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Review Article

The Impact of Antidepressants on Gut Microbiome and Depression Management

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Abstract: Depression is a widespread psychiatric disorder that significantly impacts an individual's quality of life. It affects mental and emotional well-being and has far-reaching consequences on their physical health, relationships, and overall ability to function in daily life. Recent advances in psychiatric research have revealed a connection between the gut-brain axis, a bidirectional communication system linking the brain's emotional and cognitive centers with intestinal functions. Antidepressants, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs), are commonly prescribed to alleviate symptoms of depression. However, their influence extends beyond neurotransmitter modulation in the brain to significant effects on gastrointestinal physiology. Antidepressants can alter gut motility, secretion, and microbiota composition, which in turn can influence mood and mental health. This review aims to provide insights into the impact of antidepressants on gut health and their implications for depression treatment. Additionally, it explores the potential of probiotics as an adjunct treatment to enhance the efficacy of antidepressants and mitigate gastrointestinal side effects. Restoring healthy gut microbiota can improve gastrointestinal and mental health outcomes, suggesting a promising avenue for integrated therapeutic approaches.

Keywords: Depression; gut-brain axis; antidepressants; gut health; probiotics; SDG 3 Good health and well-being

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1. Introduction

Depression is a deeply impactful mental health condition affecting millions worldwide[1–4]. It transcends mere sadness; it is a complex interplay of emotional, cognitive, and physical symptoms that can significantly impair one's daily life. Characterized by persistent feelings of sadness, hopelessness, and loss of interest in once-enjoyable activities, depression represents a profound challenge to mental well-being[5,6]. According to the World Health Organization (WHO), depression is projected to become the leading cause of global disease burden by 2030[7–9]. The COVID-19 pandemic further worsened these trends, with a notable increase in depression cases worldwide[10,11]. The increase in cases was driven by factors such as prolonged social isolation, heightened stress from health concerns and economic uncertainties, the experience of loss and grief, and disrupted routines[12,13]. The pandemic's widespread impact underscores the critical need for targeted interventions to reinforce mental health resilience in the face of ongoing global crises[12].

Antidepressants are the keystone in the management and therapies for depression[14]. The history of depression management goes back to the early twentieth century when amphetamines and barbiturates were the main therapeutics for depression[15]. It was not until the 1950s that antidepressants were developed[16]. The first antidepressant, an antitubercular drug, iproniazid, was discovered in 1953[17,18]. It was a serendipitous finding as the side effects of this drug elicited antidepressant properties such as improved mood, appetite, and sleep quality. Iproniazid was then used off-label to treat major depressive disorder (MDD)

and was known as the first monoamine oxidase inhibitor (MAOi)[19]. However, MAOi interacts with tyramine-rich foods such as cheese, wine, and other fermented foods, causing hypertensive crises and prompting further research on safer alternatives[19]. In 1959, imipramine, a tricyclic antidepressant (TCA), replaced MAOi as the first-line antidepressant due to its higher antidepressant potency[19]. Subsequently, the monoaminergic hypothesis of depression postulated in 1965 implicated a serotoninergic and noradrenergic dysfunction. This led research to focus on finding new drugs targeting serotonin (5-HT) reuptake. As a result, fluoxetine, a selective serotonin reuptake inhibitor (SSRI), was developed and later approved by the Food and Drugs Administration (FDA) in 1987 under the name Prozac®[16]. Importantly, clinical trials for fluoxetine lasted more than seven years before its release into the pharmaceutical market[19].

In clinical settings, SSRIs and selective noradrenaline reuptake inhibitors (SNRIs) are first-line antidepressants, whereas TCAs are second- or third-line antidepressants. SSRIs and SNRIs are considered first-line treatment in depression because they are linked with fewer adverse effects, and there is less danger of overdosing[20]. A multivariate analysis by Bet and colleagues reported that TCAs were independently linked to more side effects reports than SSRIs[21]. In a separate study investigating the safety of SSRIs in pregnancy, the Apgar score was deployed to evaluate neonates immediately after birth and in response to resuscitation based on appearance, pulse, grimace, activity, and respiration[22]. The Apgar scores showed that at the first and fifth minutes, there were no statistically significant links between newborns of mothers taking SSRIs and mothers taking placebos, indicating that SSRIs are relatively safe in pregnancy[23]. TCAs are reserved as second-line antidepressants due to the array of side effects related to their anticholinergic and antihistaminic effects, which could result in symptoms such as dry mouth, epigastric distress, constipation, urinary retention, delirium, and cardiovascular effects such as prolonged QT intervals[24]. However, the use of antidepressants has created new problems. One key problem is resistant depression, whereby both lines of antidepressants are ineffective against depressive symptoms. Thus, alternative ways to treat or complement antidepressants have been explored over time.

