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CURRENT PERSPECTIVES

Interactions Between Antidepressants and Intestinal Microbiota

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Abstract
The microbiota-gut-brain axis has been shown to influence human health and diseases, including depression. The interactions between drugs and intestinal microbiota are complex and highly relevant to treat diseases. Studies have shown an interaction between antidepressants and intestinal microbiota. Antidepressants may alter the abundance and composition of intestinal microbiota, which are closely related to the treatment outcomes of depression. Intestinal microbiota can influence the metabolism of antidepressants to change their availability (e.g., tryptophan can be metabolized to kynurenine by intestinal microbiota) and regulate their absorption by affecting intestinal permeability. In addition, the permeability of the blood–brain barrier can be altered by intestinal microbiota, influencing antidepressants to reach the central nervous system. Bioaccumulation is also a type of drug–microbiota interaction, which means bacteria accumulate drugs without biotransformation. These findings imply that it is important to consider intestinal microbiota when evaluating antidepressant therapy regimens and that intestinal microbiota can be a potential target for depression treatment.

Keywords Depression · Antidepressants · Intestinal microbiota · Interaction · Metabolism

Introduction

Most bacteria in the human body are present in the intestine [1]. The microbiota-gut-brain axis is used to describe the bidirectional communication between the microbiota in the gut and brain [2]. This axis may function through mechanisms such as microbial metabolites, vagus nerve, enteric nervous system, immune signaling, serotonin, tryptophan, and tryptamine metabolism [3, 4]. In the human body, some live microorganisms are beneficial to human health and are called probiotics [5, 6].

Several studies have revealed a close relationship between intestinal microbiota and human diseases, including metabolic diseases [7], cancers [8, 9], and autoimmune diseases [10]. Moreover, intestinal microbiota composition is also associated with psychiatric diseases, such as Alzheimer's disease, Parkinson's disease, autism, and post-traumatic stress disorder [11–14].

The relationship between major depressive disorder (MDD) and gut microbiota has recently received extensive attention. Huang et al. [15] concluded that increased abundances of the phylum *Actinobacteria*, order *Bacteroidales*, family *Enterobacteriaceae*, genus *Alistipes*, and decreased abundances of the family *Lachnospiraceae*, genus *Faecalibacterium*, were associated with depression. The alterations in intestinal microbiota play an important role in the pathogenesis and treatment of depression.

The most commonly used antidepressants worldwide include monoamine-oxidase inhibitors (MAOI), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors (SNRIs). The antidepressant effects of MAOI are generally related to the inhibition of MAO in the central nervous system to decrease the degradation of monoamine transmitters [16]. TCAs block serotonin and norepinephrine reuptake and maintain their levels in the synaptic cleft [17, 18]. SSRIs inhibit serotonin reuptake by the presynaptic membrane to maintain its levels in the synaptic cleft [19].

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In recent years, ketamine has been used as a rapid-acting antidepressant for treating depression. The antidepressant effects of ketamine are associated with its blockade of the N-methyl D-aspartate receptor (NMDAR), an ionotropic glutamate receptor [20], and increased function of a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors [21]. In addition to these primary mechanisms responsible for their antidepressant-like effects, some other potential mechanisms have also been investigated. For example, the anti-inflammatory effect may be one of the potential mechanisms of action of the SSRIs, SNRIs, and ketamine [22, 23]. Interestingly, the intestinal microbiota may participate in the processes mentioned above. Getachew at el. [24] showed that ketamine administration decreased the abundance of *Ruminococcus* and *Mucispirillum* in the stool samples of rats. Indeed, high levels of *Ruminococcus* may increase the severity of irritable bowel disease (IBD), while some species of *Mucispirillum* may lead to intestinal inflammation. Another study showed that ketamine could increase the levels of *Lactobacillus johnsonii* in LPS-induced depressive mice, which may play a role in improving depressive-like behaviors via the hypothalamic–pituitary–adrenal axis. The antidepressant effects of ketamine and its metabolites could also be related to improving the abundance of SCFAs-producing microbiota including *Butyricimonas*, *Turicibacter*, and *Clostridiales* [25]. Indeed, (*R*)-ketamine and lanicemine are both NMDAR antagonists but the former shows obvious antidepressant effects on treatment-resistant depressed patients, while the latter does not present antidepressant effects in such patients [26]. (*R*)-ketamine significantly attenuated the reduced levels of *Mogibacteriaceae*, *Bacteroidales*, and *Clostridiales*, as well as the increased levels of *Ruminococcaceae* and *Clostridium* in the chronic social defeat stress (CSDS) susceptible mice, while less potent effects of lanicemine on the intestinal microbiota were observed [26]. Taken together, the modulation of intestinal microbiota may partly mediate the antidepressant mechanism [27]. Notably, anxiety disorders often coexist with depression. Accumulating evidence indicates that SSRIs, dual SNRIs, and many TCAs can be used in improving lots of anxiety disorders [28, 29], regardless of the severity of mental status. IBD can lead to comorbidities of anxiety and depression by inducing neuroinflammation [30]. Given the close relationship between intestinal microbiota, anxiety symptoms, and the severity of mental status, antidepressants may not only affect the depression-related microbiota but also exert more complicated effects.

