Gastrointestinal Microbiome and related metabolites in Depression and Antidepressants - a comprehensive review

Yan-Li Lu¹, Tao Jiang², Jia-Jia Duan³

¹Yan-Li Lu and Tao Jiang are the co-first authors of this paper.

¹College of Basic Medicine and Forensic Medicine, Henan University of Science and Technology, Luoyang 471003, China. ²Department of Clinical Laboratory, The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China.

³Corresponding to: Jia-Jia Duan, Department of Clinical Laboratory, The First Affiliated Hospital of Henan University of Science and Technology, No. 24, Jinghua Road, Jianxi District, Luoyang 471003, China. E-mail: jane4123@126.com.

Author contributions
Yan-Li Lu and Jia-Jia Duan conceived this article, carried out the literature research and wrote the manuscript. Yan-Li Lu, Jia-Jia Duan and Tao Jiang reviewed and edited before submission. All authors read and approved the final manuscript.

Competing interests
The authors declare no conflicts of interest.

Acknowledgments
This project was supported by Natural Science Foundation of Henan Province of China (Grant No. 232300420266).

Peer review information
Life Research thanks Weam Saad Al-Hamadany, Yi-Ran Sun and other anonymous reviewers for their contribution to the peer review of this paper.

Abbreviations
TCAs, tricylic antidepressant agents; SSRIs, Selective Serotonin Reuptake Inhibitors; MAOIs, monoamine oxidase inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; TCM, Traditional Chinese Medicine; YS, XiaoYaQiaoSan; PBR, The Low Polarity Fraction Of Bupleuri Radix; SCFAs, Short-Chain Fatty Acids; CUMS, Chronic Unpredictable Mild Stress; MDD, Major Depressive Disorder; BDNF, Brain-Derived Neurotrophic Factor; 5-HT, 5-Hydroxytryptamine; GABA, Gamma-Aminobutyric Acid; BAs, Bile Acids; FXR, Farnesoid X receptor.

Citation

Executive editor: Shan-Shan He.
Received: 21 June 2023; Accepted: 20 July 2023; Available online: 22 July 2023.
© 2023 By Author(s). Published by TMR Publishing Group Limited. This is an open access article under the CC-BY license.

Abstract
Depression, a prevalent mood disorder, has emerged as a significant health concern in society. While the exact cause of depression remains incompletely understood, there is substantial evidence linking the gastrointestinal microbiome and its metabolites to this condition. Through combined multi-omics analysis, it has been observed that the composition of the gastrointestinal microbiome, including Firmicutes, Bacteroidetes, and Actinobacteria, undergoes significant alterations in depressed individuals. Moreover, the production of short-chain fatty acids, tryptophan, and bile acids by these gut microbes is also found to be modified in depression. Furthermore, studies have demonstrated that antidepressant medications exert their therapeutic effects by interacting with the gastrointestinal microbiome and their metabolites. This review provides an overview of the association between the gastrointestinal microbiome, related metabolites, and depression. It highlights the potential of these factors to serve as mechanisms of action for antidepressant medications. Additionally, the review summarizes the commonly used technical tools in depression research.

Keywords: Gastrointestinal microbiome; Metabolomics; Antidepressants; Depressive disorder; Traditional Chinese medicine

Submit a manuscript: https://www.tmrjournals.com/lr
Introduction

Depression is a chronic and recurrent emotional disorder that often presents clinically as persistent melancholy, lack of concentration, disrupted sleep, and loss of appetite [1, 2]. The increasing morbidity and mortality linked to depression have resulted in heightened awareness of the condition in recent years. Diagnostic techniques currently available include psychiatric consultations, psychological assessments, laboratory tests, and imaging studies. According to the World Health Organization, over 350 million people worldwide suffer from depression, but many remain undiagnosed due to factors such as inadequate treatment options, the stigma surrounding the illness, and societal reluctance to accept depression [3].

Although the exact cause of depression is still unidentified, it is generally agreed that environmental, immunological, and genetic factors all play a role [4]. The conventional first-line clinical medications primarily consist of tricyclic antidepressant agents (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs). Existing antidepressant medications have shown success in clinical treatment. Traditional Chinese medicine (TCM) has recently garnered attention due to its effectiveness and minimal negative side effects. The traditional Chinese medicine tansii liquid is commonly used to treat depression, and other herbal elements including xiaoyaosan (XYX), the low polarity fraction of Bupleuri Radix (PBR), and Saffron extract have also been found to have antidepressant effects [4]. In-depth research on antidepressant medications in the realm of Chinese medicine has opened up a novel route for treating depression [5, 6].

To establish a strong and reliable theoretical basis for therapeutic treatment, additional research into the relevant signaling pathways and key targets is required, as the exact mechanisms of action of different antidepressant drugs remain unclear. Numerous studies have indicated a close relationship between the gastrointestinal microbiome, their associated metabolites, and the mechanism of action of antidepressants [3, 4, 7, 8]. With the advancements in high-throughput omics technology, our understanding of the composition, metabolism, and intricate communication networks of the gut microbiota and the gut-brain axis is rapidly expanding [9].

The complex and diverse gut microbiota is composed of over 100 trillion bacterial cells, which is 1.3 times the number of human cells [10]. The majority of gut bacteria are either harmless or beneficial to the body [11]. For instance, they provide protection against enteropathogens, obtain nutrients and energy from food, and contribute to healthy immune function [12–16]. Recent research has also revealed potential negative consequences of gut microbiota, including the acceleration of neurodegenerative disease development. A critical link between gut microbes and depression is the microbiota-gut-brain axis, which facilitates bidirectional communication between the gut and the brain [9, 17]. The gut microbiota has emerged as a highly promising target for alleviating depressive disorders, supported by, and antidepressant medications may have antidepressant effects by modulating the composition and metabolism of gut microbes [18].