Recent research has unveiled a fascinating intersection between depression and the gut, where antidepressant medication, traditionally known for targeting neurotransmitters in the brain, might exert unexpected antimicrobial effects. One important area is the role of the gut microbiome in determining biological and psychological health. The concept of the microbiota-gut-brain axis explains the potential of gut microbiota in modulating brain and behavior[25]. Gut-brain axis modulation by the gut microbiota occurs via multiple possible direct and indirect pathways, such as endocrine (cortisol), neural (vagus and enteric nervous system), and immune (cytokine) pathways[26,27]. Importantly, depression is linked with hypothalamic-pituitary-adrenal (HPA) axis dysregulation[28]. The HPA axis has an important role in regulating cortisol secretion. A few important roles of cortisol are that it affects immune cells locally and systematically, changes gut permeability and barrier function, and changes gut microbiota composition. Additionally, the vagus nerve and modulation of systemic tryptophan levels and short-chain fatty acids (SCFAs) also play a part in brain and

behavior modulation[26]. Many studies have shown that probiotics could alleviate depressive symptoms[28–33]. For example, *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 can potentially reduce depression symptoms[34]. Hence, this review aims to provide insights into the impact of antidepressants on gut health and their implications for depression treatment. Moreover, it explores the potential of probiotics as adjunct treatments to enhance the efficacy of antidepressants and mitigate gastrointestinal side effects.

2. Mechanism of Action of Antidepressants

The antidepressants currently used in clinical practice include SSRIs, SNRIs, and TCAs (Table 1). TCAs and MAOi are first-generation antidepressants that alleviate depression by increasing the concentrations of 5-HT and/or norepinephrine[35]. Examples of TCAs include amitriptyline, nortriptyline, imipramine, and doxepin[36]. However, due to their undesirable side effects, their application is limited. Although both MAOi and TCAs increase the circulating monoamines in the synapse between the neurons, their mechanism of action differs. MAOi inhibits monoamine oxidase enzymes that metabolize catecholamines, resulting in an increase in synaptic catecholamines. On the other hand, TCAs block the reuptake of neurotransmitters, especially 5-HT, and norepinephrine, in the synapse between neurons, allowing a surge in concentration in the synapses, thereby increasing neurotransmission[36,37]. Nonetheless, TCAs are used if patients experience unwanted side effects or do not respond to SSRIs. According to Kohler-Forsberg *et al*., switching from an SSRI (escitalopram) to a TCA (amitriptyline) and vice versa is equally effective in reducing Montgomery-Asberg Depression Rating Scale (MADRS) scores in patients who are treatment-resistant to the first time antidepressant used[38].

SSRIs are the most commonly used first-line antidepressant due to their safety, tolerability, and efficacy. A possible explanation for its lower risk of side effects compared to TCAs and MAOi is that SSRIs have fewer effects on the adrenergic, histaminergic, and cholinergic receptors. Some examples of SSRIs include fluoxetine, sertraline, citalopram, escitalopram, paroxetine, fluvoxamine, and vilazodone[39]. The mechanism of action of SSRIs is specific to only serotonin, in which the reuptake of serotonin is inhibited, resulting in more serotonin activity. SSRIs inhibit the serotonin transporter (SERT) at the presynaptic axon terminal, allowing for more 5-HT to remain in the synaptic cleft so that postsynaptic receptors are stimulated for a longer period of time[39]. Interestingly, a positive-emission tomography (PET) imaging study by Meyer *et al*. found that the minimal therapeutic doses of SSRIs occupy roughly 80% of SERT in adults. This indicates an 80% 5-HT blockade is crucial for therapeutic effects[40]. However, some findings show chronic stimulation of 5-HT has effects on the norepinephrine system and vice versa. Hence, antidepressants with lesser side effects as a result of reduced affinities for other systems were developed, including SNRIs, which are dual reuptake inhibitors or multiple receptor-acting substances[35].

Table 1. Examples of commonly known antidepressants.

Class	Antidepressant examples
Selective Serotonin Reuptake Inhibitors (SSRI)	Fluoxetine, Sertraline, Citalopram, Escitalopram, Paroxetine, Fluvoxamine
Tricyclic Antidepressants (TCA)	Amitriptyline, Nortriptyline, Doxepin, Imipramine
Serotonin Norepinephrine Reuptake Inhibitors (SNRI)	Venlafaxine, Duloxetine, Desvenlafaxine

Besides inhibiting the SERT, antidepressants, including the MAOi and TCAs, result in the downregulation of 5-HT_{2A} receptors. An *in-vivo* study found that chronic treatment with desipramine reduces serotonin binding site in the cerebral cortex. A separate study showed that rats treated with TCAs had 5-HT_{2A} receptors downregulation in the frontal cortex. Nonetheless, it is important to note that not all SSRIs have the same effect on 5-HT_{2A} downregulation. For example, paroxetine has been reported to either have no effects or increases 5-HT_{2A} receptors. Conversely, citalopram downregulated 5-HT_{2A}. In summary, antidepressants have more than one mode of action in exerting its therapeutic effects in the management of depression[41].