Research has shown that intestinal microbiota and various drugs have reciprocal interactions; i.e., the drugs can influence the ecology of the gut microbiome [31], while intestinal microbiota can directly participate in the chemical transformation and bioaccumulation of drugs [32, 33], as shown in Fig. 1. When metabolizing medications, intestinal microbiota mainly conducts hydrolytic and reductive reactions. For instance, the cardiovascular drug digoxin can be inactivated via biotransformation by intestinal microbiota, and the bacterial enzyme β-glucuronidase has been reported to be associated with the toxicity of the common colon cancer chemotherapeutic CPT-11 (also known as irinotecan) [34, 35]. These examples indicate that intestinal microbiota can affect the activity and toxicity of drugs [36–38]. Furthermore, it has also been found that intestinal microbiota is a significant factor affecting the efficacy of antidepressants [39].

Although great progress has been made in treating depression, many issues remain unsolved. Despite administering sufficient doses and maintenance treatment, 30–40% of patients do not respond to the treatment [40–42]. The side effects of antidepressants are among the factors affecting treatment outcomes [43]. Headache, nausea, and insomnia are the three most common side effects of antidepressants, with incidence rates exceeding 10% [44]. In addition, tolerability, acceptability, pharmacokinetics, pharmacodynamics, and drug-drug interactions also affect antidepressant treatment outcomes [45]. Considering the possible role of intestinal microbiota in the treatment outcomes of antidepressants, we provide here a review of the recent discoveries on the possible interaction between antidepressants and intestinal microbiota, especially how intestinal microbiota can affect antidepressants and their efficacy, which might have reference value for investigating new pathways and factors influencing antidepressant effects. By describing the possible effects that the intestinal microbiota may have on antidepressants, we may provide a reference for better-applying antidepressants clinically considering intestinal microbiota. Moreover, this article also provides information about the possible therapeutic targets related to intestinal microbiota for the development of new antidepressants.

Effects of Intestinal Microbiota on Depression

Accumulating evidence demonstrates the role of the microbiota-gut-brain axis in psychiatric diseases, and more attention has been paid to the effect of intestinal microbiota on depression. Many studies have explored the relationship between intestinal microbiota and the changes in depressive phenotypes. In animal studies, fecal microbiota transplantation (FMT) of germ-free mice with "depression microbiota" derived from MDD patients, the absence of gut microbiota in germ-free mice, and antibiotic-induced microbiota perturbation all led to depression-like behaviors [46–48]. Specifically, FMT from patients with rheumatoid arthritis caused depression-like behaviors in antibiotic-treated mice via abnormal T cell differentiation [49]. These findings indicate that microbiota may have an important role in the pathogenesis of depression. Additionally, probiotic supplementation alleviates depression-like behaviors [50–53]. Meanwhile,

