Literature Review

Potential Beneficial Effects of Probiotics on Human Migraine Headache: A Literature Review

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Background: Recent studies have shown that migraine headache is often associated with concomitant gastrointestinal diseases. There is a higher prevalence of headaches in patients with gastrointestinal disorders. These associations between migraine and gastrointestinal disorders suggest a potential link to a bidirectional modulation of gut microbiota and brain function. The underlying working mechanistic links between migraine and gastrointestinal diseases may include increased intestinal epithelial permeability and inflammation.

Objective: This review presents an overview of the relationship between gut microbiota and brain function, especially with regard to migraine headache.

Study Design: Literature review.

Setting: Anesthesia and Operation Center, Department of Anesthesiology, Chinese PLA General Hospital.

Methods: The present investigation included a PubMed search using the following terms: migraine headache, gut microbiota, brain function, and probiotics.

Results: In this literature review, we mainly discussed the relationship between gut microbiota and brain function, especially with regard to migraine headache. The potential effects of probiotics supplement on migraine headache were also included.

Limitations: There is limited evidence from clinical studies of the positive effects of probiotics in patients with migraine headache. Large-scale randomized, placebo-controlled clinical trials are warranted to evaluate the clinical efficacy and safety of probiotics in patients with migraine headache.

Conclusions: Similar to migraine headache, disorders of the brain involving depression and anxiety have been demonstrated to be associated with increased gut permeability. An improvement in gut microbiota and reduction of inflammation can have positive effects on strengthening gut and brain function. Moreover, it can be inferred that probiotics may have a beneficial effect on the frequency and severity of migraine headache attacks. Large-scale randomized, placebo-controlled studies are warranted in the future to evaluate the clinical efficacy and safety of probiotics in patients with migraine headache.

Key words: Migraine headache, gut microbiota, brain function, probiotics

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Migraine headache, affecting approximately 15% of the global population, is a common chronic disorder (1). Patients with migraine headache usually suffer from moderate to severe episodes of headache, lasting several hours to days. Migraine headache is frequently concomitant with gastrointestinal symptoms, including nausea, vomiting, diarrhea, constipation,

and dyspepsia. A recent review of associations between migraine headache and gastrointestinal disorders has demonstrated that people who frequently experience gastrointestinal disorders have a higher prevalence of headaches (2). Moreover, infantile colic has been known as an early-life expression of migraine headache, with a maternal history of migraine predisposing to an approximately 2.6 times higher likelihood of colic than controls (3). Further, children with migraine headache are more likely to have experienced colic compared to controls (4). Other studies have suggested that migraine headache is significantly associated with inflammatory bowel disease and celiac disease (5,6); however, the specific relationship between migraine headache and gastrointestinal microbiology, primarily pertaining to intestinal bacteria, remains unclear. Possible underlying etiologies are attributed to increased intestinal permeability and inflammatory reactions, causing or resulting from gastrointestinal diseases. The present review aims to discuss the relationship between gut microbiota and brain function, as well as the influence of probiotic supplements on the migraine headache patient and potential mechanisms underlying such influence.

Gut Microbiota and Brain Function

The human gut contains over a thousand known bacterial species, with *Bacteroidetes* and *Firmicutesphyla* being the predominant strains (7). The colonization of gut microbiota begins when an infant is born, whereas the diversity and activity of gut bacteria depends on both genetic and environmental factors. The positive effects of normal gut microbiota on health include maintenance of the integrity of the gut epithelial barrier and gut mobility, regulation of polysaccharide degradation, and improved nutrient absorption. Recent studies have shown that gut microbiota can mediate or modulate brain development through the gut–brain axis (8). The major anatomical connections between the brain and gut system involve brain tissues, the spinal cord, vagal and spinal nerves, gut tissues, microbiota and their metabolites residing in the gut, and the endocrine and immune systems. The gut–brain axis is well known as a bidirectional neurohumoral communication system, occurring in 2 reciprocal directions, and primarily involves regulation of gastrointestinal physiology and microbiota activity by the brain and modulation of brain function by the gut microbiota. Disruption of this symbiotic relationship impairs integrity of the epithelial barrier and mucosal immune function.