Depression is the malfunction of the HPA axis and there seems to be an association between the serotonergic system and the HPA axis. In the depressed state, the surge in cortisol may decrease *l*-tryptophan availability, decrease 5-HT turnover, down-regulate presynaptic 5-HT_{1A} receptors, and upregulate 5-HT_2 receptors. Therefore, serotonin is important as it stimulates corticotropin-releasing hormone/factor (CRH) and adrenocorticotrophic hormone (ACTH) secretion and modulation of the negative feedback in the HPA axis via glucocorticoids[42]. Glucocorticoid receptors (GR) and mineralocorticoid receptors (MR) play a part in the negative feedback regulation of the HPA axis. In depression, besides the increase in baseline cortisol level, there is also an increase in functional activity of the MR system. Taken together with the decreased sensitivity to GR agonists, there seems to be an imbalance in the MR/GR ratio. Their balance affects the brain's serotonin system and may possibly have an etiologic role in serotonin receptor changes, especially 5-HT_{1A} downregulation seen in depression[43]. It has been suggested that antidepressants play a role in the upregulation of glucocorticoid and mineralocorticoid receptors.

In terms of brain plasticity, it seems that treatment with SSRI such as fluoxetine increases hippocampal and cortical volume, and this surge is associated with treatment response[16,44]. Barlett *et al*. found that patients who have a higher response to sertraline showed a thicker rostral anterior cingulate seen in magnetic resonance imaging (MRI) than those who did not respond to the drug[45]. Moreover, some studies showed that with antidepressant treatment, the peripheral measures of brain-derived neurotrophic factor (BDNF) surged and can correspond with clinical response[44]. Furthermore, a study on post-mortem patients previously treated with antidepressants demonstrated a surge in BDNF expression. Therefore, BDNF is possibly regulated by antidepressants and may be involved

in the pathophysiology of depression[46]. One study found the upregulation of BDNF plays a role in the actions of antidepressant treatment[47]. In addition, BDNF and neurotrophin 3 (NT-3) have demonstrated the ability to promote the growth and function of 5-HT containing neurons in an adult brain[35]. Moreover, the impairment of BDNF or its receptor, type 2 tyrosine kinase receptor (TrKB), seems to block the antidepressant effects of SSRI in rodents. This is of importance because there are reports of antidepressants increasing hippocampal neurogenesis, and this clearly shows the role of BDNF in this process[48]. Besides, SSRIs may have potential serotonergic effects. For instance, as the sertraline dose increases from 50mg to 200mg, the pharmacological properties of the drug change from an SSRI to a dual 5-hydroxytryptamine and dopamine reuptake inhibition, but the clinical significance remains uncertain[48].

Tryptophan depletion studies have also confirmed the association between serotonin and depression[42]. Tryptophan is mainly metabolized by two pathways (i) 5-HT pathway (ii) kynurenine pathway[49–51]. Tryptophan hydroxylase 1 (TPH1) is the rate-limiting enzyme in 5-HT biosynthesis. It converts tryptophan to 5-hydroxytryptophan (5-HTP), and is later converted to 5-HT by aromatic amino acid decarboxylase. Nonetheless, the dominant physiological pathway of tryptophan is along the kynurenine pathway. Indoleamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO) are the enzymes involved in the kynurenine production from tryptophan. It is important to note that the activation of either enzyme could have a dual impact by limiting tryptophan availability for 5-HT synthesis and increasing downstream neuroprotective or neurotoxic metabolite production[52]. Interestingly, there is evidence associating the kynurenine pathway metabolism with the gut microbiota, which will be discussed further below.

On the other hand, SNRIs which are currently used today include venlafaxine and duloxetine[36]. SNRIs are commonly recommended to those who do not respond to SSRIs[53]. Venlafaxine is the best known SNRI with a similar mechanism of action as TCAs but is safer and more tolerable[37]. The onset of venlafaxine is quicker than other antidepressants, which may be because of its acute onset of downregulation of beta-adrenergic receptors. The mechanism of action of SNRIs is that they inhibit the neuronal reuptake of 5-HT and norepinephrine at neuronal ends, resulting in a surge of both 5-HT and norepinephrine levels within the synapse[36]. In a study done by Carboni *et al*. which measures the effects of both venlafaxine and paroxetine on the Hamilton Depression Rating Scale (HDRS-17) scores, 70% of the patients taking each drug experienced a reduction in depressive symptoms. The increase in biomarkers, Il-6, IL-10, and tumour necrosis factor (TNF)-alpha is seen in MDD patients responsive to paroxetine, establishing a correlation between these biomarkers and the efficacy of the drug, but the same cannot be said for venlafaxine[54]. This is in contrast with a study conducted by Vollmar *et al*. which highlighted a decrease in IL-6 in a culture mixed with venlafaxine, along with a decrease in interferon (IFN)-gamma and the increase in transforming growth factor (TGF)-beta[55]. Nevertheless, a common biomarker affected by both drugs is the increase in BDNF, which indicates the efficacy of both drugs as the BDNF levels are decreased in patients with MDD[54,55]. The role of BDNF in depression is explained

by O'Connor *et al*., where rats with reduced BDNF showed reduced social interaction. Thus, the increase in BDNF is suggested to be linked to a drop in the severity of depression[56].