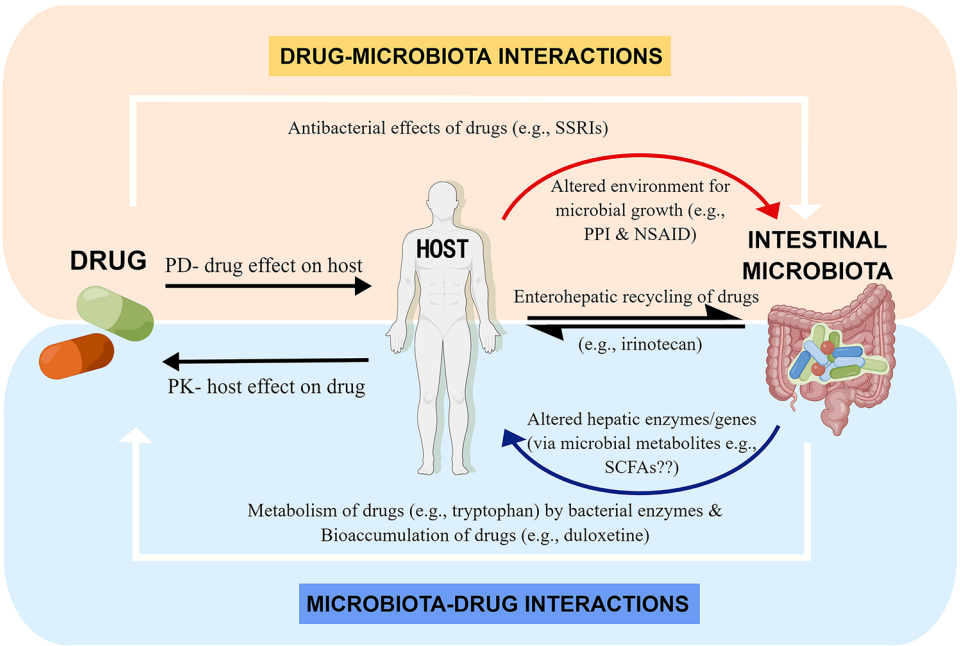

Fig. 1 Complex interplay between drugs and intestinal microbiota. The interactions between drugs and intestinal microbiota include microbiota-mediated alterations to drug pharmacokinetics and drug-mediated alterations to the function/composition of intestinal microbiota. "Drug–Microbiota Interactions": drugs can have direct antibacterial effects on intestinal microbiota (e.g., SSRIs) and can also indirectly alter the environment for microbial growth by their pharmacodynamic effect on the host (e.g., proton pump inhibitor alters gastric acid production and pH, and non-steroidal anti-inflammatory drug changes mucosal integrity, illustrated by the curved-down line arrow). The interactions between the host and intestinal microbiota cause the enterohepatic recirculation of drugs, e.g., intestinal microbiota deconjugate the hepatic-glucuronidated irinotecan metabolite by β-glucuronidase enzymes. "Microbiota-Drug Interactions": intestinal microbiota can directly metabolize drugs by bacterial enzymes (e.g., tryptophan), or bioaccumulate drugs (e.g., duloxetine). In addition, intestinal microbiota can alter hepatic enzymes/genes, which may influence the pharmacokinetic effect of the host on drugs, e.g., microbial-derived metabolites (e.g., SCFAs and secondary bile acids) may be potential mediators of this effect (illustrated by the curved-up line arrow). PK, pharmacokinetic; PD, pharmacodynamic. This figure was obtained from reference [39] with slight modification. By Figdraw

another study showed that some probiotics improved cognitive function in patients with major depression [54]. Thus, probiotics may play a role in the treatment of depression. In contrast, another study showed that microbiota variation is related to antidepressant treatment resistance in patients with MDD [55]. Intestinal microbiota can affect the structure of the brain and regulate brain-derived neurotrophic factors [56]. *Oscillibacter* may have protective modulatory functions in the brain, thus increasing amygdala and hippocampal volumes, closely related to depression [57]. Furthermore, intestinal microbiota can serve as molecular markers for diagnosing MDD and general anxiety disorders [58].

The vagus nerve plays a key role in the microbiota-gut-brain axis. FMT from CSDS-susceptible mice and Chrna7 knock-out (KO) mice exhibited anhedonia-like behaviors, inflammation, and downregulation of synaptic proteins in the prefrontal cortex in antibiotic-treated mice [59–61]. Studies showed that abnormal composition of intestinal microbiota including *F. rodentium*, *L. intestinalis*, *L. reuteri*, and systemic inflammation may be responsible for these changes via the vagus nerve [60–62]. Subdiaphragmatic vagotomy (SDV) blocked the development of depression-like behaviors in Chrna7 KO mice [62] and antibiotic-treated mice [59–61]. Moreover, plasma levels of microbe-derived metabolites like 1,5-anhydro-D-sorbitol, L-citrulline, and taurocholic acid in the KO + SDV mice were higher than those of KO + sham-operated mice, suggesting their important role in the antidepressant-like effects of SDV in Chrna7 KO mice [62]. LPS administration caused depression-like behaviors, inflammation, and downregulation of synaptic proteins in the prefrontal cortex in the sham-operated mice but not in the SDV-operated mice [63]. Moreover, LPS significantly decreased α-diversity and relative abundances of intestinal microbiota in mice, and SDV blocked this change [62]. *L. rhamnosus* (*JB-1*), the nonpathogenic bacteria, can mediate the GABAergic system in mice, and therefore, improve depression and anxiety behaviors. Vagotomy blocked the anxiolytic and antidepressant effects of *L. rhamnosus* (*JB-1*) and the changes in the GABAergic system in the amygdala and the hippocampus [64]. To conclude, the vagus nerve is an important factor in the pathogenesis of depression through the microbiota-gut-brain axis.

SCFAs are important gut microbiome-derived metabolites within the microbiota-gut-brain axis, which are

produced by bacteria fermenting dietary fiber in the gastrointestinal tract [65]. In the human body, acetate, propionate, and butyrate are the most abundant SCFAs [65]. Studies showed that SCFAs decreased significantly in depressed mice compared to control mice [66], while administration of SCFAs attenuated depression-like behaviors [67, 68]. Moreover, in depressed mice, some bacteria taxa showing low relative abundances significantly correlated with two major SCFAs with reduced levels (acetic acid and propionic acid) [66]. In a recent study focused on the depressive-like behaviors of high fructose-fed mice exposed to chronic stress, SCFA supplementation showed protective effects on hippocampal neurogenesis, ameliorated blood–brain barrier (BBB) damage, suppressed microglia activation, and neuroinflammation in these mice, which were related to antidepressant-like effects [69]. Lower butyrate levels may increase the gut barrier permeability, causing bacterial translocation into the systemic circulation and systemic inflammation [70]. The mechanisms of butyrate and other SCFAs in improving depression-like behaviors may correlate with their anti-inflammatory effects, inducing histone hyperacetylation and elevating BDNF levels [71]. These findings suggested that SCFAs may be essential mediators in depression.

Based on these findings, it is apparent that investigating the relationship between intestinal microbiota and depression is important, as shown in Fig. 2.

When drugs are consumed orally, they encounter a considerable abundance of intestinal microbiota, which can affect the ability of the drugs to treat depression. Fontana et al. [55] conducted a study to determine differences in the compositions of intestinal microbiota between patients with MDD and healthy controls (HCs) and between patients with treatment-resistant depression (TRD) and those responsive (R) to antidepressants. Several bacteria (*Thaumarchaeota*, *Yersinia*, and its species *Yersinia pseudotuberculosis*, *Peptococcus*, *Fenollaria timonensis*, *Blautia* spp. *canine oral taxon 337*, and *Papillibacter cinnamivorans*) were identified in the microbiota of TRD patients but not in that of the R patients. Compared to HC, *Flavobacteriaceae*, *Hungatella*, *Yersinia*, *Citrobacter*, *Fenollaria*, and *Fenollaria timonensis* were identified exclusively in TRD patients, whereas *Elusimicrobia*, *Flavobacteriaceae*, *Fenollaria*, and *Robinsoniella* sp. *MCWD5* were found exclusively in treatment-responsive patients with MDD. This result indicated that intestinal microbiota was related to the pathogenesis of MDD and patients' response to antidepressants.