Metabolic disorders have been reported as new features of depression, commonly observed in the plasma/serum and central nervous systems of depressed patients [19]. A wide range of metabolites, primarily Short-Chain Fatty Acids (SCFAs), trimethylamines, amino acid derivatives, and vitamins, are produced when the gut microbiota converts dietary components. These metabolites participate in various metabolic processes, possess a wide range of enzymatic functions, and regulate host homeostasis, significantly influencing human functioning [9, 18]. Several endogenous metabolites have been identified as potential biomarkers of depression, and other investigations have pointed out a potential link between metabolites related to gut microbes and the onset of depression [18, 20]. Consequently, the metabolites associated with gut bacteria may serve as targets for the action of antidepressant medications; however, further research is necessary to elucidate the underlying mechanisms of these treatments.

This review focuses on the gastrointestinal microbiome and its related metabolites in depression and antidepressants. It describes the relationship between the gastrointestinal microbiome and depression, summarizes the research progress on therapeutic agents based on the gastrointestinal microbiome and related metabolites, and provides an overview of the most popular research methodologies (Figure 1).

**Figure 1** Schematic representation of the relationship among the gastrointestinal microbiome and related metabolites, depression, and antidepressants. The levels and types of gastrointestinal microbiome and related metabolites in patients with depression may change. Antidepressants also play an antidepressant role by altering the gastrointestinal microbiome and related metabolites. Generally, multi-omics combined analysis, including 16S rRNA gene sequencing, metagenomics, and metabolomics analysis, is used to obtain these alterations.

Submit a manuscript: https://www.tmrjournals.com/lr
By considering the specific mechanisms currently known and the changes in the gastrointestinal microbiome and related metabolites caused by antidepressants, we aim to clarify the specific mechanism of action of various antidepressants. This will provide new theoretical support for the treatment of depression.

During the literature search, we utilized the keywords gastrointestinal microbiome, metabolomics, antidepressants, depressive disorder, and traditional Chinese medicine. The publication year of the retrieved literature ranged from 1981 to 2023, ensuring a comprehensive selection of relevant articles. We conducted our search on the PubMed and Web of Science databases. The inclusion and exclusion criteria for the literature were as follows: (i) Articles had to be written in English; (ii) We included both review articles and research articles; (iii) The articles focused on either human or rodent subjects; (iv) We carefully checked the retrieved articles and removed any duplicates.

Depression and gut microbes

The microbial community in the human body consists of various microorganisms, including bacteria, archaea, fungi, and viruses. The majority of these microorganisms reside in the gastrointestinal tract and are commonly referred to as the gut microbiota [21]. The gut microbiota is composed of over 1014 microorganisms, with genomes that are over 450 times larger than those of humans [22]. It is influenced by both exogenous factors (such as drugs and nutrition) and endogenous factors (such as sex and age) [23]. The major phyla within the gut microbiota are Firmicutes and Bacteroidetes, while Proteobacteria, Actinobacteria, Verrucomicrobia, and Fusobacteria are secondary phyla [24–26].

The stability and diversity of the human gut microbiota are closely associated with host health and play a vital role in maintaining homeostasis through various pathways. A growing body of clinical and preclinical studies has demonstrated a strong link between alterations in the gut microbiota and the onset and progression of depression. For example, probiotics have shown potential in the treatment of depression, while gut dysbiosis worsens depressive behavior and contributes to cognitive impairment [27]. Researchers have also conducted experiments where they transferred fecal microbiota from stressed donors to naive mice, resulting in the spread of depressive behavioral symptoms [28]. Another study found that fecal microbiota transplantation from NLRP3 KO mice significantly improved depression-like behavior induced by chronic unpredictable stress in recipient mice [29]. The pathological mechanisms involved in this relationship include changes in microbial composition, metabolites, disruption of gut barrier integrity (such as reduced expression of tight junction proteins like Claudin-5 and occludin proteins in the gastrointestinal tract), loss of goblet cells, and the entry of pathobionts and toxic metabolites into the circulation, leading to chronic local and systemic inflammatory responses [23]. The relationship between the gut microbiota and depression is further detailed below, with specific studies summarized in Table 1.

### Table 1 The drugs used in the research institute, and the changes in gastrointestinal microbiome and related metabolites