Increasingly, recent evidence has demonstrated that gut microbiota could indeed affect brain function (9,10). Evidence from a murine study suggested gut microbiota could convert complex carbohydrates into short-chain fatty acids, such as butyric acid, which regulate structure and function of the blood–brain barrier (11). Moreover, intestinal microbiota have been found to directly alter neurotransmitter levels, indicating the possibility of established communication between bacteria and neurons (12). Metabolites from gut microbiota promote production of 5-hydroxytryptamine by intestinal epithelial cells and levels of serotonin are lower in the blood of germ-free animals compared with normal controls. Germ-free mice gavaged with certain bacterial strains, such as *Lactobacillus paracasei*, have demonstrated significant improvements in serum serotonin levels and visceromotor responses (13). Therefore, mice with normal microbiota when treated with antibiotics may show reduced serum neurotransmitter levels, indicating a direct mechanism where by gut microbiota influence neurotransmitters in the host.

Furthermore, beneficial effects of gut microbiota on brain function have been shown in animal or human models of depression and anxiety. Depressed rats were gavaged with specific bacteria for 2 weeks with a consequent significant increase in plasma levels of tryptophan (14). Tryptophan is a known precursor of serotonin. Therefore, supplementation with some bacteria could possibly have antidepressant effects. Recently, a triple-blind, randomized, placebo-controlled clinical trial was carried out to test the effect of 4-week multispecies probiotics on cognitive reactivity to sad mood (15). Participants who received multispecies probiotics showed a significantly decreased cognitive reactivity to sad mood compared to the placebo control group that was largely attributed to dropping of rumination and aggressive thoughts. Likewise, probiotics have been reported to have an active influence on anxiety. In a rat model of anxiety, the use of *Lactobacillus helveticus* R0052 and *B.longum* R007 resulted in conclusive anti-anxiety effects compared with placebo (16).

Functional magnetic imaging was used to objectively ascertain changes in brain function that were induced by gut probiotics. After 4 weeks of food containing probiotics, activity in certain brain regions, including the primary interoceptive and somatosensory cortices, was decreased (17) and was associated with resting-state changes. The underlying mechanism might be related to an upregulation of the monoaminergic system through vagal afferent nerve activity induced by probiotics and their metabolites.

Gut Microbiota and Migraine Headache

Evidence has demonstrated that gut microbiota play a key role in the brain–gut axis, and disturbances of intestinal flora may be associated with neurological disorders, including migraine headache. Patients with migraine headache more frequently suffer from gastrointestinal diseases than healthy controls, and patients with gastrointestinal disease more often have migraines headache when compared to normal controls. This association between migraine headache and gastrointestinal disorders may be explained by increased intestinal permeability and inflammatory responses (18,19). Undigested food particles and bacterial metabolites can enter the bloodstream as a result of increased intestinal permeability, and these bacterial endotoxins, such as lipopolysaccharides, may act on the trigeminovascular system to consequently trigger migraine-like attacks (20). Inflammation is hypothesized to be associated with migraine headache pathophysiology, and elevated plasma levels of proinflammatory cytokines, such as tumor necrosis factor-α, have been investigated in patients with migraine headache. Thus, a significant relationship has been found between migraine headache and various inflammatory diseases, including gastrointestinal disorders, obesity, allergies, and asthma.

Evidence from a clinical trial among patients with migraine headache who also had irritable bowel syndrome reported on the estimated influence of a dietary intervention lasting 6 weeks, with significant improvement in migraine headache attack counts, duration, and maximum severity. Therefore, it is plausible that reduction of intestinal permeability is conducive to alleviation of migraine headache in certain patients in whom increased intestinal permeability plays a role in disease pathogenesis (21).

Effects of Probiotics Supplement on Migraine Headache

Probiotics are living microorganisms that are beneficial for the health of the host, and certain probiotics, mainly strains *lactobacilli* and *bifidobacteria*, can enhance the integrity of the intestinal epithelial barrier. These probiotics have proven therapeutic efficacy in gastrointestinal disorders, such as antibiotic-related diarrhea, prevention of necrotizing enterocolitis, and inflammatory bowel disease (22). One of the underlying mechanisms of probiotic supplements in the treatment and prevention of gut-related diseases is strengthening of the intestinal barrier function through several mechanisms. Results from a randomized controlled trial conducted in healthy volunteers have suggested that probiotics could improve the gut epithelial barrier via modulation of the expression of tight junction proteins in the gut epithelial layer (23).