In another study focusing on chronic unpredictable mild stress (CUMS) mice treated with escitalopram, the

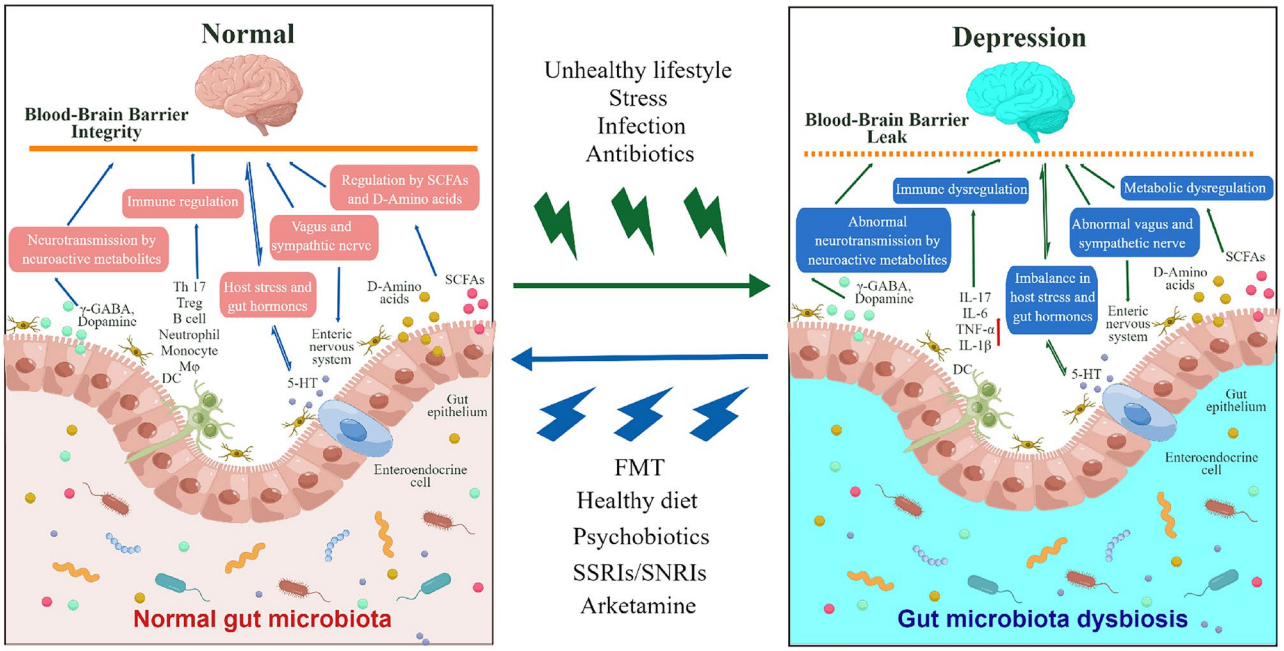

Fig. 2 Role of the microbiota–gut–brain axis in depression. An unhealthy lifestyle, increased and sustained stress, infection, antibiotics, or other factors can cause gut microbiota dysbiosis. Abnormal changes may occur in the body, which can be mediated by the microbiota–gut–brain axis via neural, immune, or chemical signals, thereby causing depression. Conversely, FMT, a healthy diet, psychobiotics, and antidepressants (e.g., SSRIs, SNRIs, and arketamine) can restore gut microbiota dysbiosis, abnormal brain function, and depressive symptoms via the microbiota-gut-brain axis. γ-GABA, γ-aminobutyric acid; CNS, central nervous system; DC, dendritic cell; 5-HT, 5-hydroxytryptamine; IL-6, interleukin 6; IL-17, interleukin 17; IL-1β, interleukin 1β; SCFA, short-chain fatty acid; TNF-α, tumor necrosis factor α. The figure is obtained from reference [72] with slight modification. By Figdraw

composition of intestinal microbiota differed between the responder and non-responder groups. The relative abundances of the genus *Prevotellaceae_UCG-003* increased in the responder group, whereas the families *Ruminococcaceae* and *Lactobacillaceae* were depleted in the non-responder group [73].

Lee et al. [74] focused on the role of intestinal microbiota as a predictor of antidepressant treatment outcomes in geriatric depression. At the level of the individual taxa, a random forest classifier created using nine genera from the baseline microbiota accurately predicted remission. Of these, baseline enrichment of *Faecalibacterium*, *Agathobacter*, and *Roseburia* relative to the reference frame was associated with remission upon treatment. Differential abundance analysis revealed significant genus-level changes from baseline to post-treatment in remitters but not in non-remitters.

Dong et al. [75] found that among patients with MDD treated with antidepressants, intestinal microbiota composition at baseline differed significantly between responder and non-responder groups. The expression of 20 metabolites, mainly involved in lipid metabolism, differed significantly between the responder and non-responder groups. Therefore, alterations in intestinal microbiota and associated metabolites may affect the antidepressant treatment outcomes.