<table>
<thead>
<tr>
<th>Interventional drugs</th>
<th>Drug dosage</th>
<th>Research object</th>
<th>Microbial changes (compared with the control group)</th>
<th>Metabolite changes (compared with the control group)</th>
<th>Technology used</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupleuri Radix</td>
<td>Venlafaxine</td>
<td>male SD (sprague dawley) rats N = 24</td>
<td>CUMS group: Bacteroides†, enrich Lactobacillaceae, Lactobacillus, Conomamonadaceae, Betaproteobacteria, Oxalobacteraceae, Capriavidus, Bifidobacterium, Bifidobacteriaceae etc.</td>
<td>CUMS group: spermindine and exonolone†, Kyurenic acid, taurocholic acid, 1beta-Hydroxycholic acid, benzoic acid, taurochenodeoxycholic acid, and cholic acid†</td>
<td>16S rRNA gene sequencing multi-omics combined analysis</td>
<td>[4]</td>
</tr>
<tr>
<td>Tiansi Liquid</td>
<td>Tiansi Liquid</td>
<td>male SD rats N = 30</td>
<td>Ruminococcaceae, Lactococcus, and Lactobacillus†</td>
<td>PRR group: 16 metabolites can be restored to near normal levels.</td>
<td>tryptophan 2.3 dioxygenase, indoleamine 2.3-dioxygenase, and quinolone† kyurenic acid and 5-HT†</td>
<td>metabolomics analysis 16S rRNA gene sequencing</td>
</tr>
<tr>
<td>Xiaoyaosan</td>
<td>Venlafaxine</td>
<td>male SD rats N = 24</td>
<td>CUMS group: Firmicutes, Lactobacillus, Sphingomonas, and Lactococcus†, Actinobacteria, Corynebacterium, Psychrobacter, and Jeotgallicoccus†</td>
<td>CUMS group: alanine, proline, lactate, valine, glycine, mannitol, and choline† Xiaoyaosan group: restore to the control group level.</td>
<td>metabolomics analysis 16S rRNA gene sequencing</td>
<td>[8]</td>
</tr>
<tr>
<td>Bifidobacterium breve</td>
<td>FHLJDQ3M5 and CCFM1025</td>
<td>male C57BL/6 mice N = 32</td>
<td>CCFM1025 group and FHLJDQ3M5 group: Allobaculum†, Bacteroides and Staphylococcus†</td>
<td>CCFM1025 group: synthesis of glutamate and tryptophan†, synthesis of histamine and propionate†, FHLJDQ3M5 group: degradation of acetate, tryptophan, and propionate† synthesis of quinolinic acid†</td>
<td>metabolomics analysis 16S rRNA gene sequencing</td>
<td>[18]</td>
</tr>
</tbody>
</table>

Submit a manuscript: https://www.tmrjournals.com/lr

**Life Research** 2023;6(3):17. https://doi.org/10.53388/LR20230016
Table 1 The drugs used in the research institute, and the changes in gastrointestinal microbiome and related metabolites (continued)

<table>
<thead>
<tr>
<th>Intervenional drugs</th>
<th>Drug dosage (mg/kg)</th>
<th>Research object</th>
<th>Microbial changes (compared with the control group)</th>
<th>Metabolite changes (compared with the control group)</th>
<th>Technology used</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaP (sodium propionate)</td>
<td>CUMS + NaP group: 1mL of NaP (200mmol/L) in PBS (pH = 7.4)</td>
<td>male SD rats</td>
<td>MDD patients: Bilophila and Alistipes† Anasorutus and Dialister</td>
<td>CUMS group: propionic acid↓ NE, DA, TRP, 5-HIAA, and 3-MA</td>
<td>metabolomics analysis</td>
<td>[20]</td>
</tr>
<tr>
<td></td>
<td>CUMS + PBS group: equivalent PBS</td>
<td>N = 50 (initial)</td>
<td>MDD patients: Bacteroides, Parabacteroides, Butyricimonas, Acetatifactor, and Tyszerella†</td>
<td>CUMS + NaP group: The above metabolites recovered compared to the CUMS group.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MDD patients</td>
<td>N = 68</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>healthy population</td>
<td>N = 45</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>germ-free mice</td>
<td>specific pathogen free mice</td>
<td>MDD patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>healthy subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>Ketamine: 30 mg/kg</td>
<td>mice</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>inosine metabolites and Precursors of excitatory neurotransmitters↓ adenosine metabolites, guanosine metabolites, precursors of inhibitory neurotransmitters, AMP and ATP↑</td>
<td></td>
<td>metabolomics analysis</td>
<td>[32]</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Fluoxetine: 10 mg/kg</td>
<td>female rats</td>
<td>Prevotella and Ruminococcus†</td>
<td>isobutyric acid↓ affects the concentration of multiple amino acids.</td>
<td>metabolomics analysis</td>
<td>[34]</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Ami: 25 mg/kg/d</td>
<td>Adult male SD rats</td>
<td>compared to the CUMS group, Ami treatment group and Flu treatment group: Fimbicutes and Ruminococaceae, UCG-014† Bacteroides, Parabacteroides, Butyricimonas, Acetatifactor, and Tyszerella†</td>
<td>compared to the CUMS group, Ami treatment group: the metabolism of glycine, serine and threonine↓ the metabolism of terpenoids and polyketides↓</td>
<td>16S rRNA gene sequencing</td>
<td>[33]</td>
</tr>
<tr>
<td>Fluoxetine vehicle</td>
<td>Fluoxetine: 10 mg/kg</td>
<td>female rats N = 32</td>
<td></td>
<td></td>
<td>metabolomics analysis</td>
<td>[34]</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Venlafaxine: 12.5 mg/kg</td>
<td>male C57BL/6 mice</td>
<td>CUMS group: reduced diversity and abundance of gut microbiota. Venlafaxine group: restoration of gut microbiota diversity.</td>
<td>Venlafaxine group: Venlafaxine restored the changes of 5-HT, 5-HIAA and Glu levels in CUMS mice.</td>
<td>16S rRNA gene sequencing</td>
<td>[35]</td>
</tr>
<tr>
<td>Xiaoyaosan</td>
<td>One dose per day</td>
<td>depression patients</td>
<td>N = 16</td>
<td>Xiaoyaosan group: The levels of alanine, lactate, glutamine, and choline in depression patients have returned to normal levels.</td>
<td>metabolomics analysis</td>
<td>[36]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>healthy volunteer</td>
<td>N = 16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTE Fluoxetine</td>
<td>Fluoxetine: 10 mg/kg</td>
<td>male SD rats N = 40</td>
<td>Bacteroides, Weissella, and Parabacteroides† Ruminococcus and Deinococcus†</td>
<td>CTE group: the expression levels of 5-HT and BDNF are restored, and the expression of SCFA is affected.</td>
<td>16S rRNA gene sequencing</td>
<td>[37]</td>
</tr>
<tr>
<td></td>
<td>High dose CTE: 400 mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low dose CTE: 200 mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD, Sprague Dawley; CUMS, chronic unpredictable mild stress; MDD, major depressive disorder; Ami, Amitriptyline; CTE, Cistanche Tubulosa Extract; BDNF, Brain-Derived Neurotrophic Factor; 5-HT, 5-Hydroxytryptamine.