There are also newer antidepressants that block the reuptake of 5-HT while also having effects on a variety of 5-HT receptor subtypes. Examples are vortioxetine and vilazodone. Vortioxetine can bind to a few 5-HT receptor subtypes, including 5-HT_{1A}, 5-HT_{1B}, F-HT_{1D}, 5-HT_3, and 5-HT_7[53]. Vilazodone is a newer antidepressant that has been approved by the U.S. Food and Drug Administration (FDA) and is termed a 5-HT partial agonist and reuptake inhibitor (SPRAI). It works by blocking the SERT, desensitizes 5-HT receptors (particularly 5-HT_{1A} autoreceptors), and presumably increases the serotonergic neurotransmission[57]. According to Kadam *et al*., vilazodone is more efficacious than sertraline and amitriptyline, but the results of the study should not be generalized due to its small sample size[58].

3. Depressive Gut Microbiota

The gut microbiome plays a crucial role in maintaining the overall human health. Any disruptions in the delicate balance of the gut microbiome, known as dysbiosis, have been implicated in the pathogenesis of numerous diseases across our body systems[59–64]. There is evidence of a bidirectional communication via the gut-brain axis (GBA) between the gut microbiota and the brain and vice versa[65,66], and this crosstalk has been associated with major depressive disorder (MDD). Numerous human and animal studies have reported on the association between gut microbiota and mental illness, including MDD[67]. Depression is associated with inflammation, and there is evidence of MDD patients having an increased proinflammatory cytokine[68,69]. This leads to an imbalance of the gut flora. Hence, the gut microbiome profile differs between healthy and depressed patients. MDD patients showed significant alterations within the phyla *Actinobacteria*, *Bacteroidetes*, *Proteobacteria*, and *Firmicutes*[70].

Based on a study, patients with MDD have lower alpha diversity indices than healthy controls (HCs). Compared to HCs, MDD patients showed lower species richness and lower species diversity in their gut microbiome. Although the study found the relative abundance of *Bacteroides* and *Firmicutes* to be the highest among both HCs (92%) and MDD patients (90%), the average relative abundance of *Firmicutes* was significantly different, with 43.46% in HCs and 28.72% in MDD patients[71]. At the phylum level, Rong *et al*. and Chen *et al*. reported a rise in *Firmicutes* and *Actinobacteria* levels but a decrease in *Bacteroidetes* in MDD patients[70,72]. Zheng and colleagues also found that compared to healthy controls (HCs), the Actinobacteria level increased while the Bacteroidetes level decreased in MDD patients[73]. Although findings by Rhee *et al*. agree that MDD patients showed increased *Firmicutes* levels, they also found an increase in *Bacteroidetes* levels[74]. However, this increase in Bacteroidetes level is inconsistent with other studies[72,73,75]. The differences in the change in *Bacteroidetes* levels in the studies are currently unknown due to many confounding factors, such as the diet of the patients during the study period. Furthermore, considering depression is associated with inflammation and reduced *Bacteroidetes* levels are

also found in inflammatory bowel disease (IBD), the low levels of *Bacteroidetes* can be linked with intestinal inflammation and could act as an indicator of depression-related intestinal inflammation[70]. Nonetheless, more research is needed to verify the correlations between lowered *Bacteroidetes* levels and intestinal inflammation.

Findings on *Firmicutes* also showed inconsistencies as both Jiang *et al*. and Huang *et al*. found reductions in *Firmicutes* levels[71,76]. Nonetheless, Zheng and colleagues suggested that the inconsistencies in MDD patients could be due to the increase in some operational taxonomic units (OTU) of *Firmicutes,* while there is a decrease in other OTUs. This could also be why no significant difference was detected in the overall relative abundance of *Firmicutes* between MDD patients and HCs[73]. According to Huang *et al*., at the genus level, the majority of *Firmicutes* with decreased levels were from three families, *Faecalibacterium* from the *Ruminococcaceae* and *Dorea*, whereas *Coprococcus* of the *Lachnospiraceae* had the most significant difference ($P<0.001$)[71]. Moreover, Zheng and colleagues found MDD patients had 29 over-represented OTUs assigned to the families of *Erysipelotrichaceae incertae sedis*, *Coriobacterineae*, *Streptococcaceae*, *Actinomycineae*, *Lactobacillaceae*, *Clostridiales incertae sedis XI* (*Parvimonas*), *Ruminococcaceae* (*Clostridium IV*), *Lachnospiraceae* (*Anaerostipes*, *Blautia*, *Dorea*, *Lachnospiracea incertae sedis*), and *Eubacteriaceae*. Meanwhile in HCs, 28 over-represented OTUs were assigned to families of *Sutterellaceae*, *Bacteroidaceae*, *Veillonellaceae* (*Megamonas*), *Rikenellaceae* (*Alistipes*), *Acidaminococcaceae* (*Phascolarctobacterium*), and *Lachnospiraceae* (*Coprococcus*, *Clostridium XlVa*, *Lachnospiracea incertae sedis*, *Roseburia* and *Faecalibacterium*)[73]. Findings from both studies seem to associate MDD, particularly with the decrease in *Firmicutes*. In addition, Valles Colomer and colleagues highlighted that in MDD patients, *Faecalibacterium* and *Coprococcus* showed lowered levels while there was an increase in *Flavonifractor*[77]. This is consistent with other studies that showed reductions in *Coprococcus* and *Faecalibacterium* and increased *Flavonifractor* in MDD patients[73,76].