The rat model of adrenocorticotrophic hormone (ACTH) treatment has been widely accepted for TR depression. Chronic administration of ACTH leads to resistance to imipramine treatment in the forced swimming test, and resistance to other antidepressants [76–78]. Research has shown that ACTH-induced depression disturbs the gut microbiota composition, like *Oscillospira*, *Ruminococcus*, *Akkermansia*, *Lactobacillus*, and *Klebsiella* [79]. Changes in intestinal microbiota may be relevant to TR effects in ACTH-treated rats.

Based on the above studies, alterations in intestinal microbiota composition may be associated with the response to antidepressants and clinical treatment outcomes.

Antidepressants May Alter the Abundance and Composition of Intestinal Microbiota

Studies have shown that many intrinsic and extrinsic factors, such as diet, medication, smoking, lifestyle, host genetics, and diseases, affect intestinal microbiota in healthy individuals [80–82]. In recent years, numerous studies have revealed that many antidepressants may alter the abundance and composition of intestinal microbiota and that their antidepressant-like effects may also be related to these changes. The SSRIs fluoxetine (Flu) and escitalopram were found to reduce the abundance of intestinal microbiota, especially that of *Ruminococcus*, *Adlercreutzia*, and an undefined *Alphaproteobacteria*; the same was verified for two SNRIs, namely, venlafaxine and duloxetine. A decrease in intestinal microbiota richness may result in possible side effects. Further investigation showed that introducing a single *Ruminococcus* species (*R. flavefaciens*) can attenuate the effects of an antidepressant by inducing changes in synaptic and mitochondrial gene expression and alterations in monoamine neurotransmitter levels. It is also beneficial for alleviating antidepressant-induced constipation [83]. In addition, Zhang et al. [84] reported that the administrations of Flu and the tricyclic antidepressant amitriptyline (Ami) were associated with a low abundance of the phylum *Firmicutes* and a high abundance of the phylum *Bacteroidetes*, while a reduced ratio of *Firmicutes/Bacteroidetes* appears to be associated with an improvement in neurological conditions. At the genus level, the relative abundances of *Bacteroides*, *Parabacteroides*, and *Butyricimonas* were significantly increased in the feces of Ami- and Flu-treated rats compared to those in rats exposed to CUMS, suggesting that these microbes and their metabolites are related to brain health. Moreover, Ami and Flu treatments may also affect potentially harmful bacteria and intestinal microbiota metabolic functions, such as carbohydrate metabolism, membrane transport, and signal transduction. The mechanism of SSRIs' antimicrobial action may be related to the inhibition of efflux pumps, as is observed in experiments, whereby SSRIs interact synergistically with antibiotics, thus decreasing the minimum inhibitory concentration for these antibiotics [85, 86]. TCAs present antiplasmid activity [87], possibly by targeting replicating plasmid DNA and the DNA gyrase enzymes, both crucial for DNA structural conformation [88].

Ketamine, a glutamate NMDAR blocker, has a rapid yet sustained antidepressant effect [21]. A study using male Wistar rats showed that chronic administration of ketamine significantly increased the levels of low-abundance bacterial genera (e.g., *Lactobacillus*, *Turicibacter*, and *Sarcina*) and significantly decreased opportunistic pathogens (e.g., *Ruminococcus* and *Mucispirallum*), which may partly contribute to its antidepressant and anti-inflammatory effects [24, 89]. Ketamine is a racemic mixture comprising equal parts of (*R*)-ketamine and (*S*)-ketamine. The (*R*)-ketamine (or arketamine) has superior and longer-lasting antidepressant effects and fewer side effects than (*S*)-ketamine in the animal models of depression. Study showed that (*R*)-ketamine changed the intestinal microbiota composition in the CSDS-susceptible mice [26]. However, because behavioral experiments using germ-free mice were not performed, these studies do not directly prove the effects of intestinal microbiota on the antidepressant actions of (*R*)-ketamine [26, 90].

Except for the former commonly used antidepressants, some potential novel antidepressants may have similar abilities to regulate intestinal microbiota. Inulin-type fructo-oligosaccharides purified from *Morinda officinalis* increased the abundance of Cyanobacteria in a rat stress

model, producing metabolites such as hydrogen sulfide that have antidepressant-like effects [91]. A neuroprotectant, the C-terminal domain of the heavy chain of the tetanus toxin, may also exhibit antidepressant effects, as it has been reported to boost the abundance of probiotic bacteria (e.g., *Lactobacillus*, *Bifidobacterium*, and *Butyrivibrio*) and suppress the levels of bacteria associated with inflammation (e.g., *Provettela* and *Mucispirallum*) [92]. A dihydroquinoline analog of agomelatine, N-(2-(7methoxy-3,4-dihydroisoquinolin-1-yl)ethyl)acetamide hydrochloride, was found to alter the composition of the gut microbiota, reverse the dysbiosis caused by chronic stress, and regulate neuroinflammatory marker levels, thus attenuating depression-related behaviors [93]. The aqueous extract of *Gastrodia elata* Blume may prevent depression by regulating monoaminergic neurotransmission and intestinal microbiota composition and function [94]. Chlorogenic acid pretreatment improves depression-like behavior, with its effect likely related to serum proinflammatory cytokines and monoamine neurotransmitters; this treatment can modulate gut bacteria with certain phylotypes in rats with ACTH-induced depression [95].

