# Advances in Research on Gut Microbiota and Heart Failure Comorbid with Depression (Post-print)

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## Abstract

Patients with heart failure are prone to depression, and these two conditions mutually influence each other, resulting in reduced quality of life and poor prognosis. The gut microbiota, as the largest microecosystem in the human body, undergoes alterations in composition, structure, and function that are closely correlated with host physiological and pathological states. Currently, the "gut-heart/brain axis" has been utilized to explain the link between gut microorganisms, vascular diseases, and emotional states, serving as an important comorbidity basis for heart failure and depression. This review summarizes the mechanisms by which gut microbes, metabolites, the vagus nerve, and other factors contribute to the pathogenesis and progression of heart failure and depression, and proposes that interventions such as the Mediterranean diet, probiotics, and fecal microbiota transplantation hold potential for modulating the microbiota-gut-heart/brain axis, thereby offering a novel therapeutic target for heart failure patients with comorbid depression.

## Full Text

### Advances in Gut Microbiota Research in Heart Failure Comorbid with Depression

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**Abstract**

Heart failure patients are prone to developing depression, and these two conditions interact reciprocally, leading to reduced quality of life and poor prognosis. As the largest microecosystem in the human body, alterations in the composition, structure, and function of gut microbiota are closely associated with host physiological and pathological states. The "gut-heart/brain axis" has emerged as a framework for understanding the connections between gut microbes, vascular disease, and mood states, representing an important comorbidity basis for heart failure and depression. This review summarizes the mechanisms through which gut microbiota, their metabolites, and the vagus nerve contribute to the development and progression of heart failure and depression. We propose that Mediterranean diet, probiotics, and fecal microbiota transplantation hold potential for modulating the microbiota-gut-heart/brain axis, offering novel therapeutic entry points for heart failure patients with comorbid depression.

**Keywords:** Heart failure; Depression; Gut microbiota; Metabolite; Review

## 1. Literature Search Strategy

We conducted a comprehensive literature search using the following English terms: "Heart failure" and "Depression," "Heart failure" and "Gut microbiota," "Depression" and "Gut microbiota," "Heart failure" and "Metabolite," and "Depression" and "Metabolite" in PubMed and Web of Science databases. Chinese databases (CNKI and Wanfang Data Knowledge Service Platform) were searched using corresponding Chinese terms. The search period spanned from January 2008 to March 2023. Inclusion criteria comprised: (1) studies investigating associations between gut microbiota/metabolites and heart failure or depression; (2) literature with robust arguments and evidence closely related to the topic. Exclusion criteria included: (1) studies with low thematic relevance; (2) literature with poor logical rigor and credibility. A total of 76 relevant articles were ultimately included.

## 2. Gut Microbiota

The human intestine harbors a dynamic and complex microecosystem containing approximately 1$×10^{14}$ bacteria from hundreds of different species. The normal gut microbiota is primarily composed of six bacterial phyla: Bacteroidetes, Firmicutes, Proteobacteria, Actinobacteria, Fusobacteria, and Verrucomicrobia. The structure and proportions of these microbial communities vary among individuals, with diversity primarily influenced by host factors (genetic variation, age, and sex) and environmental factors (lifestyle, diet, and antibiotic use). Gut microbiota participate in food digestion and absorption through two main metabolic pathways: saccharolytic and proteolytic fermentation. In the saccharolytic pathway, microbes ferment dietary fibers that are otherwise

indigestible to the host, producing the majority of short-chain fatty acids (SCFAs) and small amounts of branch-chain fatty acids (BCFAs). The proteolytic pathway generates not only SCFAs and BCFAs but also various bioactive compounds including ammonia, amines, thiols, phenols, and indoles. Beyond aiding digestion, gut microbiota influence host physiology through multiple mechanisms, such as regulating intestinal mucosal barrier function, assisting immune tissue activation, modulating antigen tolerance to gut contents, and preventing pathogen proliferation. Furthermore, through various signaling molecules, gut microbes interact with pattern recognition receptors on the intestinal mucosal surface, triggering multiple downstream signaling cascades that stimulate inflammatory or anti-inflammatory immune responses. Consequently, dysbiosis serves as a driving force in the pathogenesis of numerous diseases.