Submit a manuscript: https://www.tmrjournals.com/lr
Firmicutes and Actinobacteria

Currently, there is extensive research on the connection between depression and Lactobacillus in the Firmicutes, while research on the relationship between depression and Bifidobacterium in the Actinobacteria is rapidly expanding. Bifidobacterium and Lactobacillus were counted using reverse transcription-polymerase chain reaction techniques in fecal samples from 43 depressed patients and 57 healthy controls. The results showed that the abundance of both bacteria was reduced in the patient group, with Bifidobacterium being more significant [38]. According to research, Bifidobacterium and Lactobacillus provide various benefits to the host, including nutrition, immunity, anti-aging effects, and modulation of stress response and depression [39]. Several bacteria belonging to the Lactobacillus genus, such as Lactcaseiibacillus rhamnosus JB-1, Lactobacillus helveticus R0052, and Lactobacillus plantarum PS128, have been found to alleviate the signs and symptoms of depression [7]. The mechanism may involve the reduction of inflammatory cytokines, competition with harmful intestinal infections, and modulation of neurotransmitter functions through interaction with vagal sensory fibers and the central nervous system [40]. Additionally, Lactobacillus has been shown to protect mice from anxiety and depression-like behaviors by reducing stress-induced hypothalamic-pituitary-adrenal activation and increasing levels of brain-derived neurotrophic factor (BDNF) in the hippocampus and 5-hydroxytryptamine (5-HT) in the prefrontal cortex [41]. Another clinical study revealed that specific strains of both Bifidobacterium and Lactobacillus can secrete gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter that regulates various physiological processes in the brain. Dysregulation of GABA is associated with anxiety and depression [39]. Additionally, alterations in other bacteria within the Firmicutes have been observed in both depressed patients and animals. For example, Candidatus Arthromitus, a member of the Clostridiaceae family, showed a decreased abundance in a rat model of depression [7]. In patients with active major depressive disorder, Anaerostipes was significantly increased, while Dialister was completely depleted [30]. Valeric acid, the primary metabolic product of typical strains of Oscillibacter, shares structural similarities with GABA and has been observed to interact with GABAa receptors. This suggests a potential association between bacteria involved in the production and metabolism of valeric acid and depression [42]. These findings provide further support for the hypothesis that specific bacterial strains within the Firmicutes may be linked to depression.

Bacteroidetes

Changes in the Bacteroidetes phylum, which makes up the majority of the gut microbiota, have received significant attention in depression research. Previous findings showed that 5.3% of the differential operational taxonomic units between individuals with major depressive disorder (MDD) and healthy individuals, as well as 33.3% of the different operational taxonomic units between depressed and healthy mice, belong to the Bacteroidetes phylum [31]. Using 16S rRNA sequencing to compare the gut microbial communities of healthy individuals and those with MDD, researchers discovered a decreased abundance of Bacteroides in individuals with MDD [31]. In unipolar depression, the gut microbiota is characterized by a prominent presence of the Bacteroides genus, while bipolar depression is associated with a higher abundance of Prevotella [43]. Another study found that patients with MDD had a lower abundance of Prevotella and a higher abundance of Bacillariophyceae in their gut microbiota compared to healthy controls [43, 44]. In a rat model of depression, the relative abundance of Prevotella was also found to be lower compared to controls in another study that utilized 16S rRNA sequencing and metabolomics. However, the difference was not statistically significant, possibly due to the small sample size [7]. Furthermore, it was discovered that Prevotella may have an influence on serum marker levels in the depression model [7].

Studies have also revealed that Bacteroides and Prevotella are more frequently found in men than in women [45]. Considering that the prevalence of MDD is 1.5 times higher in women than in men, this suggests a potential link between sex differences in gut microbiota and the prevalence of the disease. Through metagenomics, it was observed that males exhibited a higher diversity of enriched bacteria, with Bacteroides being predominant. However, larger sample sizes are necessary to obtain conclusive evidence regarding gender differences in the gut microbiome in MDD [46].

Allistipes species, known for their indole positivity, may influence the availability of tryptophan. A previous study showed that Allistipes is enriched in depressed individuals [44]. Increased abundance of Allistipes may disrupt the balance of the intestinal 5-hydroxytryptaminergic system, as tryptophan acts as a precursor to 5-HT. To clarify the involvement of this genus in the 5-hydroxytryptaminergic system in depression, more in-depth research is required [44].

The precise mechanisms by which the gut microbiome interacts with depression are still unknown. To provide new avenues and a theoretical foundation for the development of antidepressant medications, further studies are now needed to better explore the signaling pathways and key metabolites related to gut bacteria that affect depression.

Metabolites associated with gut microbiome and depression

Intestinal metabolites, including important functional metabolites such as SCFAs, branched-chain amino acids, bile acids (BAs), and catecholamines, as well as neurotransmitters like histamine, 5-HT, glutamate, and GABA, are secreted directly or indirectly by gut microbiota and play a crucial role in communication between microorganisms and hosts [23, 47]. These metabolites serve as nuclear receptors, regulating a wide range of immunological processes and contributing to the production of neurotransmitters. They interact with the central nervous system and enteric nervous system, which are closely associated with human health [23, 48]. A significant amount of existing experimental evidence suggests a potential link between the metabolites of gut microbiota and the occurrence of depression. The relevant experiments are summarized in Table 1.