There is an important correlation between the biodiversity of the gut microbiome and the mental status of living beings, including animals. In a study conducted by Zheng and team, rats exposed to chronic unpredicted mild stress (CUMS) showed depressive-like behaviour after 11 weeks. There is also gut dysbiosis, as the metabolic products of amino acids by the gut microflora are altered. This was demonstrated by the reduction of indoxyl sulphate and indoxyl-3-acetate and the increase in hippurate, phenylacetylglycine, and N_2-succinyl-*L*- ornithine[78]. Interestingly, studies have also shown that transplanting the gut microbiota of depressed patients into germ-free mice[73] or rats with depleted gut microbiota[79], depressed-like behaviour was induced. In summary, all the literature suggests that the gut microbiome may have a role in the pathophysiology of MDD and could be targeted to treat or prevent MDD.

4. Effect of Antidepressant on Gut Microbiome

Antidepressants act mainly by inhibiting the cognate transporters in the brain, leading to an increased neurotransmitter concentration in the synaptic cleft. These depression-linked

receptors and transporters are also in the gut and modulated by the gut microbiome[67]. Moreover, more than ninety percent of 5-HT in the body is synthesized in the gut by the enterochromaffin cells (EC), myenteric neurons, and mucosal mast cells before being distributed to other body sites[80]. Host regulation, adequate nutrients, and competitive inhibition promote the stability of the microbial community. However, drug consumption, such as the use of antibiotics, could cause gut microbiome dysbiosis. Antidepressants could elicit similar effects by exerting constant microbial pressure and influencing community diversity in the gut[81].

The link between the restoration of the normal gut flora and the severity of depression is shown in a CUMS-induced depression rats model study conducted by Zhang *et al*.[82]. This study found that the fecal microbiota of CUMS rats that received 6 weeks of treatment with fluoxetine or amitriptyline showed a reduction in *Firmicutes* to *Bacteroidetes* ratio, with fluoxetine being more portent in causing the alteration. Fluoxetine and amitriptyline also increased the abundance of *Porphyromondaceae* family members and the genus *Alistipes* significantly compared to HCs and CUMS group. Additionally, the amitriptyline group showed an increased relative abundance of *Bacteroidaceae* compared to the CUMS group. Furthermore, rats in both fluoxetine and amitriptyline groups had an increased relative abundance of *Parabacteroides* and *Butyricimonas*, with the level of *Butyricimonas* increased to a similar level in HCs. This is beneficial as the genus *Butyricimonas* are butyrate producers with anti-inflammatory potential[82].

Butyrate is a short-chain fatty acid (SCFA) that plays a role in the colonic mucosal function, including inhibition of inflammation and carcinogenesis, oxidative stress reduction, colonic defence barrier reinforcement, promoting satiety, and maintaining colonic homeostasis[83]. A separate study on CUMS rats treated with fluoxetine showed an increase in *Erysipelotrichia* and *Proteobacteria* classes. The level of *Parasutterella* was also ameliorated after fluoxetine treatment. Moreover, the OTU level, bacterial taxa in *Aerococcus*, *Bacteroides*, *Enterorhabdus*, *Enterococcus*, *Escherichia*/*Shigella*, *Olsenella*, *Vagococcus*, and *Romboutsia* were increased in the CUMS group but was attenuated after fluoxetine treatment. Treatment with fluoxetine also resulted in the amelioration of bacterial diversity[84]. Results from these studies suggest the association between antidepressants and the gut microbiome and their role in restoring gut dysbiosis induced by stress.

Another study investigating the effects of escitalopram on the gut microbiome of rats with CUMS found increased alpha diversity of the gut microbiome in the treated rats. The study found that the rats that responded to escitalopram showed an increase in the genus *Prevotellaceae* UCG-003 and a decrease in families *Eggerthellaceae* and *Lactobacillaceae*[85]. Additionally, after fluoxetine treatment, at the OTU level, 17 OTUs were enriched, whereby 3 OTUs belonged to the genus Lachnospiraceae_NK4A136, and 3 OTUs belonged to the genus *Parabacteroides*[85]. This is beneficial as *Lachnospiraceae* is a SCFA butyrate producer[86]. These findings were consistent with the study mentioned above by Zhang *et al*.[82], which investigated the effects of amitriptyline and fluoxetine[82]. *Parabacteroides* have been shown to demonstrate protective effects in neurological

disorders, altering the levels of neurotransmitters in the brain, such as glutamate and gamma-aminobutyric acid (GABA) in the hippocampus[87].

