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Abstract

Probiotics are known for providing health benefits, calling for clinical result testing on subjects. We focus on the biological effects of the following probiotics to find their potential to help neurological disorders: *Lactobacillus brevis, Enterococcus, and Bifidobacterium longum*. We delve into how probiotics work with the gut-brain axis—the communication center between the central and the enteric nervous system—and its effect on different neurological disorders through an extensive literature review. We found that *Lactobacillus brevis* helps the immune system with the potential to help with stress and anxiety disorders. *Bifidobacterium longum* has been shown to help age-associated disorders like Alzheimer's and reduce severe stress levels. *Enterococcus* has been shown to help neuroinflammation-based diseases like Parkinson's. *Enterococcus is also* shown to be more present in people with depression than without. These results bring attention to specific probiotic potential in helping neurological disorders. They will help to create more treatments and bring attention to new areas of preventing disorders.

Introduction

In a world where consumers are obsessed with the remedial health effects of probiotic commodities, over-the-counter supplements, food, and drinks, studying the gut-brain axis has become of popular interest. The gut-brain axis is a network that links the entire enteric (intestinal) and central nervous system (Appleton, 2018). Probiotics are often advertised to play a vital role in preventing cognitive decline and/or neurological diseases. This strategy of advertisement attracts attention because neurological disorders affect hundreds of millions of people and claim the lives of over 6 million annually. The neurological disorders focused on in studies about the gut-brain relationship are

Alzheimer's, Parkinson's, Schizophrenia, epilepsy, and autism. The word "probiotic" itself promotes the claim that live microorganisms offer health benefits via the maintenance of the gut microbiome. While most research emphasizes the clinical results of testing probiotics on subjects, we are more focused on the biological effects of 3 probiotics: *Lactobacillus brevis, Enterococcus,* and *Bifidobacterium longum*, that could address whether probiotics help neurological disorders. We will fill this gap by conducting a literature review on how specific probiotics affect the microbiome and how changes in the gut microbiome affect neurological disorders. This will be different from testing on subjects as we holistically review the selected probiotics' relationships to neurological health through their communication system and gut-brain axis.

Utilized in favorite foods like cheese, pickles, and sourdough bread, *Lactobacillus brevis* is a versatile probiotic. The genus, *Lactobacillus,* is a genera of gram-positive, catalase-negative lactic acid bacteria that can create lactic acid through fermentation. *L. brevis* is a microaerophilic—requiring little oxygen—in the *Lactobacillus casei-Pediococcus group.* The rod-shaped cell structure has rounded ends in separate or short chains. The antimicrobial activity of *L. brevis* stems from its additional production of inhibitory agents such as acetic acid, bacteriocins, CO2, hydrogen peroxide, ethanol, and diacetyl. The impact *Lactobacillus* has on food safety, health, and preparation is undeniable in its connection to neurological disorders.

Enterococci probiotics belong to a large genus of lactic acid bacteria of the phylum *Bacillota*. *Enterococcus* is a gram-positive cocci that often occurs in pairs or short chains and is difficult to distinguish from *Streptococci* on physical characteristics alone (Said et al., 2022). *Enterococci* have been isolated from a variety of habitats and natural biomes such as digestive systems in organisms, sewage, soil, and agricultural land, suggesting possible viability in entering humans. *Enterococci* can boost the immune system as a probiotic and play an important role in food technology as the starting culture in

meat and cheese fermentation and food preservation (Krawczyk et al., 2021). Its common subspecies, *Enterococcus faecalis* and *Enterococcus faecium,* are often found in humans. Its significance in human health is that it aids in the modulation of the immune system (Krawczyk et al., 2021).

Bifidobacterium longum (B. longum) is a probiotic found in the intestines. It creates lactic and acetic acids in the intestines. This bacteria can aid in the digestion of food, the absorption of nutrients, and the defense against organisms that may cause disease. *B. longum* has two subspecies, *B. longum subsp. infantis* and *B. longum subsp. longum*, which are present in the human gut and used in probiotic supplements. The significance of *Bifidobacterium* to human health may be seen in the early colonization of the neonatal gut, where *B. longum* is the most prevalent species. While its relative abundance decreases with aging, it is even lower in some disorders. Research into *B. longum's* beneficial qualities have revealed several pathways, including the generation of bioactive compounds such as short-chain fatty acids, polysaccharides, and serine protease inhibitors. *B. longum* is composed to date of four subspecies, *B. longum ssp. infantis*, *B. longum ssp. longum, B. longum ssp. suis, and B. longum ssp. suillum.* Specifically, the *B. longum strain, longum* BB536*,* is a widely recognized probiotic strain that provides various significant health advantages in humans. The ingestion of BB536 provides a consistent beneficial effect in the improvement of gastrointestinal conditions, maintenance of intestinal microflora balance, regulation of immune response, anti-allergy, and protection against microbial infections.