## 3. Gut Microbial Dysbiosis in Heart Failure and Depression

Recent studies have demonstrated that gut microbiota and their metabolites participate in the development of cardiovascular and psychiatric disorders through the gut-heart or gut-brain axis. This section reviews alterations in gut microbiota and their metabolites in heart failure and depression patients, aiming to strengthen the theoretical foundation of the "gut-heart/brain axis" and provide novel insights for clinically identifying and alleviating depressive symptoms in heart failure patients.

**3.1 Alterations in Microbial Diversity** Advances in 16S rRNA and metagenomic sequencing technologies have enabled comprehensive characterization of gut microecological changes in heart failure and depression. Early research revealed that compared with healthy individuals, heart failure patients exhibit reduced gut microbial diversity and translocation of major microbial populations, with significant depletion of Coriobacteriaceae, Erysipelotrichaceae, and Ruminococcaceae. Subsequent omics studies further confirmed that heart failure patients show markedly decreased abundance of beneficial bacteria (butyrate-producing bacteria and lactobacilli) and increased abundance of pathogenic bacteria (Collinsella, Campylobacter, and Shigella). Similarly, depression is associated with intestinal dysbiosis. YANG et al. identified through metagenomic sequencing that major depressive disorder patients harbor altered phage and bacterial species, with reduced abundance of Blautia and Eubacterium significantly correlating with depressive symptoms. A meta-analysis further demonstrated enrichment of Bacteroides, Parabacteroides, and Barnesiella in depressed patients, while Firmicutes, Oscillospiraceae (UCG 003, UCG 002), and common Bacteroides were significantly depleted. Importantly, KELLY et al. showed that transplantation of "depression-associated microbiota" into germ-free mice induced depressive-like behaviors and characteristics, including anhedonia and despair. Collectively, these findings indicate that specific microbial alterations are associated with disease susceptibility in heart failure or depression.

**3.2 Short-Chain Fatty Acids (SCFAs)** SCFAs, primarily produced by beneficial gut bacteria through dietary fiber metabolism, participate in numerous biological processes both within the intestine and systemically (cardiovascular system, brain, etc.). Research indicates that SCFAs can bind G protein-coupled receptors to mediate blood pressure changes through endothelium-dependent mechanisms. Another study demonstrated that reduced mitochondrial carnitine palmitoyltransferase 1 activity in heart failure patients impairs long-chain fatty acid oxidation, whereas SCFA-related energy metabolism, independent of this pathway, can serve as an alternative carbon source for oxidative ATP production. A clinical study revealed that compared with non-depressed individuals, depressed patients exhibit significantly lower intestinal concentrations of acetate and propionate, with propionate levels negatively correlating with depression scores after propensity matching. SONG et al. found that intestinal propionate or butyrate can cross the blood-brain barrier to reduce microglial activation in germ-free mice, promote brain Ac-H3K9 expression, and ameliorate neuroinflammation and depressive symptoms. Additionally, SCFAs can function as signaling molecules to influence white adipose tissue, pancreatic islet cells, and inflammatory response cells, thereby participating in the pathogenesis of heart failure and depression.

**3.3 Trimethylamine N-Oxide (TMAO)** TMAO is a common gut-derived metabolite primarily generated through the metabolism of choline via gut microbial cleavage and hepatic flavin monooxygenase oxidation. In 2014, researchers first observed elevated plasma TMAO levels in heart failure patients, with high TMAO levels independently associated with increased all-cause mortality risk (HR=2.2, 95%CI=1.42-3.43, P<0.001). Subsequent preclinical experiments demonstrated that TMAO can directly exacerbate heart failure progression by inducing myocardial fibrosis, endothelial inflammation, and cardiac mitochondrial dysfunction. Recent studies have found significantly elevated plasma TMAO in post-myocardial infarction patients with severe mental disorders. Moreover, TMAO can reduce tight junction protein expression at the blood-brain barrier, stimulate microglial activation and neuroinflammation, and further aggravate cognitive dysfunction.

**3.4 Tryptophan** Tryptophan, an essential amino acid regulated directly or indirectly by gut microbiota, yields metabolites with immunomodulatory, metabolic, and neuroregulatory functions. Over 90% of serotonin is produced from tryptophan by intestinal enterochromaffin cells, which communicate with brainstem neurons through gut vagal synaptic receptors to exert antidepressant effects. LUKIĆ et al. observed significantly reduced tryptophan and serotonin levels in the hippocampus and prefrontal cortex of germ-free mice, accompanied by increased depressive behaviors. Additionally, gut microbiota can promote indoleamine 2,3-dioxygenase 1 expression, affecting the tryptophan-kynurenine metabolic pathway and leading to elevated circulating kynurenine levels that induce depressive-like behaviors. Notably, circulating kynurenine and

its metabolites can impair endothelium-dependent vasodilation and induce oxidative stress, contributing to cardiovascular disease development. A clinical study observed positive correlations between serum kynurenine levels and high-sensitivity C-reactive protein and leukocyte counts in chronic heart failure patients, with univariate regression analysis indicating that serum kynurenine could predict adverse cardiovascular events after hospital discharge (HR=1.43, P=0.033).

