INNOVATION FOREVER
Open Access

Physical and Health Education

ISSN 3078-4662 (Online)

Research Article

Current Understanding of the Role of Gut Microbiota in the Treatment of Post-Stroke Depression

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Received: February 15, 2025 **Revised:** February 17, 2025 **Accepted:** March 1, 2025 **Published:** March 3, 2025

Abstract

Post-stroke depression (PSD) is a common complication following stroke, significantly affecting patients' quality of life and rehabilitation outcomes. Traditional treatments, including antidepressant medications and psychotherapy, often have limited efficacy due to side effects, individual variability, and long-term dependency issues. This paper explores emerging non-pharmacological therapies and multi-target interventions for PSD, with a focus on gut microbiota modulation, short-chain fatty acid (SCFA) supplementation, anti-inflammatory treatments, and dietary interventions. The gut microbiota communicates bidirectionally with the brain via the gut-brain axis, influencing mood and cognitive functions. Mechanisms include neurotransmitter regulation, immune system modulation, maintenance of gut barrier integrity, enhancement of neuroplasticity, direct action on the vagus nerve, and regulation of stress responses. Certain beneficial microbiota, such as Lactobacillus, Bifidobacterium, and Akkermansia muciniphila, have been found to alleviate depressive symptoms through these mechanisms. Recent clinical trials and animal studies support the effectiveness of gut microbiota interventions as adjunctive therapeutic strategies for PSD. However, challenges remain, including limited understanding of mechanisms, individual variability in microbiota composition, small sample sizes in studies, lack of standardized intervention protocols, and unverified long-term safety. In conclusion, while gut microbiota modulation offers a promising approach to improving PSD management, further high-quality research is needed to optimize treatment protocols and evaluate long-term outcomes.

Keywords: Post-stroke depression (PSD), gut microbiota, gut-brain axis

Citation: Zhou J, Yan W, Li X. Current Understanding of the Role of Gut Microbiota in the Treatment of Post-Stroke Depression. *Phys Health Educ*, 2025; 1: 5. DOI:10.53964/phe.2024005.

1 BACKGROUND AND RESEARCH SIGNIFICANCE

Post-stroke depression (PSD) is a common complication following stroke, with a high incidence rate and profound impacts on patients' quality of life and recovery process[1]. Traditional PSD treatments primarily include antidepressant medications and psychotherapy; however, these methods have significant limitations, such as drug side effects, individual variability in efficacy, and long-term dependency issues. Consequently, traditional treatment strategies often struggle to address these complex factors comprehensively, resulting in limited therapeutic efficacy[2]. The lack of multi-target treatment options further restricts the effectiveness of interventions for PSD.

Emerging treatment modalities for PSD currently focus on non-pharmacological therapies and multi-target interventions, including gut microbiota modulation, short-chain fatty acid (SCFA) supplementation, anti-inflammatory treatments, and dietary interventions. These approaches provide flexible and personalized psychological support,

enabling patients to better manage their emotions[3]. Through multi-level, multi-target mechanisms, these novel therapies hold promise for improving treatment efficacy while reducing the side effects associated with traditional methods, thereby offering more comprehensive rehabilitation strategies for patients.

2 RELATIONSHIP BETWEEN GUT MICROBIOTA AND THE GUT-BRAIN AXIS

The gut microbiota communicates bidirectionally with the brain via the gut-brain axis, influencing mood and cognitive functions, thereby playing a potential role in the development and progression of post-stroke depression (PSD)[4]. Specific mechanisms include:

Neurotransmitter Regulation: The gut microbiota can produce and regulate various neurotransmitters, such as serotonin, dopamine, and GABA, which directly influence brain mood and behavior. For example, Lactobacillus and Bifidobacterium can promote GABA synthesis, an inhibitory neurotransmitter that aids relaxation and alleviates anxiety, thereby helping to relieve depressive symptoms [5].

Immune System Modulation: Post-stroke patients often experience systemic inflammatory responses, and inflammation is a key factor in depressive symptoms [6]. The gut microbiota modulates immune responses to influence inflammation levels, such as by producing short-chain fatty acids (e.g., butyrate) and regulatory cytokines while reducing pro-inflammatory cytokines (e.g., IL-6, TNF-α) [7,8], thereby alleviating brain inflammation and depressive symptoms.