Methodology

We largely relied on existing research to understand the correlation between probiotics and their impact on human health. Using multiple search engines, we searched the “relationship between the gut microbiome and brain function.” Our search included other keywords such as “role of probiotics and prebiotics on psychiatric disorders,” “effects of probiotics on the gut microbiome,” and “neurological

benefits of probiotics." Our exclusion criteria consist of filtering out articles older than 15 years, articles not affiliated with an institution or trusted center, reviews, and studies using an observational design. An institution or center affiliation is necessary to ensure credibility. Further, eliminating literature reviews will prevent redundancies from other studies and selection bias from observational studies (studies that examine effects and data without experimentation).

Results

Lactobacillus brevis (1)

Lactobacillus brevis is shown to have a positive contribution towards hippocampus activity through experimentation on *L. brevis*-killed mice (Ishikawa et al., 2019). The hippocampus-dependent nonaversive social memory also improved. Experimentation included mice being exposed twice to a young male mouse for three minutes in a 24-hour interval and displayed a great reduction in social investigation time at the second exposure (Ishikawa et al., 2019). The ability to recognize fear was also examined by having the mice form a hippocampus-dependent aversive memory. The mice were given a single footshock and their behavioral freezing was assessed 24 hours later. Mice that were fed the *L. brevis* had a significantly higher freezing compared to the control group. *L. brevis* was additionally confirmed to assist the survival of newborn neurons during 5-bromo-2-deoxyuridine positive cell injection and examination (Ishikawa et al., 2019). *L. brevis* improves the hippocampus by aiding the survival of newborn neurons.

The incorporation of *L. brevis* also aids in stress management. When examining the human body to understand its stress processing, the gut microbiota showed a connection to the microbiota in the gut-brain axis. A beverage fermented with *L. brevis, L. planetarium,* and *L. paracasei* was ingested by stressed medical students in an experimental, longitudinal, single-blind, and non-randomized sampling

(Márquez-Morales et al., 2021). The students drank 100 mL per day for two months, with consistent reminders. Stool samples were collected before and after the study to analyze the microbial DNA. Out of 45 participants ages 20 to 25, 77.8% reported low stress levels after the trial based on the SISCO Inventory of Academic Stress instrument.

In addition to stress, *L. brevis* aids in reducing inflammation. Mercury, along with other heavy metals, can often be encountered in consumed fish, but its exposure is harmful to various organs and increases inflammation in the gut. Based on mice experimentation, *L. brevis* can prevent the absorption of mercury in the intestines (Jiang et al., 2018). The two groups of mice were dosed with *L. brevis* for at least five days and then orally given mercury. The second of the two groups was given *L. brevis* for six more days after the mercury exposure. Mercury exposure increased the inflammatory cytokines in the duodenum and colon. Groups of mice given the probiotic could inhibit and block the inflammation itself. The second group was additionally able to reduce *NF*-κ*B* and p-*NF*-κ*B* expression in the colon, which are protein complexes that serve as a sign of inflammation. As a result, *L. brevis* has the potential to relieve depression and anxiety disorders as a gut microbial through its aid to the hippocampus and stress management in addition to the relief of inflammation.

Enterococcus faecium (2)

Enterococcus faecium was one of the isolated species along with *Pediococcus acidilactici* that deteriorated neuroinflammation, colitis, and anxiety or depression-like behaviors in germ-free mice (Jang et al., 2022). Colitis is an inflammatory bowel disease that affects the colon and rectum. Compared to other isolated bacteria, *E. faecium* did not have a hand in causing said stressful symptoms. Additionally, *E. faecium* is regarded as a “generally recognized as safe” (GRAS) probiotic.

Recent research (Jang et al., 2022) focused on the microbiota-gut-brain (MGB) axis, which explains the intricate interaction between gut bacteria and the brain. This interaction not only controls the onset of intestinal inflammation but also plays an important role in the progression of neuropsychiatric diseases. The study (Jang et al., 2022) discovered significant differences in gut bacteria composition between healthy people and those with IBD and/or depression. Bacterial populations such as *Klebsiella* species, *Escherichia coli*, *Enterococcus* species, and *Pediococcus acidilactici* were shown to be more prevalent in persons with IBD and/or depression than in healthy controls. Surprisingly, the prevalence of beneficial bacteria such as *Bifidobacterium* species was highest in healthy controls, revealing a potential preventive role against these illnesses. The study also focused on *Enterococcus faecium's* possible pathogenic features, such as medication resistance and biofilm formation. Given these findings, more research is needed to establish the efficacy of probiotic therapy that targets specific bacterial imbalances in patients with IBD and/or depression.

