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# Association between intestinal microbiota and major depressive disorder: a literature review

*Guilherme Bochi<sup>1</sup>, João Alberto Vieira Quincozes<sup>2</sup>*

1 Universidade Federal de Santa Maria (UFSM), Santa Maria, RS, Brasil.

E-mail: guilherme.bochi@ufsm.br | ORCID: <https://orcid.org/0000-0003-1871-1356>

2 Universidade Federal de Santa Maria (UFSM), Santa Maria, RS, Brasil.

E-mail: joaquincozes@hotmail.com | ORCID: <https://orcid.org/0000-0002-0872-1238>

## Abstract

**Objective:** major depressive disorder is a psychiatric disorder characterized by a set of symptoms, including necessarily depressed mood and/or anhedonia. Here the connection between intestinal microbiota and Major Depressive Disorder will be described and the recent advances in understanding their dysregulation in the etiopathogenesis of depression will be reviewed. **Methods:** for the literature review, it was consulted the PubMed database. **Results and discussions:** dysbiosis induced depressive-like behavior in animals. These animals presented characteristics observed in other models of induction of depression as a reduction in the Neurotrophic Factor Derived from the Brain (BDNF), increased inflammatory mediators, exaggerated response to the hypothalamic-hypophysis-adrenal (HHA) axis, and changes in the metabolism of serotonin and tryptophan. In humans, changes in the amount and microbial diversity of the gut are related to depression. In addition, the administration of probiotic bacteria reduced depressive symptoms. **Conclusions:** therefore, studies indicate that dysbiosis is closely related to the development of depressive symptoms.

**Descriptors:** Intestinal Microbiota; Major Depressive Disorder; Dysbiosis; Probiotics

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**Endereço correspondente / Correspondence**  
**address**

Hospital de Clínicas de Passo Fundo - Rua  
Tiradentes, 295 - Passo Fundo/RS - Brasil.  
CEP 99010-260

## Associação entre microbiota intestinal e transtorno depressivo maior: uma revisão da literatura

### Resumo

**Objetivo:** transtorno depressivo maior é uma desordem psiquiátrica caracterizada por um conjunto de sintomas, incluindo necessariamente humor deprimido e/ou anedonia. Neste estudo será descrito a relação entre microbiota intestinal e Transtorno Depressivo Maior e serão revisados recentes avanços no entendimento desta regulação na etiopatogênese da depressão. **Métodos:** para esta revisão narrativa, foi consultada o banco de dados PubMed. **Resultados e discussões:** disbiose induz comportamento semelhante ao da depressão em animais. Estes animais apresentaram características moleculares observadas em outros modelos de indução de depressão em animais, como redução do fator neurotrófico derivado do cérebro (BDNF), aumento de mediadores inflamatórios, resposta exagerada ao eixo hipotalâmico-hipófise-adrenal (HHA) e modificações no metabolismo da serotonina e triptofano. Em humanos, as mudanças na quantidade e na diversidade microbiana do intestino estão relacionadas à depressão. Além disso, a administração de bactérias probióticas reduziu os sintomas depressivos. **Conclusões:** portanto, estudos indicam que a disbiose está intimamente relacionada ao desenvolvimento de sintomas depressivos.

**Descritores:** Microbiota Intestinal; Transtorno Depressivo Maior; Disbiose; Probióticos

## Asociación entre microbiota intestinal y trastorno depresivo mayor: una revisión de la literatura

### Resumen

**Objetivo:** trastorno depresivo mayor es un trastorno psiquiátrico que se caracteriza por un conjunto de síntomas, que incluyen necesariamente un estado de ánimo deprimido y/o anedonia. Revisión de la literatura sobre la relación entre la microbiota intestinal y el trastorno depresivo mayor. **Métodos:** para esta revisión narrativa, se consultó la base de datos PubMed. **Resultados y discusiones:** disbiosis inducía un comportamiento similar al de la depresión en animales. Estos animales tenían reducción del factor neurotrófico derivado del cerebro, aumento de mediadores inflamatorios, respuesta exagerada al eje hipotalámico-pituitario-adrenal y cambios en el metabolismo de la serotonina y el triptófano. En los seres humanos, los cambios en la cantidad y la diversidad microbiana del intestino están relacionados con la depresión. Además, la administración de bacterias probióticas redujo los síntomas depresivos. **Conclusiones:** de hecho, los estudios indican que la disbiosis está estrechamente relacionada con el desarrollo de síntomas depresivos.

