., Casas, I. A., Isolauri, E., Mykkänen, H., & Vesikari, T. (1997). Lactobacillus reuteri as a therapeutic agent in acute diarrhea in young children. Journal of Pediatric Gastroenterology and Nutrition, 24(4), 399–404.
136. Li, P., Ji, B., Luo, H., Sundh, D., Lorentzon, M., & Nielsen, J. (2022). One-year supplementation with Lactobacillus reuteri ATCC PTA 6475 counteracts a degradation of gut microbiota in older women with low bone mineral density. NPJ Biofilms and Microbiomes, 8, 84.
137. Ojetti, V., Ianiro, G., Tortora, A., D'Angelo, G., Di Rienzo, T. A., Bibbò, S., et al. (2014). The effect of Lactobacillus reuteri supplementation in adults with chronic functional constipation: A randomized, double-blind, placebo-controlled trial. Journal of Gastrointestinal and Liver Diseases, 23(4), 387–391.
138. Coccorullo, P., Strisciuglio, C., Martinelli, M., Miele, E., Greco, L., & Staiano, A. (2010). Lactobacillus reuteri (DSM

17938) in infants with functional chronic constipation: A double-blind, randomized, placebo-controlled study. Journal of Pediatrics, 157(4), 598–602.
139. Patro-Gołąb, B., & Szajewska, H. (2019). Systematic review with meta-analysis: Lactobacillus reuteri DSM 17938 for treating acute gastroenteritis in children—An update. Nutrients, 11(11), 2762.
140. Mesnage, S., & Foster, S. J. (2013). N-acetylmuramoyl-l-alanine amidase. In Handbook of Proteolytic Enzymes (Vol. 1, pp. 1401–1407).
141. Sueoka, N. (1997). Cell membrane and chromosome replication in Bacillus subtilis. Progress in Nucleic Acid Research and Molecular Biology, 59, 35–53.
142. Daneshazari, R., Khorasgani, M. R., Hosseini-Abari, A., & Kim, J. (2023). Bacillus subtilis isolates from camel milk as probiotic candidates. Scientific Reports, 13, 3387.
143. Su, Y., Liu, C., Fang, H., & Zhang, D. (2020). Bacillus subtilis: A universal cell factory for industry, agriculture, biomaterials and medicine. Microbial Cell Factories, 19, 173.
144. Boguszewska, K., Szewczuk, M., Kaźmierczak-Barańska, J., & Karwowski, B. T. (2020). The similarities between human mitochondria and bacteria in the context of structure, genome, and base excision repair system. Molecules, 25(12), 2857.
145. Li, C., Li, Y., Li, S., Chen, S., Liu, G., Deng, X., et al. (2022). Bacillus subtilis protects the ducks from oxidative stress induced by Escherichia coli: Efficacy and molecular mechanism. Antioxidants, 11(10), 1951. https://doi.org/10.3390/antiox11101951
146. Su, Y., Liu, C., Fang, H., & Zhang, D. (2020). Bacillus subtilis: A universal cell factory for industry, agriculture, biomaterials and medicine. Microbial Cell Factories, 19, 173. https://doi.org/10.1186/s12934-020-01428-7
147. Benítez-Chao, D. F., León-Buitimea, A., Lerma-Escalera, J. A., & Morones-Ramírez, J. R. (2021). Bacteriocins: An overview of antimicrobial, toxicity, and biosafety assessment by in vivo models. Frontiers in Microbiology, 12, 632539. https://doi.org/10.3389/fmicb.2021.632539
148. Zhang, Q., Kobras, C. M., Gebhard, S., Mascher, T., & Wolf, D. (2022). Regulation of heterologous subtilin production in Bacillus subtilis W168. Microbial Cell Factories, 21(1), 57. https://doi.org/10.1186/s12934-022-01730-w
149. Shelburne, C. E., An, F. Y., Dholpe, V., Ramamoorthy, A., Lopatin, D. E., & Lantz, M. S. (2007). The spectrum of antimicrobial activity of the bacteriocin subtilosin A. Journal of Antimicrobial Chemotherapy, 59(2), 297–300. https://doi.org/10.1093/jac/dkl488
150. Mondot, S., de Wouters, T., Doré, J., & Lepage, P. (2013). The human gut microbiome and its dysfunctions. Digestive Diseases, 31(3–4), 278–285. https://doi.org/10.1159/000354678
151. Varesi, A., Pierella, E., Romeo, M., Piccini, G. B., Alfano, C., Bjørklund, G. G., et al. (2022). The potential role of gut microbiota in Alzheimer’s disease: From diagnosis to treatment. Nutrients, 14(3), 668. https://doi.org/10.3390/nu14030668
152. Uusitupa, H., Rasinkangas, P., Lehtinen, M. J., Mäkelä, S. M., Airaksinen, K., Anglenius, H., et al. (2020). Bifidobacterium animalis subsp. lactis 420 for metabolic health: Review of the research. Nutrients, 12(4), 892. https://doi.org/10.3390/nu12040892
153. Zhang, X. (2015). Strain interactions as a mechanism for dominant strain alternation and incidence oscillation in infectious diseases: Seasonal influenza as a case study. PLoS ONE, 10(11), e0142170. https://doi.org/10.1371/journal.pone.0142170
154. El-Deeb, N. M., Yassin, A. M., Al-Madboly, L. A., & El-Hawiet, A. (2018). A novel purified Lactobacillus acidophilus 20079 exopolysaccharide, LA-EPS-20079, molecularly regulates both apoptotic and NF-kappaB inflammatory pathways in human colon cancer. Microbial Cell Factories, 17, 29. https://doi.org/10.1186/s12934-018-0875-y
155. Plaza-Diaz, J., Ruiz-Ojeda, F. J., Gil-Campos, M., & Gil, A. (2019). Mechanisms of action of probiotics. Advances in Nutrition, 10(Suppl_1), S49–S66. https://doi.org/10.1093/advances/nmy063
156. Nwoko, E. Q. A., & Okeke, I. N. (2021). Bacteria autoaggregation: How and why bacteria stick together. Biochemical Society Transactions, 49(3), 1147–1157. https://doi.org/10.1042/BST20200691