Bifidobacterium longum (3)

A combination of *Bifidobacterium bifidum* (*B. bifidum*) and *Bifidobacterium longum* (*B. longum*) has been shown to alleviate Alzheimer's disease pathology and increase mental flexibility by restoring the brain-derived neurotrophic factor (BDNF) gene, essential for learning and memory, in the hippocampus (Kim et al., 2022). In a study with two treatment groups of mice, 3-month-old and 16-month-old, these mice were administered the combination of *B. bifidum* and *B. longum* via oral administration. 30 days later a significant increase in the BDNF neuron was found in both hippocampi, suggesting that these probiotics improved hippocampal synaptic plasticity (Kim et al., 2022).

Furthermore, these probiotics reduced the aging phenotype in the hippocampus of 16-month-old mice. After 30 days of administration of *B. bifidum* and *B. longum*, the amount of caspase-3+ apoptotic

cells significantly decreased, cells responsible for programmed cell death. Additionally, the phosphorylation of histone H2AX, signifying DNA damage associated with aging, revealed a major decrease in the number of γ-H2AX+neurons in the hippocampus - suggesting that these probiotics may play a role in anti-aging (Kim et al., 2022).

Finally, *B. bifidum* and *B. longum* were found to decrease age-associated cognitive deficits in these mice. The open-field test was conducted for ten minutes to determine locomotor activity. After administration of these probiotics, age-dependent decreases—measured by total distance, moving time, and velocity, were observed in mice. Additionally, to observe effects on short-term memory, the Y-maze test was conducted which revealed that probiotic-treated mice showed improved spatial recognition memory than non-treated mice, indicating these probiotics do not just increase cognitive ability but improve it as well (Kim et al., 2022).

The use of *B. longum* alone has been found to decrease stress levels, improve sleep, and improve mental health in humans. In a 6-week intervention with *B. longum* on 45 healthy adults with mild-to-moderate stress using a randomized, placebo-controlled designed study, the decrease in perceived stress in the probiotic group (21.4%) was significantly higher compared to that of the placebo group (−10.2%) (Boehme et al., 2023). Additionally, there was a significant improvement in subjective sleep in the probiotic group (5.25 higher odds risk ratio) compared to the placebo group. Furthermore, multivariate analysis revealed a positive correlation between stress reduction and reductions in anxiety and depression in the group with adults who received the treatment versus the placebo, indicating that *B. longum* is beneficial in reducing stress and improving mental health (Boehme et al., 2023).

Discussion

Lactobacillus Brevis improvement of mental health

Lactobacillus brevis shows growing potential for improving mental health: the trend of improving psychological symptoms of stress and depression because of the gut-brain axis. Gut microbes influence the brain and nervous system by creating neurotransmitters and signal proteins for the brain to release or suppress different hormones. *Lactobacillus brevis* produces y-aminobutyric acid (GABA). GABA works as an inhibitory neurotransmitter of the central nervous system to relieve symptoms of pain, low sleep, and acid secretion. GABA is already known to have low concentrations in people with depression and anxiety.

Additionally, the understanding of *L. brevis*'s contribution towards hippocampus activity suggests the potential for *L. brevis* to improve neurological diseases such as Huntington's disease. Huntington's disease is a genetic disorder that causes neurons to die and attacks the parts of the brain that control voluntary movement. Most individuals with Huntington's disease have wild uncontrolled movements and postures (National Institute of Neurological Disorders and Stroke, 2023). Though future research will need to be conducted on the probiotic, *L. brevis* may be able to aid the survival of new neurons, helping ease the effects of Huntington's disease. It is crucial to note that experimentation on *L. brevis* resulted in not the creation of new neurons but rather helped to promote the survival of neurons, and thus should not be assumed to be a cure for Huntington's.

Stress is a major issue invading numerous lives. Stress is the common risk factor for 75-90% of diseases, especially cardiovascular diseases (Liu et al., 2017). Stress activates inflammatory responses in the brain through the HPA axis and inflammation is also connected to many chronic diseases such as hypertension and obesity. *L. brevis* having the ability to reduce inflammation and stress shows its potential in aiding one's quality of life and overall health. Consumption of *L. brevis* can stand as a general prevention treatment for stress-related and inflammation diseases, such as depression (Zhang et al., 2013) and Alzheimer's disease (Chen et al., 2011).

Enterococcus faecium's help to reducing neuroinflammation

Enterococcus faecium had a great hand in reducing neuroinflammation. Its significance lies in how neuroinflammation is linked to Parkinson's disease, which is an age-related neurodegenerative disorder. When examining post-mortem patients with Parkinson's disease, many shared activation of glial cells and intense inflammation (Wang et al, 2015). Neuroinflammation causes neural death or damage, a greatly impacting factor to Parkinson's that current treatments focus on alleviating but can't cure. Thus, though more research will have to be done to be certain, consuming *E. facium* could be able to prevent neuroinflammation-based diseases like Parkinson's.