In recent years, many studies have focused on traditional Chinese medicine for the treatment of depression, wherein some are used to treat depression or have potential antidepressant-like effects. These medicines include total iridoids of Valeriana jatamansi Jones (TIV), Semen Sojae Praeparatum, Puerarin, Xiaoyaosan, Jia Wei Xiao Yao San, Baihe Jizihuang Tang, Chaihu-Shugan-San, and Shugan Jieyu Capsule, and they can change the abundance and composition of intestinal microbiota [73, 96–102]. It is generally believed that the action of traditional Chinese medicine on intestinal microorganisms is an important mechanism for its antidepressant effects. Rosemary extracts, the crucial active constituents extracted from *Rosmarinus officinalis*, considerably alleviated depressive-like behaviors in mice subjected to chronic restraint stress by rebalancing intestinal microbiota [103]. In our previous study, we explored the antidepressant properties of neferine (Nef) in a mouse model of chronic stress–induced depression. Nef displayed an antidepressant-like effect and increased the relative abundance of *Lactobacillus* at the genus level. This result indicates that Nef may improve depression by regulating *Lactobacillus* levels, which can impact serotonin/norepinephrine/dopamine triple reuptake. Nef also mitigated depression by reducing hippocampal pyramidal cell necrosis and alleviating hippocampal lesions [104]. Some antidepressants and their effects on intestinal microbiota are included in Table 1. Conventional antidepressants may sometimes be ineffective and cause a series of side effects; therefore, new strategies to treat depression should be introduced to overcome this deficiency. Research on intestinal microbiota can help in the development of medication regimens.

Mechanisms of Intestinal Microbiota Influencing the Efficacy of Antidepressants

Intestinal Microbiota Influence Drug Metabolism

Intestinal microbiota can not only directly but also indirectly affect drug metabolism. For example, intestinal microbiota can chemically transform drugs and modulate host xenobiotic metabolism, including drug metabolism pathways [36]. With an increasing number of studies focusing on factors influencing the efficacy of antidepressants, many researchers have found that intestinal microbiota plays an important role in the metabolism of antidepressants.

Paeoniflorin, the main component of the Chinese traditional medicine Xiaoyaosan, displays antidepressant-like effects in rats treated with chronic unpredictable stress (CUS) [105]. It is difficult to be absorbed and to cross the BBB [106]. After oral administration of paeoniflorin in a rat model of CUS, the bioavailability was only 2.32% [107]; low permeability and metabolism of paeoniflorin may be one of the reasons for this result [108]. A study showed that the major metabolite of paeoniflorin in vivo may be paeoniflorgein [109]. Intestinal microbiota can convert paeoniflorin into benzoic acid using carboxylesterase [107]. Benzoic acid can cross the BBB and act as an inhibitor of D-amino acid oxidase in the brain, thus improving brain function and presenting antidepressant activity [110]. Therefore, when antibiotics reduce the abundance of microbiota in the intestine, the metabolic conversion of paeoniflorin to benzoic acid is also reduced, leading to low bioavailability [107].

Tryptophan (Trp) is an amino acid that cannot be produced by animal cells; therefore, humans must obtain it from the outside environment, mostly through diet. Trp is considered a supplementation for the treatment of depression and may be effective by increasing the precursor for 5-hydroxyindole (5-HT) synthesis and normalizing its release to recover serotonin deficiency. However, the availability of Trp is reduced in the mental disorders [111]. In the gut, Trp can be metabolized to kynurenine (Kyn) and its derivatives by the rate-limiting enzyme indoleamine 2,3-dioxygenase (IDO) 1. Intestinal microbiota plays a key role in stimulating IDO1 activity. In addition, specific intestinal microbiota can directly transfer Trp to Kyn and its derivatives, as they encode enzymes homologous to those of the eukaryotic kynurenine pathway [112, 113]. Therefore, it can be inferred that if the Kyn pathway overacts, Trp will mainly be diverted to Kyn instead of entering the brain to display an antidepressant effect, thus affecting its bioavailability [114].

5-Hydroxytryptophan (5-HTP) is used in some therapeutic regimens to treat depression [115]. It is converted to 5-HT via tryptophanase in various intestinal microbiome strains [116]. However, 5-HT cannot pass through the BBB [117]; therefore, 5-HTP must first cross the BBB, where it can be transformed to 5-HT, thus displaying an antidepressant-like