Furthermore, a study on rats treated with one of five antidepressants, namely fluoxetine, escitalopram, venlafaxine, duloxetine, and desipramine, found that compared to the control group, the gut bacteria of the treated rats showed increased beta diversity. In terms of alpha diversity, all antidepressants except desipramine showed decreased richness in microbial while evenness was unaffected[88]. The finding on microbial diversity is consistent with the metacommunity theory that states the decreased alpha diversity of the gut microbial community leads to decreased dispersal of symbionts, resulting in a larger difference between the local community, which is higher beta diversity. The study also found that at the genus level, antidepressant-treated mice showed a decreased abundance of an unclassified genus in the order RF32, class *Alphaproteobacteria*, *Ruminococcus*, and *Adlercreutzia*. However, when using pairwise comparison to compare the control and each antidepressant, all antidepressants except fluoxetine showed the same genera to be less abundant[88]. This is similar to Sun and colleagues' findings, where the abundance of *Alphaprobacteria* increased after fluoxetine treatment[84]. A summary of the effects of antidepressants on the gut microbiome of depressed rodents is illustrated in Figure 1.

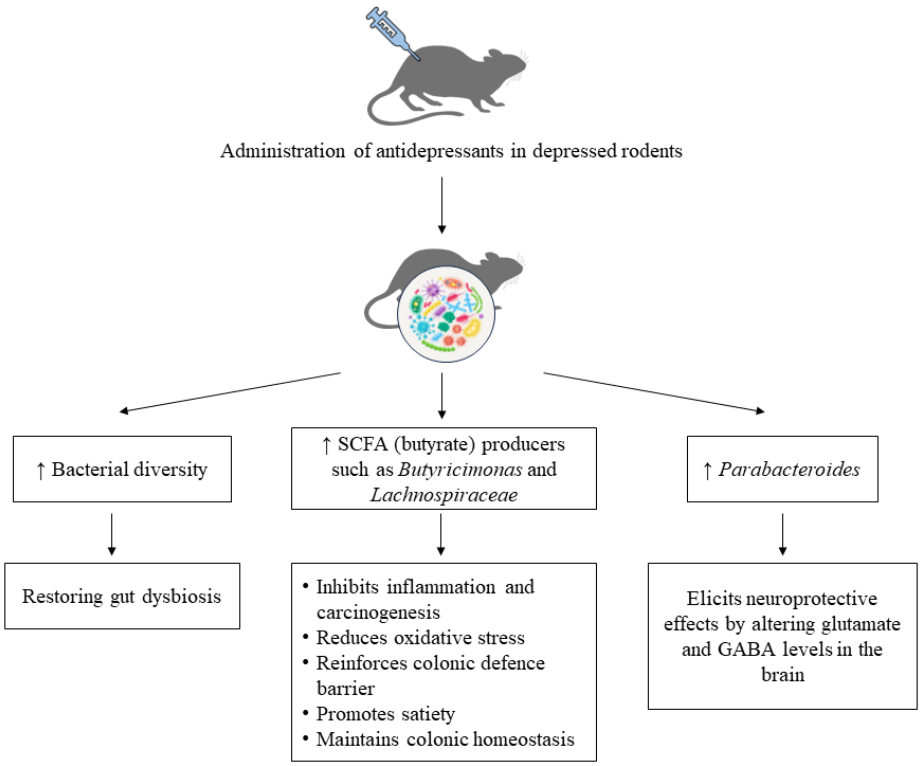

Figure 1. Effects of antidepressants on the gut microbiome of depressed rodents.

5. Probiotics as an Adjunct to Antidepressants

Although the efficacy of antidepressants has been well evidenced over the years, the preference for alternative treatments for depression is still strong among the public due to the risk of adverse effects[89]. Therefore, there is ongoing research on complementary and

alternative treatments for antidepressants. With the growing interest and evidence of using gut microbiome homeostasis to prevent and alleviate diseases, probiotics have become one of the potential adjunct treatments in managing mental illnesses[10,90,91]. Probiotics possess anti-inflammatory, anti-pathogenic, and antimicrobial properties, which are beneficial in restoring and maintaining intestinal homeostasis and microbial balance[10,91,92]. Hence, probiotics can be an adjunct treatment to antidepressants to restore the balance in the gut microbiome, subsequently reducing the severity of depression. The two most studied probiotics with antidepressant properties are *Lactobacilli* and *Bifidobacteria*[93].