E. faecium also shows great potential in therapy for depression. Between people with depression and those without, a significant gap in their gut bacteria was observed and proved to be a factor in symptoms (Hyo-Min Jang, Jeon-Kung-Min,..., 2022). Specifically, *E. faecium* was more active in people with depression, indicating its absence correlates with the absence of depressive symptoms. Knowing this, more treatments can be done to help the disease and prevent other disorders linked to the balance of gut bacteria.

Bifidobacterium longum's improvement of microbial balance

With continuous decreased stress assisted by *B. longum,* as similarly described for *L. brevis, B. longum* can additionally aid in numerous stress-related diseases. The impact of the probiotic *B. longum* on the gut microbiome unveils intricate and multifaceted effects, offering therapeutic advantages for overall gut health. Through thorough research, we identify the subtle interplay between *B. longum* and the gut microbiome, giving insight into its potential as a key agent in supporting microbial balance and establishing an environment conducive to overall intestinal health. From birth, the microbiome is susceptible to easy alterations, and the involvement of *B. longum* has been demonstrated to confer

therapeutic benefits within the intricate landscape of the microbiome. *B. longum* has emerged as a leading candidate in probiotic development for both infants and adults due to its extensive host benefits, which include nutrient metabolism and cross-feeding network generation, antimicrobial peptide production, and competitive pathogen exclusion, among other health-promoting functions. One study focused on the impact of probiotics on premature infants and their microbiome (Mercer and Arrieta, 2023). These interventions underscored the probiotic's capacity to inadvertently modify the gut microbiome. The utilization of multiple strains of *Bifidobacterium longum* showcased significant advancements.

Despite the potential for probiotic strains to influence the metabolic state of the intestinal milieu and microenvironments, creating novel niches that could be colonized by successive microbial community members, remains an intriguing avenue for further exploration. The immune system of premature infants displays immaturity, including fewer mature immune cells surveying the gut, reduced secretory Iag expression, and higher levels of pro-inflammatory cytokines and many more active concerns.

Due to the factors that influenced the state of the infants microbiome, the method of probiotic supplication was done with prolonged hospitalization, increased antibiotic exposure, and delayed enteral feeds. Through these mechanisms the composition of the microbiome was affected due to the higher proportion of aerobic and facultative anaerobic bacteria. Incorporating the probiotic into a microbial community as a therapeutic intervention not only serves a treatment but also signifies a proactive pathway toward achieving stability within the microbiome

The deliberate introduction of *Bifidobacterium longum* into the microbial milieu demonstrates a planned approach to developing a harmonious and balanced microbial community. This therapeutic approach has the potential to address not only specific health conditions but also to create a resilient and

well-regulated microbiome, highlighting the dynamic interplay between probiotic interventions and the intricate dynamics of microbial ecosystems. The intentional inclusion of *B. longum* in the microbiome demonstrates the ongoing attempts to increase our understanding and management of microbial communities for better health outcomes.

Conclusion

The health benefits of probiotics have been agreed upon on a public standard—understanding their ability to aid and support the beneficial bacteria in the body. When further examining the capabilities of probiotics for neurological disorders, three of the most common probiotics: *Lactobacillus brevis*, *Enterococcus faecium,* and *Bifidobacterium longum* were chosen. *Lactobacillus brevis*, *Enterococcus faecium,* and *Bifidobacterium longum* all show great potential in helping stress-related neurological disorders. *Lactobacillus brevis* can be linked to improving stress and inflammation-based disorders. Similarly, *Enterococcus faecium* can target inflammation-based disorders. *Bifidobacterium longum* shows increasing potential in alleviating symptoms from age-related disorders. With these connections, the goal is to introduce possible non-invasive treatments all starting with the diet. From here, more research should be done on *Enterococcus* treatment to prevent neuroinflammatory diseases and *Lactobacillus brevis* in treating mental health disorders. Bifidobacterium longum's improvement of microbial balance should induce more research in its development as a possible treatment for impaired gut health. Many neurological disorders linked to gut health like Alzheimer's and Parkinson's may benefit from this source of treatment. This research review has shown the potential benefits of using *Lactobacillus brevis*, *Enterococcus faecium,* and *Bifidobacterium longum* as treatments for neurological disorders, explaining why and how each probiotic is important to improving different disorders. Future studies of these probiotics may focus on their help to a specific disorder, finding their effect on each to see the magnitude of their impact. Other studies may

also investigate how other probiotics improve or prolong neurological disorders, delving into the importance of probiotics to good health.

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