Table 1 Antidepressants and their effects on intestinal microbiota

Antidepressants		Effects on intestinal microbiota	Reference
SSRI	Fluoxetine	Enhance the abundance of phylum *Bacteroidetes*, family *Porphyromonadaceae*, genus *Parabacteroides*, genus *Butyricimonas*, and genus *Alistipes*; reduce the abundance of phylum *Firmicutes*, *Ruminococcus*, *Adlercreutzia*, and an undefined *Alphaproteobacteria*	[83, 84]
	Escitalopram	Reduce the abundance of *Ruminococcus*, *Adlercreutzia*, and an undefined Alphaproteobacteria	[83]
SNRI	Venlafaxine, and duloxetine	Reduce the abundance of *Ruminococcus*, *Adlercreutzia*, and an undefined *Alphaproteobacteria*	[83]
Tricyclic antidepressant	Amitriptyline	Increase the abundance of phylum *Bacteroidetes*, family *Porphyromonadaceae*, family *Bacteroidaceae*, genus *Parabacteroides*, genus *Butyricimonas*, and genus *Alistipes*; reduce the abundance of phylum *Firmicutes*	[84]
N-Methyl-D-aspartate receptor (NMDAR) antagonist	Ketamine	Increase the abundance of bacteria genera (e.g., *Lactobacillus*, *Turicibacter*, and *Sarcina*); reduce the abundance of opportunistic pathogens (e.g., *Ruminococcus* and *Mucispirallum*)	[24]
	(R)-ketamine (or arketamine)	Attenuated the reduced levels of *Butyricimonas*, *Mollicutes*, *Mogibacteriaceae*, *Bacteroidales*, and *Clostridiales*, as well as the increased levels of *Deltaproteobacteria*, *Clostridium*, and *Ruminococcaceae* in the CSDS susceptible mice	[26, 90]
Extracts from traditional Chinese medicine	Neferine	Increase the relative abundances of species belonging to phylum *Firmicutes*; decrease those of species belonging to phylum *Bacteroidetes*	[103, 104]
	Rosemary extracts	Enhance the sequences proportion of *Lactobacillus* and *Firmicutes*; reduce the sequences proportion of *Bacteroidetes* and *Proteobacteria* in feces	[103]
Others	Inulin-type fructo-oligosaccharides	Increase the abundance of the phylum *Cyanobacteria*	[91]
	C-terminal domain of the heavy chain of tetanus toxin	Increase the abundance of *Lactobacillus*, *Bifidobacterium*, and *Butyrivibrio*; reduce the abundance of *Mucispirallum*	[92]
	N-(2-(7methoxy-3,4-dihydroisoquinolin-1-yl)ethyl) acetamide hydrochloride	Reverse the phenomenon that CUMS increases the richness of the gut bacterial community, resulting in a return to a normal level of richness	[93]

effect [118–122]. Therefore, the metabolism of 5-HTP by intestinal microbiota may be the reason why 5-HTP itself only slightly elevates the brain's extracellular 5-HT [123]. Interestingly, *M. officinalis* oligosaccharides, which are used to treat depression in China, can accelerate 5-HTP production from tryptophan and at the same time reduce 5-HT generation by alerting the activity of relevant enzymes in intestinal microbiota, thus accumulating 5-HTP. Then, 5-HTP from intestinal microbiota can be transported through the blood and cross the BBB to improve 5-HT levels in the brain [124].

Some intestinal microbiota is capable of N-demethylation, especially N-demethylating a tricyclic antidepressant, imipramine [125], causing fluctuations in the plasma concentration of this drug [126]. *Cistanche tubulosa*, a species of Cistanches Herba, has been confirmed to elicit antidepressant activity by regulating bacterial composition. *Cistanche tubulosa* extract (CTE) is metabolized to aglycones and the degradation products of phenylethanoid glycosides (PhGs) and iridoid glycosides by intestinal microbiota. The PhGs and iridoid glycosides in CTE were readily metabolized to secondary glycosides and aglycones in rats with CUS. These metabolites typically display high intestinal absorption and bioavailability, thereby exerting satisfactory biological activity [127–130].

Intestinal Microbiota Influence Drug Absorption

An altered microbiota state in patients with MDD is linked to increased gut permeability and regulation of intestinal

drug transport and absorption [131]. Depression can modulate intestinal permeability and barrier function, which in turn may alter the drug absorption [132]. Acute stress has been reported to be associated with the expression of the tight junction proteins zonula occludens-1 (ZO-1) and occludin in the duodenal mucosa of rats subjected to water-immersion restraint stress [133], thus changing gut permeability. The bacterial enzyme tryptophanase produces indole and its derivatives from tryptophan. Indole also regulates the permeability of the intestinal barrier [134, 135]. Therefore, intestinal microbiota may affect gut permeability, thus influencing drug absorption.

Intestinal Microbiota Changes the Permeability of the BBB

Studies have shown that antibiotic-induced changes in gut microbial composition increase BBB permeability by intestinal microbiota-produced metabolites that change central nervous system functions. A study showed a consistent increase in BBB permeability in the hippocampus, which may explain why intestinal microbiota dysbiosis is strongly correlated with neurological and psychological diseases such as Alzheimer's disease, autism spectrum disorder, and depression [136]. TIV may enhance the abundances of *Firmicutes* (e.g., *Lactobacillus* spp.) and *Bacteroidetes* to mediate the composition and function of intestinal microbiota and change the expression of ZO-1 and occludin, thus protecting the BBB to exert an antidepressant effect [137]. Yi et al. [138] reported that borneol can increase the permeability of the BBB and dose-dependently improve the distribution of puerarin in the brain. Puerarin is the main active ingredient in *Puerariae Radix*, a traditional Chinese medicinal herb. The self-microemulsifying drug delivery system co-loading borneol and puerarin resulted in the highest area under the curve $(AUC)_{brain}$ of all three oral formulations (nanocrystals suspension, inclusion compound solution, and self-microemulsifying drug delivery system) in the study, which was 10.27 times that of puerarin nanocrystals suspension without borneol. In addition, another study showed that the release of encapsulated 5′-(N-ethylcarboxamido)adenosine, an adenosine 2A receptor agonist, increased BBB permeability, thus amplifying the therapeutic efficacy of clinical drugs and immune checkpoint blockade antibodies in the treatment of glioblastoma [139]. Interestingly, puerarin can also alleviate CUMS-induced depression-like behaviors, possibly owing to the restoration of stress-induced disruptions of normal intestinal microflora [73]. Moreover, SCFAs derived from intestinal microbiota significantly increased the protein levels of ZO-1, claudin-5, and occludin in the brain vasculature of high fructose-fed mice exposed to chronic stress [69]. (*R*)-ketamine could ameliorate demyelination in cuprizone-treated mice possibly by normalizing the abnormal composition of intestinal microbiota, and could facilitate remyelination in the brain after cuprizone withdrawal possibly by improving the decreased levels of lactic acid [140]. Thus, it can be estimated that the permeability of the BBB greatly influences the treatment outcomes of drugs, potentially indicating the importance of intestinal microbiota in altering BBB permeability during depression treatment.