Maintenance of Gut Barrier Function: A healthy gut microbiota is crucial for maintaining gut barrier integrity, preventing "leaky gut" syndrome. Impaired gut barriers allow harmful substances to enter the bloodstream, triggering systemic inflammation and adversely affecting brain health [9]. Specific gut bacteria, such as Akkermansia muciniphila, promote gut barrier health by reducing toxin and inflammatory substance entry [10], indirectly lowering depression risk.

Enhancement of Neuroplasticity: Certain gut bacteria can promote the secretion of neurotrophic factors through the release of metabolites, thereby enhancing neuroplasticity [11]. Reduced neuroplasticity in post-stroke patients may hinder recovery and emotional regulation, while gut microbiota modulation can promote the formation and functional remodeling of new synapses in the brain, improving mood and cognitive functions [12].

Direct Action on the Vagus Nerve: The vagus nerve is a key pathway connecting the gut and brain. Certain gut bacteria can influence brain emotion regulation centers via the vagus nerve. For example, some probiotics (e.g., Lactobacillus) can activate the vagus nerve, stimulating the brain to release hormones and neurotransmitters associated with emotional stability, thereby exerting antidepressant effects [13].

Regulation of Stress Responses: The gut microbiota also influences the hypothalamic-pituitary-adrenal (HPA) axis, which regulates stress responses. Studies show that microbiota dysbiosis may lead to HPA axis overactivation, resulting in elevated cortisol levels and emotional disorders [14]. Restoring HPA axis balance through gut microbiota modulation may help reduce anxiety and depressive symptoms [15].

In summary, the gut microbiota influences the development of PSD through multiple mechanisms, including neurotransmitter regulation, immune response modulation, maintenance of gut barrier integrity, and enhancement of neuroplasticity. These mechanisms suggest that targeting the gut microbiota may be a promising approach for treating PSD.

3 CURRENT RESEARCH PROGRESS ON THE RELATIONSHIP BETWEEN GUT MICROBIOTA AND DEPRESSION

Research has identified specific gut microbiota that play a regulatory role in alleviating depressive symptoms. Beneficial microbiota currently identified include:

Lactobacillus: Lactobacillus can produce gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter that helps alleviate anxiety and depression. Additionally, Lactobacillus modulates inflammatory responses and reduces oxidative stress, positively impacting emotional health [16]. Studies show that Lactobacillus supplementation can alleviate depressive symptoms [17].

Bifidobacterium: Bifidobacterium promotes the production of short-chain fatty acids (e.g., butyrate), helping to reduce inflammation in the gut and brain [18]. This genus also regulates neurotransmitter production, improving serotonin levels in the brain and positively influencing mood [19].

Prevotella: Prevotella is more prevalent in healthy individuals and can produce short-chain fatty acids while supporting gut barrier function [20]. Studies suggest that Prevotella abundance is associated with better mental health, while its deficiency may correlate with worsened depressive symptoms [21].

Bacteroides: Bacteroides can produce short-chain fatty acids and other beneficial metabolites through metabolism, helping to regulate immune responses and maintain gut health [22]. This genus is associated with lower levels of anxiety and depressive symptoms, indicating its potential role in emotional stability [23].

Akkermansia muciniphila: Akkermansia muciniphila plays a key role in maintaining gut mucosal health and barrier integrity [24]. It helps reduce systemic inflammation and oxidative stress, potentially improving depressive symptoms [25].

Faecalibacterium: Specifically, butyrate-producing species within Faecalibacterium can generate significant amounts of butyrate, helping to suppress inflammatory responses and improve gut health [26]. Butyrate is believed to facilitate positive communication between the gut and brain, correlating with improved depressive symptoms [27].

Clostridium: Certain species within Clostridium (e.g., Clostridium butyricum) can promote butyrate production and modulate immune function, helping to alleviate inflammation in the brain and body, thereby potentially regulating depressive symptoms [28].

Eubacterium: Eubacterium is another butyrate-producing bacterium with anti-inflammatory and immune-modulating properties. Studies show that its metabolites positively influence mood and help reduce depressive symptoms [29].

To increase the abundance of these beneficial microbiota, the following strategies are recommended:

Probiotic Supplements: Probiotics containing specific strains such as Lactobacillus, Bifidobacterium, and Akkermansia muciniphila can directly increase the abundance of these beneficial bacteria. Multi-strain probiotic formulations may be more effective in balancing gut microbiota [30].