SCFAs

SCFAs are small organic monocarboxylic acids synthesized in the gut through anaerobic microbial fermentation of dietary fiber and complex plant polysaccharides [9, 23]. They play a crucial role in host gut metabolism and immune function [47]. Studies have indicated that mice treated with SCFAs showed improved acute stress-induced hyperthermia and altered corticosterone levels. Additionally, the expression of the CRFR1, CRFR2, and MR genes in colonic and brain tissue was decreased [47]. The three primary SCFAs, acetate, propionate, and butyrate, are associated with the development of neurodegenerative disorders, depression, and pain [48, 49]. In a study, male rats exhibited decreased depression-like behavior in the open field test and the forced swim test after supplementation with a mixture of sodium acetate, sodium propionate, and sodium butyrate in drinking water. Furthermore, the SCFA group showed decreased gene expression of stress-related signaling receptors in the colon, hippocampus, and hypothalamus [47]. Propionate levels exhibited significant changes in the feces and plasma in animal models of depression. Another study demonstrated that rectal administration of propionate to chronic unpredictable mild stress (CUMS) rats for one week reversed depressive behavior and selectively restored neurotransmitter levels in the prefrontal cortex, highlighting the potential therapeutic value of propionate in depression treatment [20]. Butyrate has also been reported to exert antidepressant-like effects through various mechanisms, including elevating 5-HT concentrations in the brain, enhancing BDNF expression, repairing blood-brain barrier damage, and acting as a histone deacetylase inhibitor to affect microglia activation or gene expression in the hippocampus [49-51].

Tryptophan

Tryptophan, an essential amino acid and a precursor for various
metabolites synthesized by microorganisms and their hosts, holds significant importance in current depression research. Intestinal-derived tryptophan crosses the blood-brain barrier, and a deficiency in dietary tryptophan can impair neuronal 5-hydroxytryptaminergic transmission, resulting in depressive symptoms [18]. A study on Bifidobacterium breve CCFM1025 demonstrated its potential to alleviate depression-like behavior and neurological abnormalities in stress-induced depressive mice. This was achieved by increasing the abundance of beneficial microorganisms and the production of neuromodulatory metabolites such as xanthines, tryptophan, and SCFAs in mice [18]. Another investigation found that the injection of glucocorticoids may activate tryptophan-2,3-dioxygenase, leading to the degradation of tryptophan and lower levels of central presynaptic 5-HT, resulting in a state of depression [52-54]. Abnormal tryptophan metabolism mediated by the gut microbiome has been observed in both depressed individuals and depression-like animal models [55, 56]. This dysregulation of tryptophan metabolism triggers the activation of the kynurenine pathway, leading to changes in kynurenine, 3-hydroxykynurenine, and quinolinic acid, all of which have been strongly associated with depression [57]. Furthermore, relevant research has demonstrated that patients maintained on SSRIs may experience a relapse of depression due to depleted central 5-HT. However, after tryptophan supplementation, patients' depressive symptoms improved [58].

One of the crucial metabolites derived from tryptophan is 5-HT, which is predominantly found in the brain and gastrointestinal tract, with lower levels present in the peripheral circulation. Among the three major metabolic pathways of enteric-derived tryptophan, the production of 5-HT by enterochromaffin cells through tryptophan hydroxylase 1 is significant [59]. It has been established that low levels of 5-HT are directly associated with the pathophysiology of depression. Clinical trials have shown that patients with MDD exhibit lower concentrations of 5-HT that are only half as low or even lower than those of healthy controls [60]. Therefore, 5-HT has been proposed as one of the neurotransmitters most closely linked to depression.

BAs
BAs are synthesized from cholesterol in the liver and play a crucial role in lipid absorption and cholesterol homeostasis [4]. These BAs undergo further metabolism by colonic bacteria through various enzymatic pathways, resulting in the formation of other BAs such as lithocholic acid, deoxycholic acid, and ursodeoxycholic acid [61]. Recent research has established a connection between BAs and depression. For example, in a rat model of depression induced by CUMS, a significant decrease in BA concentrations was observed, likely due to hepatocyte injury and reduced intestinal excretion [4]. BAs exert a wide range of physiological effects, primarily through the activation of specific receptors in the cell nucleus and cell membrane [62]. The Farnesoid X receptor (FXR), a nuclear receptor, can be influenced by BAs, and the activation of FXR ligands is a critical factor in the development of depression. Studies have demonstrated that excessive FXR expression in the hippocampus of neonatal rats leads to depression-like symptoms and reduces the production of BDNF [63]. Furthermore, BAs can activate FXR in the ileum, resulting in the release of fibroblast growth factor 19 or its homologous fibroblast growth factor 15. These factors can enter the bloodstream, cross the blood-brain barrier, and inhibit the hypothalamic-pituitary-adrenal axis, providing protection against depression [64-66]. Additionally, treatment with taurosodeoxycholic acid has been shown to prevent depressive behavior induced by lipopolysaccharides, possibly by attenuating neuroinflammation and oxidative stress [48, 62].

Other metabolites
Indole is recognized as one of the most significant metabolites produced by the gut microbiota, and research has shown that higher levels of indole are associated with increased anxiety and depression-like behaviors in rats [67]. Additionally, indole has been found to be linked to susceptibility to chronic stress in mice and interferes with catecholamine biosynthesis [68]. The relationship between vitamin B3 and depression has also been investigated. A study involving 1634 Japanese elderly individuals revealed that participants with depressive symptoms had significantly decreased levels of Vitamin B3 and the entire vitamin B group [18]. Alterations in purine metabolism have also been associated with depression. Research has demonstrated a positive correlation between depression and lower levels of hypoxanthine and xanthine in the cerebrospinal fluid [69]. Similarly, women with MDD exhibited significantly lower urinary hypoxanthine levels [70]. Another study utilizing a mouse model of lipopolysaccharide-induced depression observed decreased hypothalamic hypoxanthine levels [71].