Other Effects of Intestinal Microbiota

A recent study showed that intestinal microbiota can also modulate the availability and efficacy of antidepressants in another way, bioaccumulation. Klunemann et al. [32] found that the efficacy of duloxetine on the behavior of *Caenorhabditis elegans* was reduced due to bioaccumulation by intestinal microbiota. During the experiment, the researchers confirmed that four selected strains (*Streptococcus salivarius*, *Bacteroides uniformis*, *Escherichia coli* IAI1, and *E. coli* ED1a) depleted duloxetine from the gut microbiome medium without biotransformation. This led to a direct reduction in drug availability. In addition, bioaccumulation can change metabolite secretion, which leads to changes in community composition, side effects, or even the mode of action of some drugs [141–143]. During the cultivation of *S. salivarius* in the presence of duloxetine, several metabolites were found to be accumulated, thus improving the growth of *Eubacterium rectale*. In terms of the drug duloxetine, gut bacterial interactions are involved in side effects such as weight gain, as well as in its mode of action [88, 144, 145]. Interestingly, another study indicated that *R. flavefaciens*, a type of intestinal microorganism, can reduce the antidepressant-like effect of duloxetine by impairing mitochondrial oxidative phosphorylation and neural plasticity in the medial prefrontal cortices [83].

Conclusions and Future Perspectives

There is a bidirectional relationship between antidepressants and intestinal microbiota. Antidepressants may alter the abundance and composition of intestinal microbiota, which is closely related to the treatment outcomes of depression. The mechanisms by which antidepressants mediate intestinal microbiota to alleviate depressive-like behaviors are unclear but some explanations have shed light on the microbial metabolites, neurotransmitters, and inflammatory factors in the brain-gut axis [3, 4, 146]. However, antidepressants may produce their effects through multiple mechanisms, and intestinal microbiota may just be one of them. Most recent studies have not performed behavioral experiments using germ-free mice, so these do not provide direct evidence of the effects of intestinal microbiota on the antidepressant actions of the drugs. Further investigations of the specific underlying

mechanisms are needed, to help us fully understand the role of the brain-gut axis in treating depression.

Intestinal microbiota can determine the efficacy of antidepressants by influencing their metabolism, drug absorption, BBB permeability, and bioaccumulation. These findings imply that it is important to consider intestinal microbiota when considering antidepressant therapy regimens. However, studies on the interaction between antidepressants and intestinal microbiota are insufficient. Forslund et al. [147] showed that medication intake, including dosage, drug combination, and previous exposure to antibiotics, can cause variations in the microbiome and clinical phenotypes. As there has been an increase in polypharmacy involving antidepressants [148, 149], it is necessary to investigate the combinatorial effects and dosage on the microbiome and treatment outcomes and how intestinal microbiota affect the efficacy of these drugs, especially at the molecular level. After understanding the molecular mechanisms by which intestinal microbiota influence the efficacy of antidepressants, new medications targeting the corresponding molecular sites may be developed. Further studies should focus on the detailed mechanisms of how intestinal microbiota influence the efficacy of different antidepressants and how doctors can better utilize the advantages and bypass the disadvantages in treating depression. Some techniques have been developed to predict and identify pharmacokinetic changes mediated by the microbiome [150, 151], including tools that can map the ability of the human gut microbiome to metabolize small-molecule drugs [152]; these may be helpful for doctors to administer personalized medicine and appropriate therapy regimens. However, several factors, including diet, mental illness status, exercise, and other medications can also cause alterations in the intestinal microbiota [80, 153–155], while few studies have been conducted and concluded their confounding effects on the treatment of depression. Most antidepressants are effective in reducing anxiety disorders, too [29]. General anxiety disorder and MDD share many common features [58], and there is considerable comorbidity between them [28]. However, the gut-microbial compositions in patients with general anxiety disorder and MDD are different, and there is a correlation between the bacteria and clinical symptoms [58]. As such, antidepressants may alleviate depressive behaviors by mediating anxiety-related microbiota. However, most studies targeting MDD patients have not considered the effects of anxiety comorbidity, which may cause some bias. More studies should be conducted to demonstrate the combined effects of confounding factors on intestinal microbiota and the treatment of depression.

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Declarations

Conflict of Interest The authors declare no competing interests.

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