Prebiotics: Prebiotics, the "food" for probiotics, include dietary fibers and oligosaccharides (e.g., inulin, fructooligosaccharides), which promote the growth of beneficial bacteria such as Bifidobacterium and Lactobacillus, indirectly increasing mood-improving microbiota [31].

High-Fiber Diets: Foods rich in dietary fiber (e.g., fruits, vegetables, whole grains, legumes) can promote the growth of beneficial bacteria [32]. Specifically, fiber-degrading bacteria (e.g., Faecalibacterium, Eubacterium) can utilize fiber to produce butyrate, helping to reduce inflammation and regulate mood.

Fermented Foods: Fermented foods (e.g., yogurt, kimchi, natto, miso) contain natural probiotics, particularly Lactobacillus, which significantly contribute to gut health and mood improvement [33].

Polyphenol-Rich Foods: Foods rich in polyphenols (e.g., green tea, blueberries, dark chocolate, olive oil) can promote the growth of beneficial bacteria such as Prevotella and Bacteroides. Polyphenols are metabolized by gut bacteria into beneficial metabolites, helping to alleviate depressive symptoms [34].

Short-Chain Fatty Acid Supplements: Direct supplementation of butyrate or compounds that promote its production can support the growth of butyrate-producing bacteria such as Faecalibacterium, helping to reduce inflammation in the gut and brain while stabilizing mood [35].

Reduced Antibiotic Use: Antibiotics can disrupt gut microbiota balance and reduce the abundance of beneficial bacteria. It is recommended to avoid unnecessary antibiotic use or supplement with probiotics and prebiotics after antibiotic treatment to restore beneficial microbiota [36].

By effectively implementing these strategies, the abundance of beneficial bacteria such as Lactobacillus and Bifidobacterium can be increased, thereby improving mood and gut health and supporting the recovery of post-stroke

depression patients.

4 POTENTIAL OF GUT MICROBIOTA IN POST-STROKE DEPRESSION TREATMENT

In recent years, increasing research has explored the potential of gut microbiota interventions as adjunctive therapeutic strategies for post-stroke depression (PSD) [37]. Below are some representative findings:

Probiotic Clinical Trials: A randomized controlled trial found that supplementation with multi-strain probiotics (e.g., Lactobacillus and Bifidobacterium) significantly improved the emotional state and quality of life of stroke patients. Results showed that the probiotic group had significantly lower depression scores than the control group, indicating the potential of probiotics in alleviating PSD [38].

Gut Microbiota and Gut-Brain Axis Effects in Animal Studies: Animal model studies have shown that administering specific probiotics (e.g., Bifidobacterium and Lactobacillus) to stroke model mice can improve anxiety- and depression-like behaviors. These studies also revealed that gut microbiota interventions can alleviate post-stroke depressive symptoms by reducing brain inflammation, regulating neurotransmitters (e.g., serotonin), and mitigating immune system activation [39].

Mood Regulation by Short-Chain Fatty Acids: Some studies suggest that short-chain fatty acids (e.g., butyrate) produced by gut microbiota can improve post-stroke depressive symptoms by protecting the blood-brain barrier and reducing brain inflammation. A study on butyrate found that it can modulate hypothalamic-pituitary-adrenal (HPA) axis activity, thereby alleviating stress responses and improving emotional states.

Dietary Interventions and Microbiota Modulation: A clinical study on dietary fiber found that high-fiber diets can promote the growth of beneficial bacteria (e.g., Prevotella and Bifidobacterium), increase short-chain fatty acid production, and reduce inflammatory markers, thereby improving depressive symptoms [40]. Stroke patients receiving high-fiber dietary interventions showed improvements in emotional state and cognitive function, further supporting the potential of dietary modulation of gut microbiota.

Anti-Inflammatory Treatments and Gut Microbiota: Research also suggests that modulating gut microbiota through anti-inflammatory pathways can indirectly influence PSD. A study found that using anti-inflammatory drugs in stroke patients altered gut microbiota composition, increased the abundance of beneficial bacteria, reduced inflammatory responses, and alleviated depressive symptoms [41]. This finding supports the potential of restoring gut microbiota balance through anti-inflammatory modulation as an adjunctive therapeutic strategy.

Bidirectional Interaction Between the Vagus Nerve and Gut Microbiota: In post-stroke vagus nerve stimulation experiments, stimulating the vagus nerve modulated gut microbiota composition, increased the abundance of Lactobacillus and Bifidobacterium, and improved depressive symptoms [42]. The vagus nerve plays a key bidirectional regulatory role in the gut-brain axis, suggesting that modulating gut microbiota may positively influence brain function through this pathway.