In a study done by Xie and colleagues, depressed mice treated with *Lactobacillus reuteri* 3 demonstrated greater sucrose preference in the sucrose preference test (SPT), more exploring behaviour in the open field test (OFT), less avoidance of novel social stimuli compared to vehicle-treated mice, and longer immobility time in the tail-suspension test (TST), indicating a reduction in depression severity. The group of *L. reuteri* 3 treated mice also showed higher resilience to depression induced by stress relative to vehicle-treated mice (30% vs 14%). In addition, the blood and colon 5-HT levels were also enhanced in depressive-like mice by 1.2 and 1.4-fold after receiving *L. retueri* 3. Furthermore, the mean total SCFAs and acetate concentration initially higher in the depressive-like mice reduced significantly after treatment with *L. reuteri* 3[80]. This is in agreement with findings by Kelly *et al*., in which rats that received fecal microbiota transplant (FMT) treatment from depressed patients showed increases in fecal acetate and SCFA concentrations[79].

A study involving major depressive disorder (MDD) patients showed that MDD patients received SSRIs together with a daily dose of probiotics consisting of two capsules with 10×10^9 CFU of *Lactobacillus plantarum* 299v in each capsule for eight weeks. The patients demonstrated improved cognitive performance and decreased kynurenine concentration compared to those receiving only SSRIs and placebo[94]. These findings are beneficial as the kynurenine pathway has a potential role in the pathophysiology of depression[95]. As such, the gut microbiome could affect depression via the regulation of tryptophan metabolism both directly and indirectly. The gut microbiota can directly synthesize tryptophan through enzymes such as tryptophan synthase, while some bacterial strains have tryptophanase enzymes that produce indole from tryptophan, potentially limiting the availability of tryptophan to the host[49,52]. Bhattacharyya and colleagues reported that within the tryptophan pathway of the SSRI citalopram/escitalopram, there are reduced levels of 5-HT and an increase in indoles, which are affected by the human gut microbial metabolism[96]. Tryptophan availability and 5-HT synthesis can also be indirectly affected by the beneficial bacteria capable of reducing the activity of enzymes responsible for the degradation of tryptophan along the kynurenine pathway[52,97]. This is consistent with a meta-analysis that found probiotics can reduce the expression of indoleamine 2, 3-dioxygenase (IDO) and tryptophan 2, 3-dioxygenase (TDO), both enzymes responsible for the conversion of tryptophan to kynurenine[98].

Lactobacillus plantarum can modulate tryptophan and kynurenine metabolism, thus affecting 5-HT synthesis. Therefore, the surge in 5-HT synthesis results in reduced

tryptophan availability for the kynurenine pathway and a subsequent decrease in kynurenine concentration[94]. Hence, the gut microbiota and probiotics have important roles in regulating the kynurenine pathway of metabolism, affecting mood and cognition via the humoral route at the level of the central nervous system and gastrointestinal function[52]. One study involving depressed mice found increased plasma kynurenine to tryptophan ratio, which is consistent with the findings by Kazemi *et al*., where the MDD group taking daily probiotics showed a decrease in kynurenine to tryptophan ratio after adjusting for serum isoleucine[49,79]. Probiotics reduce the activity of enzymes that convert tryptophan to kynurenine, driving tryptophan along the 5-HT pathway. Hence, the drop in kynurenine to tryptophan ratio in the probiotic arm may be a mechanism for the observed effects on depression[49]. Nonetheless, more research is needed to identify further the associations between probiotics and the modulation of metabolic activity along the kynurenine pathway.

Bifidobacterium is another candidate of interest currently studied for its antidepressant properties. It was postulated that *Bifidobacterium* has serotonin regulation properties besides gut microbiome regulation. However, it is important to note that the abundance of *Bifidobacterium psedolongum* is negatively associated with colonic 5-HTP level, while *Bifidobacterium breve* has the opposite effect. Additionally, *B. breve* improved the metagenomic function of tryptophan biosynthesis, a crucial branch pathway that acts as a precursor for 5-HTP and 5-HT biosynthesis[99].

Tian and colleagues reported that the reduction in immobilization time in tail suspension and forced swim tests in rats give *B. breve* CCFM1025 is greater than that of fluoxetine. These rats also showed a higher sucrose preference than rats treated with fluoxetine. They also found both *B. breve* CCFM1025 and fluoxetine could normalize the ratio of *Actinobacteria* to *Proteobacteria*. However, they failed to restore the ratio of *Bacteroidetes* to *Firmicutes*[99]. Furthermore, treatment with *B. breve* CCFM1025 increased the abundance of *B. breve*, resulting in a decrease in *B. pseudolongum* due to competitive colonization. Other genus taxa that were normalized other than *Bifidobacterium* were *Allobaculum*, *Coprococcus*, *Bacillus*, and *Ruminococcus*[99]. A separate study also found *Bifidobacterium longum* subsp. *infantis* E41 and *B. breve* M2CF22M7 reduced depressive behaviour in mice in the SPT, step-down tests and force swim tests. It also increased the level of 5-HT and BDNF concentration in the brain, suggesting that probiotics possibly improve the synaptic signaling pathway and neuronal connections. Moreover, E41 also increased the concentration of cecal butyrate, possibly by increasing the SCFAs-producing bacteria, for instance, the *Candidatus* S24-7 family[100].