As probiotics have been able to repair increased intestinal permeability and maintain the gut barrier function, these microorganisms may relieve migraine headache through improved gut epithelial permeability in patients. In a clinical study, 40 patients with migraine headache received several nutrients including vitamins, minerals, micronutrients, herbs, and probiotics for 3 months (24). At the beginning of this trial, participants had a mean quality of life score of 38 via the Medical Outcomes Trust Migraine Specific Quality of Life Questionnaire. After 3 months of effective treatment, the mean quality of life score of these patients with migraine headache significantly increased to 76, and 60% experienced near-total alleviation of migraine headache attacks, with quality of life scores ranging between 80 and 100. In a new open-label pilot study in migraine headache volunteers, participants received 2 g of multispecies probiotic products daily for 12 weeks (25). The probiotic products contained the effective and beneficial bacterial strains: *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19, and *Lactococcus lactis* W58. This was the first study to use probiotic products to treat patients with migraine headache. At baseline and after 12 weeks of probiotic treatment, participants completed 2 headache questionnaires, The Migraine Disability Assessment Scale (MIDAS) and the Henry Ford Hospital Headache Disability Inventory (HDI), to assess the intensity of the migraine attack. The study proved that 67% of participants showed a decrease in the number of migraine days, compared to 15% who showed an increase. Antihypertensive and antiepileptic drugs are known to prevent migraine and decrease migraine days with 21% to 62% efficacy. In this study, migraine days decreased to 23%. Moreover, the biggest advantage of probiotics is that they have almost no severe side effects. Relatively mild side effects of probiotic ingestion in this study were constipation, nausea, bloating, and diarrhea, all of which subsided within 3 weeks of starting the intervention. Thus far, no randomized controlled clinical trials have been published where migraine headache patients were treated with probiotic products (Table 1).

Table 1. *The involved mechanisms of migraine action intervened by probiotics in the published studies.*

Authors (reference)	Study Design	Intervention	Main results	The Involved Mechanisms
Tillisch K et al (17)	A single center, randomized, controlled, parallel-arm design	Healthy women were randomly assigned to 3 groups respectively given a fermented milk product with probiotic (FMPP), a nonfermented milk product, or no intervention for 4 weeks. The FMPP included Bifidobacterium animalis subsp Lactis, Streptococcus thermophiles, Lactobacillus bulgaricus, and Lactococcus lactis subsp Lactis.	FMPP intake was associated with reduction in activity in brain functional network containing the primary viscerosensory and somatosensory cortices, parahippocampal gyrus, and the periaqueductal gray. Connectivity alterations within the periaqueductal gray centered resting-state network which contained interoceptive, affective and prefrontal regions were noted with FMPP ingestion.	This study speculated that these changes may be related to altered vagal afferent signaling to the nucleus tractus solitaries and connected brain regions via the periaqueductal gray, or metabolic modulation induced by FMPP intake.
Sensenig J et al (24)	An open label design	Forty migraine patients were instructed to take 2 nutritional formulations for 90 days. One nutritional combination contained bioactive peptides, amino acids, 4 probiotics (Lactobacillus acidophilus, L. bulgaricus, Enterococcus faecium, and Bifidobacterium bifidum), and chlorophyll. The other formulation was a blend of 21 different ingredients which included vitamins, minerals, micronutrients, glandular, and herbs.	Eighty percent of the migraine participants experienced almost total relief from migraine attacks, which also significantly improved the quality of life during the 90 days of the study.	This study supports the theory of migraine in part stems from underlying intestinal dysbiosis and dysfunction of normal body absorption and assimilation of nutrition. However, it remains unknown if this sustained improvement was due to placebo effects, probiotics, or due to the other nutrients.
de Roos NM et al (25)	An open-label pilot study	Twenty nine migraine patients took the multispecies probiotic food supplements (bacterial strains: Bifidobacterium bifidum W23, Bifidobacterium lactis W52, Lactobacillus acidophilus W37, Lactobacillus brevis W63, Lactobacillus casei W56, Lactobacillus salivarius W24, Lactococcus lactis W19 and Lactococcus lactis W58) for 12 weeks.	Both the number of days and intensity of migraine decreased significantly compared to baseline data. Migraine associated disability also significantly improved through Migraine Disability Assessment Scale score. Relevant adverse reactions did not occur and compliance was high.	This study supported the leaky gut hypothesis. The theory means the increased intestinal permeability can allow leakage of undigested food particles and bacterial components like lipopolysaccharides into the bloodstream. These endotoxins can trigger a response provoking migraine. Consequently, probiotics may reduce migraine by diminishing gastrointestinal permeability supporting a positive role in migraine management.

Conclusions

Similar to migraine headache, disorders of the brain involving depression and anxiety have been demonstrated to be associated with increased gut permeability. An improvement in gut microbiota and reduction of inflammation can have positive effects on strengthening gut and brain function. Moreover, it can be inferred that probiotics may have a beneficial effect on the frequency and severity of migraine headache attacks. Large-scale randomized placebo-controlled studies are warranted in the future to evaluate the clinical efficacy and safety of probiotics in patients with migraine headache.

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