**3.5 Lipopolysaccharide (LPS)** LPS, a unique component of Gram-negative bacterial cell walls, is released into the intestinal microenvironment and enters the circulation following microbial death and lysis. Consistent with the heart failure-gut hypothesis, LPS levels are significantly elevated in the blood of decompensated heart failure patients, and this heart failure-associated endotoxemia may contribute to systemic inflammation. LPS can induce cardiac inflammation through stimulation of mitochondrial dysfunction and macrophage polarization. QIN et al. found that LPS activates microglia and increases glutaminase synthesis, leading to hyperactivation of the hypothalamic-pituitary-adrenal axis in depression. Furthermore, a recent animal study demonstrated that LPS can exacerbate neuroinflammation in post-heart failure rats through Toll-like receptor 4, representing a potential mechanism underlying heart failure-depression comorbidity.

**3.6 $\gamma$-Aminobutyric Acid (GABA)** GABA is an important neurotransmitter derived from the gut, primarily synthesized through glutamate metabolism in food. CHEN et al. found that exogenous GABA supplementation could inhibit the cardiac Bax/Bak apoptotic pathway and attenuate cardiomyocyte apoptosis in spontaneously hypertensive rats. Studies have shown that inhibition of central GABAergic neurons in left ventricular hypertrophy rats further mediates autonomic nervous dysfunction, increasing myocardial workload and accelerating heart failure progression. Conversely, GABA also participates in depression pathogenesis. STRANDWITZ et al. identified through 16S rRNA analysis that reduced levels of GABA-producing bacteria are closely associated with depression. Notably, enhancing GABAergic neuronal activity and increasing GABA neurotransmitter levels have shown promising antidepressant effects in animal models. Collectively, gut GABA metabolism is intimately involved in heart failure-depression comorbidity.

## 4. Vagal Nerve Pathway

The vagus nerve represents a crucial information regulation pathway in the "gut-brain axis,"and its disruption or dysfunction may lead to mental disorders affecting cognition, behavior, and emotion. NEUFELD et al. found that compared with mice with intact gut microecology, germ-free mice exhibit hyperresponsiveness of the hypothalamic-pituitary-adrenal axis after stress, with elevated circulating cortisol levels. Additionally, the severity of depressive symptoms in heart failure patients correlates with immune migration in peripheral blood

mononuclear cells, which increases $\beta$-adrenergic receptor sensitivity. Elevated cortisol levels and enhanced $\beta$-adrenergic receptor sensitivity reduce vagal tone, further exacerbating peripheral and central inflammation. Given that SCFA receptors, neurotransmitter receptors, and intestinal peptides are abundantly expressed in vagal afferents, the vagal pathway may participate in the remote regulation of cardiac and cerebral functions by gut-derived metabolic molecules. Notably, the anxiolytic and central neuroreceptor-modulating effects of probiotics such as *Bifidobacterium longum* in mice depend on vagal afferent signaling. Furthermore, HAN et al. confirmed through neuronal projection and labeling that the lateral parabrachial nucleus pathway regulated by intestinal vagal afferents plays a key role in reward behavior and dopamine activity.

## 5. Modulating Gut Microecology

Gut microecological imbalance is closely associated with the development and progression of heart failure and depression. Restoring microbial structure and improving the microbiota-gut-heart/brain axis provides novel therapeutic entry points for heart failure patients with comorbid depression. This section explores the feasibility of treating heart failure-depression comorbidity through gut microbiota modulation, focusing on Mediterranean diet, probiotics, prebiotics, and fecal microbiota transplantation.