The relationship between gut microbial metabolites and depression is becoming increasingly evident, and the underlying mechanisms are gradually being elucidated. This is expected to pave the way for new avenues and directions in the development of clinical antidepressant medications.

**Antidepressants based on gut microbes and related metabolites**

Depression, a psychiatric disorder, has a complex pathogenesis and is characterized by persistent and prolonged sadness [72]. Various medications are used for the treatment of depression. The primary pharmacological characteristic of commonly prescribed first-line therapeutic drugs is their impact on monoamine neurotransmission [73]. These medications can be categorized into four main types based on their mechanism of action: TCAs, SSRIs, SNRIs, and MAOIs [74]. TCM encompasses substances guided by TCM theory, which are utilized for disease prevention, treatment, diagnosis, rehabilitation, and health maintenance. Most TCM treatments are derived from plants. In recent years, TCM has gained increased attention due to its utilization of multiple herbs, targets, and components [8]. Additionally, it offers a solution to the issue of drug dependence associated with conventional clinical first-line medications. Numerous studies have now demonstrated that TCM can interact with the gastrointestinal microbiome, thereby exerting antidepressant effects through the regulation of the microbiome and its associated metabolites. Specific studies are summarized in Table 1. This presents a novel approach to the treatment of depression.

**Common clinical medication**

Ketamine, an antagonist of the high-affinity N-methyl-D-aspartate receptor, exhibits its highest bioavailability through intravenous injection, followed by intramuscular injection [75-77]. The efficacy of ketamine may be correlated with its bioavailability. Studies have demonstrated that subanesthetic doses of ketamine result in a rapid onset and sustained antidepressant effects in patients with MDD, bipolar depression, and treatment-resistant depression [78]. In a randomized, double-blind clinical investigation, a significant improvement in depressive symptoms was observed within 72 hours of ketamine infusion [75]. The specific mechanism by which ketamine exerts its antidepressant effects remains unclear; however, emerging evidence suggests a potential association with gut microbes and their metabolites. Research data indicate that chronic low doses of ketamine can significantly alter specific bacterial genera in the gut, with up to 2- to 42-fold variations [79]. In a related study, ketamine administration significantly increased the levels of Lactobacillus johnsonii in lipopolysaccharides-induced depressed mice. Additionally, Actinobacteria, Coriobacteria, and Clostridiales exhibited a significantly negative correlation with immobility time in the forced swimming test, while Prevotellaceae and the genus Alloprevotella showed a significantly positive correlation [80]. These findings suggest that changes in the gut microbiota may influence the antidepressant effects of ketamine. Moreover, research has revealed that ketamine and its metabolites can enhance the antidepressant impact of ketamine by promoting the microbiota associated with SCFAs such as Butyricimonas, Turicicactor, and Clostridiales [78]. Another study demonstrated that ketamine administration led to alterations in eight metabolites in the prefrontal cortex and
hippocampus, with notable changes observed in purine and pyrimidine metabolism. Additionally, an increase in precursors of inhibitory neurotransmitters and a decrease in precursors of excitatory neurotransmitters were observed [32]. These findings further support the connection between gut microbial metabolites and the antidepressant effects of ketamine.

Fluoxetine, a commonly prescribed drug for depression, belongs to the class of SSRIs. It has been proposed that SSRIs can modulate the gut microbial environment by affecting the function of the host’s serotonin transporter and intestinal homeostasis [81]. These changes in the gut microbiota are believed to contribute to the antidepressant effects of SSRIs. In a preclinical study using CUMS rats, fluoxetine was found to alter the abundance of Firmicutes and Bacteroidetes, while also attenuating depression symptoms [33]. The mechanism of action through which fluoxetine alleviates depressive symptoms may involve the modulation of the Firmicutes-to-Bacteroidetes ratio. Further analysis at the genus level revealed that rats treated with fluoxetine exhibited significantly higher concentrations of Bacteroides, Parabacteroides, and Butyricimonas in their fecal microbiota compared to rats treated with CUMS alone [33]. Previous studies have shown that members of Bacteroides and Parabacteroides actively express pathways involved in the production of the inhibitory neurotransmitter GABA [82]. This suggests that fluoxetine may exert its antidepressant effects by altering the composition of the gut microbiome, ultimately improving GABA transmission [83]. Another study involving pregnant and lactating depression rat models found that fluoxetine treatment led to a significant increase in the relative abundance of Prevotella and Ruminococcus [34]. Analysis of the fecal microbiome using 16S rRNA sequencing and metabolomics revealed that fluoxetine treatment in female rats resulted in lower concentrations of fecal amino acids, which were negatively correlated with the relative abundance of bacterial taxa such as Prevotella and Bacteroides [34]. This finding suggests that metabolites produced by gut microbes may influence the antidepressant effects of fluoxetine, although further research is needed to determine the precise mechanism of action.