Besides, there are studies conducted on MDD patients using various probiotic formulations. Wallace and team found that daily supplementation of the combination of *Lactobacillus helveticus* R0052 (90%) and *Bifidobacterium longum* R0175 (10%) for 8 weeks reduced the MADRS scores in clinically naïve MDD patients from 24.9 at baseline to 12.7 at the end of the study, improving depression severity from moderate to mild[101]. Additionally, a randomized clinical trial conducted in Iran recruited MDD patients who took antidepressants (amitriptyline, citalopram, fluoxetine, sertraline) for ≥3 months prior to the

beginning of the trial. The participants were given daily probiotics containing freeze-dried *L. helveticus* R0052 and *B. longum* R0175 at a dosage of ten billion colony-forming units per five-gram sachet for 8 weeks. The results showed that the probiotics group (9.0–18.25) had a greater reduction in beck depression inventory (BDI) score than the placebo group (15.55–18.74)[49]. Based on the available literature, both *Lactobacillus* and *Bifidobacterium* are comparable in alleviating depression and restoring the gut microbiome, exerting positive effects in alleviating symptoms of depression (Figure 2).

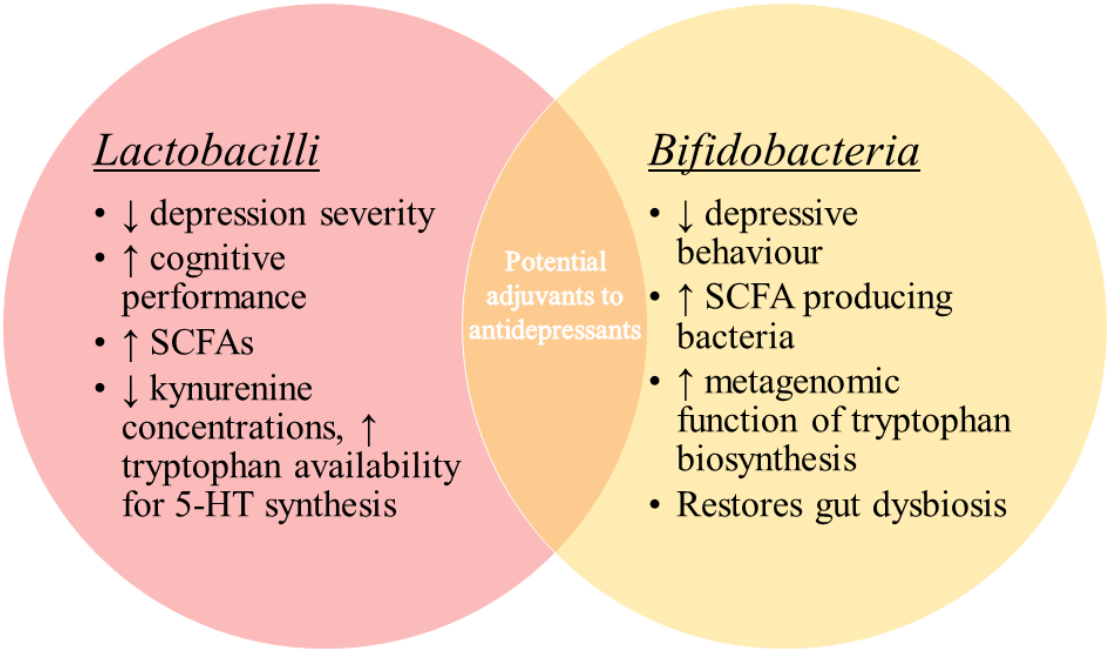

Figure 2. Positive outcomes of *Lactobacilli* sp. and *Bifidobacteria* sp. in depression.

6. Conclusion

Initially, clinically useful antidepressants work by increasing the synaptic concentration of 5-HT or NE; later, antidepressants that increase monoamine transmission were introduced[53]. Antidepressants have antimicrobial properties against certain gut microbiota but facilitate the growth and multiplication of other gut bacteria in returning the gut composition to a pre-depressive state. The antimicrobial properties of antidepressants are mainly seen in the decrease in the population of *Firmicutes* and *Actinobacteria*. In line with the reviewed literature, probiotics are seen to be a potential adjunct treatment for depression as they restore the gut microbiome, consequently alleviating depression. Probiotics help in gut modulation by reducing the inflammatory markers in the gut, and a combination of antidepressants and probiotics has a more optimal effect on the gut microbiome than antidepressants alone. In conclusion, this review provides insight into the mechanisms of action of antidepressants and their subsequent effect on the gut microbiome, followed by the investigation of the potential role of probiotics as an adjunct in depression therapeutics. These findings can facilitate future studies in finding effective probiotic strains that could be

administered with antidepressants to elicit synergistic effects in the management of depression.

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