**5.1 Mediterranean Diet** The Mediterranean diet is a dietary pattern recommended by modern nutrition science, emphasizing intake of dietary fiber, unsaturated fatty acids, and high-quality protein. The 2019 consensus statement from the Heart Failure Society of America emphasized that the Mediterranean dietary pattern is an appropriate and beneficial choice for patients at risk for or diagnosed with heart failure. A multicenter intervention study found that heart failure patients adhering to the Mediterranean diet demonstrated better cardiopulmonary function and activity willingness. Additionally, WALKER et al. evaluated Framingham Heart Study data and found that adherence to the Mediterranean diet helps maintain neurocognitive health and attenuates cardiac remodeling. Similarly, a case-control study revealed that high adherence to the Mediterranean diet in patients with anxiety or depression was negatively associated with acute myocardial infarction and other cardiovascular events, suggesting that the Mediterranean diet may be a significant protective factor for patients with comorbid cardiovascular disease and depression.

**5.2 Probiotics** Probiotics are live microorganisms that confer health benefits when consumed in adequate amounts, including *Lactobacillus*, butyrate-producing bacteria, and *Lactobacillus rhamnosus*. A meta-analysis showed that probiotic administration significantly reduced depression scores in subjects (95%CI=-0.51 to -0.09, P=0.005). Another study found that feeding *Lactobacillus rhamnosus* for six weeks significantly enhanced GABA receptor gene expression in the brains of experimental mice, promoting cerebral GABA secretion and alleviating anxiety- and depression-related behaviors. Similarly,

*Lactobacillus rhamnosus* supplementation attenuated left ventricular hypertrophy and improved left ventricular systolic and diastolic function in rats with ischemic heart failure, with benefits persisting long after discontinuation. However, despite progress in adjuvant probiotic therapy, factors such as dosage, administration duration, and drug interactions require further investigation.

**5.3 Prebiotics** Prebiotics are dietary supplements that selectively stimulate the activity and growth of gut microbiota to confer beneficial effects on the host. An animal study demonstrated that a fermented wheat bran-based prebiotic complex stimulated intestinal lactobacilli growth in heart failure rats, improving gut dysbiosis and attenuating endotoxemia. Additionally, galactans reduced myocardial injury and improved ventricular remodeling in myocardial infarction rats by inhibiting apoptotic cascades. A randomized controlled study showed that inulin supplementation assisted *Lactobacillus rhamnosus* in reducing circulating inflammatory factor levels and depression scores in coronary artery disease patients. Similarly, okra polysaccharide ameliorated chronic stress-induced depressive-like behaviors by relieving gut dysbiosis and reducing inflammatory levels in the colon, serum, and hippocampus.

**5.4 Fecal Microbiota Transplantation** Fecal microbiota transplantation reshapes microbial structure by implanting functional microbiota from healthy donors to assist disease treatment. Animal studies have shown that microbiota transplantation alleviates depressive-like behaviors by restoring serotonin levels and inhibiting glial cell activation. Clinical trials demonstrated that compared with placebo, fecal microbiota transplantation improved gut diversity and significantly reduced depression scores. In cardiovascular disease, ZHANG et al. found that gut microecology and atrial inflammasome activity in aged rats susceptible to atrial fibrillation could be restored through transplantation of young rats' healthy microbiota, thereby preventing atrial fibrillation development. Additionally, ZHONG et al. confirmed that washed microbiota transplantation effectively lowered blood pressure in hypertensive patients, with antihypertensive effects lasting longer than conventional oral medications. Unfortunately, no animal or clinical trials of fecal microbiota transplantation have been conducted specifically in heart failure-depression comorbidity, necessitating further research to advance microbiota-based therapies for this patient population.

## Conclusion

Growing research has elucidated the mechanisms through which gut microbiota participate in heart failure-depression comorbidity, with modulation of the "gut-heart/brain axis"offering novel therapeutic approaches. In heart failure, reduced intestinal perfusion and barrier disruption lead to dysbiosis and metabolic disturbances of various gut-derived products, including decreased SCFAs, tryptophan, and GABA, and increased LPS and TMAO. These metabolites directly or indirectly (via vagal pathways) trigger peripheral and neuroinflammation,

cardiomyocyte oxidative stress, and glial cell activation, thereby worsening cardiac function and inducing depressive behaviors. Conversely, depression further exacerbates microbial dysbiosis, creating a vicious cycle. While Mediterranean diet, probiotics, prebiotics, and fecal microbiota transplantation have shown promising therapeutic effects in heart failure or depression, their specific mechanisms and potential adverse effects remain unclear. Future research must clarify and establish the relationship network of the "microbiota-gut-heart/brain axis" to enable microbiota-based interventions that improve clinical symptoms and prognosis in heart failure patients with comorbid depression.

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*Note: Figure translations are in progress. See original paper for figures.*