Venlafaxine, a classical bicyclic antidepressant belonging to the serotonin-norepinephrine reuptake inhibitors class, exerts its effects by increasing the levels of 5-HT and norepinephrine [35, 84]. Additionally, emerging evidence suggests that venlafaxine can modulate the composition of the gut microbiome as another mechanism of its antidepressant action. Preclinical research has identified Blautia, Oscillobacter, Tyzzerella, Butyrivibrio, and Enterorhabdus as the primary bacteria targeted by venlafaxine to restore gut microbiota diversity and alleviate depression symptoms in CUMS mice [35]. Venlafaxine has also been found to reverse the decrease in serum glutamate levels observed in CUMS mice. Another study demonstrated that venlafaxine affects gonadal steroid hormones and aromatic amines in rats [85]. Previous research has established a close association between gonadal steroid hormones and depression [86]. Notably, Tyzzerella, one of the key bacteria mentioned earlier, has the capability to produce significant amounts of aromatic amines, which are essential for 5-HT production [87, 88]. Taken together, these findings indicate that venlafaxine may exert its antidepressant effects through significant interactions with gut metabolites and microorganisms. Furthermore, studies have revealed that venlafaxine partially or fully reverses changes in various pathways, such as glutamate metabolism, valine degradation, and fatty acid metabolism, in the gut bacteria of CUMS mice, suggesting that the drug can modulate multiple functional pathways that may contribute to its antidepressant effect [35].

**Traditional Chinese medicine**

Bupleuri Radix is a widely used herbal remedy for depression known for its main effect of distressing the liver and relieving depressive symptoms. PBR has been identified as an effective treatment for depression by controlling intestinal bacteria and increasing metabolite levels. Through metabolomics and 16S rRNA gene sequencing, it was observed that PBR intervention increased gut microbiota diversity and significantly reduced the abundance of Prevotella and Ochrobactrum in CUMS rats. These changes in the gut microbiota are believed to modulate the immune system and contribute to the antidepressant effects of PBR [4]. Additionally, PBR was found to elevate the levels of BAs in rats with depression, leading to speculation that PBR may exert its antidepressant effects by reducing hepatocyte damage [4]. Another study demonstrated that Chaihu Shugan San, a herbal formula containing Bupleuri Radix, increased the relative abundance of Parabacteroides distasonis in the colons of CUMS mice. Chaihu Shugan San also restored various BAs such as hyaluronic acid and 7-ketocholesol acid to serum levels comparable to those of normal mice [89]. Therefore, it is hypothesized that the changes in serum BAs levels may be influenced by alterations in the gut microbiota, and both factors contribute to the antidepressant effects of Bupleuri Radix. Additionally, Chaihu Shugan San has been found to improve depression-like behavior through the reprogramming of lipid metabolism [90].

XYS is a traditional Chinese medicine composed of various ingredients such as Radix Bupleuri, Radix Angelicae Sinensis, and Radix Paeoniae Alba. Its antidepressant mechanism has been demonstrated to involve the regulation of multiple pathways, including the neural pathway, neuroendocrine system, and immune system [91]. Previous studies have found that the antidepressant mechanism of XYS is associated with the regulation of microbial metabolism through fecal metabolomics [92]. In a recent preclinical investigation using 16S rRNA and metabolomic rRNA sequencing, XYS was found to normalize the levels of alanine, proline, and valine in CUMS rats. It also significantly decreased the levels of Actinobacteria, Corynebacterium, and Facklamia while increasing the abundance of Firmicutes. Moreover, XYS reversed the abnormal lactic acid levels observed in rats with CUMS-induced depression. These findings suggest that XYS may increase the abundance of Lactobacillus, which in turn enhances the production of lactic acid and exerts an antidepressant effect [8]. Related clinical research has also revealed significant differences in plasma levels of trimethylamine oxide, glutamine, lactate, alanine, choline, and glucose between depressed individuals and healthy controls. After receiving prolotherapy, the levels of these compounds returned to normal, indicating the involvement of gut microbiota and associated metabolites in the antidepressant effect of prolotherapy [36]. These results suggest that gut microbiota and associated metabolites could potentially serve as biomarkers for the auxiliary diagnosis of depression, offering a direction for further improvement of diagnostic procedures for depression.

Furthermore, the antidepressant mechanisms of other traditional Chinese medicines have also been gradually explored. Cistanche tubulosa extract has been found to exhibit effective antidepressant activity by restoring the levels of 5-HT, BDNF, and SFCAs in chronic unpredictable stress rats. Additionally, it modifies the relative abundance of gut microbiota at the genus level [37]. Another traditional Chinese medicine, Tiansi Liquid, has shown the ability to decrease the levels of tryptophan (2,3-dioxigenase, indoleamine 2,3-dioxigenase, and quinoline, while increasing the relative abundance of Ruminococcaceae, Lactococcus, and Lactobacillus in rats. This indicates that Tiansi Liquid modulates the composition and metabolites of the gut microbiota in the TRP-KYN pathway, which contributes to alleviating depression in rats [7].

**Commonly used technical tools in depression research**

Currently, popular high-throughput nucleotide sequencing techniques utilized in microbiome research include 16S rRNA gene sequencing analysis based on PCR amplicons, DNA-based shotgun metagenomic analysis, RNA-based metatranscriptome sequencing, and virome sequencing. These techniques have provided insights into alterations in the composition and function of microorganisms, as well as abnormalities in metabolites and metabolic pathways in depressed patients and depression-like animals. As a result, there is a better understanding of the role of the gut microbiome in the pathogenesis of depression and the mechanism of action of antidepressant drugs [93].
Microbiome analysis

Microbiome analysis comprises 16S rRNA gene sequencing and shotgun metagenomic analysis techniques. The 16S rRNA gene, a component of the prokaryotic ribosome’s 30S subunit, is utilized for deep sequencing, particularly targeting the V4, V3-V4, and V4-V5 regions. This technique enables simultaneous detection of dominant, rare, and potentially unknown species in the sample, allowing determination of the microbial community’s composition and relative abundance. Understanding the changes in gut microbes and associated metabolites caused by depression is facilitated by this approach. It also provides essential information for studying the pathophysiology of depression and the mechanism of action of antidepressant medications, offering significant theoretical and practical value. For example, 16S rRNA sequencing of rifaxamin-treated CUMS rats revealed increased Bacteroides content, decreased Firmicutes content, and enhanced secretion of anti-inflammatory cytokines by microglia.