Combined Probiotic and Psychological Interventions: Some trials have explored combined probiotic and psychological interventions. In these studies, patients receiving probiotic supplementation showed significantly enhanced effects from psychological interventions (e.g., cognitive behavioral therapy), indicating that gut microbiota modulation may improve the efficacy of psychological treatments [43]. This combined approach not only alleviated depressive symptoms but also reduced the need for antidepressant medications.

These studies suggest that gut microbiota interventions may serve as a promising adjunctive therapeutic strategy for managing post-stroke depression by modulating multiple pathways within the gut-brain axis, including reducing inflammation, regulating neurotransmitters, and enhancing vagus nerve activity. However, further clinical research is needed to fully validate their safety and efficacy.

5 RESEARCH GAPS AND PAPER OBJECTIVES

Although gut microbiota interventions show potential efficacy in post-stroke depression (PSD) patients, several limitations and challenges remain, including:

Limited Mechanistic Understanding: Although some studies suggest that gut microbiota interventions can alleviate depressive symptoms via the gut-brain axis, the specific molecular and cellular mechanisms remain incompletely understood [44]. Further research is needed to identify which microbial populations critically influence the nervous system and their mechanisms of action.

Individual Variability: Gut microbiota composition varies significantly among individuals [45], meaning that the same probiotics or prebiotics may yield different effects in different patients. Factors such as dietary habits, lifestyle, and genetic background may influence the efficacy of microbiota interventions, leading to inconsistent treatment outcomes.

Small Sample Sizes: Most current studies on gut microbiota interventions have small sample sizes, resulting in limited statistical significance and generalizability of findings [46]. This limitation hinders the extrapolation of conclusions and makes it difficult to accurately assess the efficacy of gut microbiota interventions for PSD.

Lack of Standardized Intervention Protocols: Gut microbiota intervention methods are diverse, including probiotics, prebiotics, dietary fibers, and fermented foods, but intervention protocols vary widely across studies. For example, the probiotic strains, dosages, and intervention durations used differ, leading to a lack of standardization and affecting the comparability and reproducibility of results.

Unverified Long-Term Safety and Efficacy: Many studies focus on short-term effects, with insufficient validation of the long-term safety, potential side effects, or risks of dependency on gut microbiota modulation [47]. Long-term safety is particularly important for stroke patients.

Unclear Synergistic Effects with Traditional Treatments: It remains unclear whether gut microbiota interventions can enhance the efficacy of antidepressant medications or psychotherapy. There is a lack of research on combined therapies. Additionally, the effects of different medications on gut microbiota are not fully explored, and unknown interactions between microbiota interventions and drug treatments may exist [48].

Limitations in Detection and Analysis Technologies: The complexity of gut microbiota structure and function makes it difficult for current detection and analysis technologies to fully elucidate changes in microbiota composition and metabolites, hindering accurate measurement of intervention efficacy. These technological limitations may introduce bias and affect the accuracy of conclusions [49].

Patient Compliance Issues: Gut microbiota interventions require patients to consistently consume specific probiotics or prebiotics or adjust dietary patterns, but many patients struggle to adhere to these changes long-term, especially when effects are not immediately apparent. This may negatively impact intervention outcomes [50].

Ethical and Regulatory Challenges: For more direct interventions such as fecal microbiota transplantation, safety and efficacy raise ethical concerns. Additionally, regulatory policies for gut microbiota-related products are not yet well-established, and standardized quality control measures are lacking.

Addressing these challenges is crucial for advancing gut microbiota interventions as effective adjunctive therapies for post-stroke depression.

6 SUMMARY

In conclusion, although gut microbiota interventions show potential advantages in treating post-stroke depression, they face numerous challenges, including unclear mechanisms, significant individual variability, lack of standardization, and unknown long-term safety. Future research should focus on conducting more high-quality clinical trials and basic studies to optimize intervention protocols, identify target populations, standardize treatment methods, and evaluate long-term outcomes.

Acknowledgements

Not applicable.

Conflicts of Interest

The authors declared no conflict of interest.

Author Contribution

The author contributed to the manuscript and approved the final version.

Data Availability

Data sharing is not applicable to this review as no datasets were generated or analyzed during the current study.

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