Hence, we hypothesize that the antidepressant mechanism of rifaximin is associated with alterations in gut microbes and metabolites [94]. Additionally, due to the tight relationship between phylogeny and biomolecular function, it is now feasible to predict the functional content of metagenomic data using software tools based on 16S rRNA sequencing [93].

Metagenomics involves cloning the total DNA (metagenomic) of microorganisms present in a specific environment and constructing a large-scale library for studying the genetic composition and community function of those microorganisms using genomic research strategies. It enables the examination of microorganism composition, diversity, and the discovery of new physiologically active substances or genes. Currently, metagenomics is being utilized in depression-related research. Compared to 16S rRNA sequencing, metagenomic sequencing provides higher resolution and accuracy by sequencing entire genomic regions. This enhances the detection of microbial species, microbial diversity, and functional genes, while also allowing analysis of gene functions, biological pathways, and antibiotic resistance capabilities. For instance, metagenomic analysis revealed an increased abundance of genes associated with carbohydrate metabolism E.C. in depressed mice compared to control mice, including the pentose phosphate pathway (EC: 4.1.2.4, deoxyriboholaldase, Etc. 2.7.1.45, 2-dehydro-3-deoxyxlyconokinase), starch and sucrose metabolism (EC: 3.2.3.1; alpha-amylose), and more [31].

Metabolomics analysis

The metabolome refers to all the low molecular weight metabolites present in an organism or cell during a specific physiological period. Metabolomics, derived from the concept of the metabolome, focuses on the qualitative and quantitative analysis of these metabolites. It approaches the human body as a supraorganism and plays a crucial role in exploring the relationship between the gut microbiota and the host’s metabolic phenotype [84]. It aids in understanding how the microbial community influences metabolic function and identifies abnormal metabolites and metabolic pathways associated with complex diseases [95]. Therefore, metabolomics holds significant value and potential for advancement in clinical research. Currently, metabolic dysregulation is considered a major factor in psychiatric disorders, including MDD. The application of metabolomics provides fresh insights into the prognosis and treatment of MDD at the metabolic level, offering new avenues for investigating the underlying mechanisms of MDD [96]. For instance, a metabolomic analysis in a related study identified proionic acid as a distinct metabolite between CUMS rats and control rats. Metabolomic investigations have revealed changes in the gut microbiota of MDD patients, suggesting a potential link to decreased SCFA production, impaired gut barrier integrity, and reduced neurotransmitter production [97].

Other omics

With the advancement of the post-genomic era, various techniques and studies, such as transcriptomics and proteomics, have emerged and are being utilized in depression-related research. The transcriptome represents the complete set of RNAs produced by a specific cell, tissue, or organ during a particular developmental stage or physiological condition. Transcriptome sequencing techniques, which provide reduced background noise, a wider dynamic range of detection, and direct sequence identification, are now the preferred method for analyzing gene expression and identifying novel RNA species [98]. Through transcriptomics, studies have identified alterations in genes such as human-like 8, interleukin-8, and chemokine ligand 4 in suicides with DSM-IV major depressive disorder [99]. On the other hand, proteomic analysis involves studying the proteome to gain a comprehensive understanding of cellular metabolism, illness development, and other protein-level activities. In a preclinical study using proteomics on depressed mice, alterations in protein expression levels were observed in various regions of the gut-brain axis. These protein changes were found to impact multiple biological processes, including metabolic processes and inflammatory responses [100].

Individual omics studies have obvious limitations due to the complexity and multi-level nature of organisms [101]. Consequently, the emergence of multi-omics combined analysis has provided a means to simultaneously perform multidimensional genome sequencing and parallel synthesis analysis, enabling a more comprehensive understanding of organisms. By integrating the data and information generated by multi-omics combined analysis at different molecular levels, we can simultaneously study thousands of proteins (proteomics), genes (genomics), RNA (transcriptomics), and metabolites (metabolomics), thus revealing interaction networks between the molecular levels [102]. In the field of depression research, multi-omics analysis allows for the effective integration of diverse omics information from multiple layers. It facilitates the construction of extensive omics networks, offering researchers a more comprehensive perspective and increased opportunities to unravel complex issues such as the pathogenesis of depression. In the future, the development and widespread application of multi-omics approaches will provide robust technical support for understanding the interactions between depression and gut microbes, as well as the relationship between depression and metabolites associated with gut microbiota. This advancement will significantly enhance the depth and progress of research in this field.

Conclusion

With the rapid advancement of high-throughput sequencing technology, an increasing number of studies have demonstrated a close relationship between changes in gut microbes, related metabolites, and the onset and progression of depression. Furthermore, it has been revealed that many antidepressant medications exert their therapeutic effects through these mechanisms. However, most current research findings only highlight the fluctuations in gut microbiomes and metabolites without fully elucidating the underlying mechanisms of these changes and the corresponding signaling pathways. This limitation calls for further investigation. Nevertheless, the regulation of microbes and metabolites holds promising potential as a strategy for the treatment of depression, opening up new avenues and targets for the development of antidepressant drugs. Future research focused on the ecology, metabolism, and signaling networks of the gut microbiome may lead to the development of highly effective approaches for the prevention and treatment of depression, with the microbiota at the center of these advancements.

References


2. Shao J, Wei Y, Wei XL. A comprehensive review on...


http://doi.org/10.1016/j.biopsych.2004.10.010