**Descriptorios:** Microbiota Intestinal; Trastorno Depresivo Mayor; Disbiosis; Probióticos

## Introduction

In 2015, according to the World Health Organization (WHO), approximately 322 million people were diagnosed with depression worldwide.<sup>1</sup> Even under medical treatment, about 30% of patients diagnosed with Major Depressive Disorder (MDD) are refractory to currently available pharmacological therapy and do not achieve symptom remission.<sup>2</sup> In addition, the latency time for therapeutic action, as well as the appearance of adverse effects, contribute to the abandonment of treatment.<sup>3</sup> These indices may be justified by the fact that MDD is a heterogeneous disorder and is not fully understood.

The pathophysiological and biochemical mechanisms of depression are still poorly understood.<sup>4</sup> There are many hypotheses to explain the development of this disorder. However, neither hypothesis fully explains the pathophysiology of depression. Alterations in neurotransmitters (mainly monoaminergic), inflammatory process (an increase of proinflammatory cytokines), neuroanatomic changes (mainly in the hippocampus and prefrontal cortex) and decreased levels of neurotrophins (including brain-derived neurotrophic factor - BDNF) seem to be processes involved in the development of this disorder.<sup>5</sup> More recently, there is evidence suggesting the involvement of the intestinal microbiota (IM) in processes relevant to the etiopathology of depression, making it a potential research topic.<sup>6</sup>

In general, IM is composed of approximately 100 trillion microorganisms in an adult individual, that is, around 10 times the number of human cells.<sup>7</sup> Among these, include virus, protozoa, archaea, fungi, and especially, strictly anaerobic bacteria.<sup>8</sup> Dysbiosis is the term used to refer to an IM imbalance and has been implicated in the development or exacerbation of mental disorders, including MDD.<sup>9</sup> The relationship between dysbiosis and MDD may involve different pathways. In this context, studies suggest that IM may influence the serotonergic neurotransmission, alterations in BDNF, dysregulation of the hypothalamic-hypophysis-adrenal axis (HHA axis), neuroimmune activation, and increased cytokines.<sup>10,11</sup>

In animals exposed to chronic stress protocol to induce a depressive-like behavior, the microbiota played an important role in the development of this behavior.<sup>12-14</sup> Germ-free animals presented responses similar to those observed in depressive patients, as well

as greater responsiveness of the HHA axis to stress, microglial deficit, and reduction of BDNF.<sup>11,15,16</sup> In addition, animals submitted to fecal microbiota transplantation (FMT) from depressive patients showed similar behavior to depression (the term “depression-like behavior” is used for animal studies).<sup>17,18</sup>

Considering that many findings point to IM as an important factor in the development of MDD, this study aims to develop a narrative literature review on the relationship between IM and MDD, as well as to describe the effects of probiotic compounds in the treatment of MDD. In addition, the investigation of more physiological factors and pathways has the potential to provide a broader base of data that may contribute to the understanding of the mechanisms and biochemical origins of MDD. For the literature review, it was consulted the *PubMed* database and the search was performed using the following *MeSH* terms and their associations: “gut microbiota and major depressive disorder”, “microbiome and major depressive disorder”, “microbiome and mental diseases”, “microbiome and mental disorders”, “microbiome and mood disorders”, “probiotics and mood”. In addition to these, the *MeSH* terms “probiotics” or “Bifidobacterium” or “Lactobacillus”, associated with “depression” or “major depressive disorder” were included. The search limits and categorization of the studies were: articles published in the last five years, human and animal studies, study methodology (review articles, clinical trials, and scientific papers from preclinical studies).

## Major depressive disorder

MDD is a psychiatric disorder whose main alteration exhibited by the patient is depressive mood and/or anhedonia during most of the day.<sup>19</sup> Other symptoms include unintentional weight gain or loss, insomnia or hypersomnia, psychomotor agitation or apathy, fatigue or loss of energy, permanent feelings of guilt and worthlessness, difficulty concentrating, and recurrent thoughts of suicide or death.<sup>20</sup> According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), the requirements for the diagnosis of MDD include, obligatorily, depressed mood, or anhedonia for at least two weeks, associated with other symptoms characteristic of the disorder.<sup>20</sup>

Depression has a multifactorial etiology, and there are both genetic and environmental factors related to the disease. Despite advances in the pathophysiology of depression, no established mechanism can explain all aspects of the disease.

## Physiopathology of depression

The pathophysiology of depression is not fully elucidated and the hypotheses that suggest the biochemical and molecular mechanisms involved in MDD are many.<sup>21</sup> For many years the monoaminergic hypothesis was predominant. Depression would be caused by reduced levels of monoaminergic neurotransmitters, especially serotonin and noradrenaline.<sup>22</sup> Today, it is suggested that MDD is not caused solely by a monoamine deficiency.<sup>23</sup>

One of the most emphasized hypotheses of depression today is the imbalance in the HHA axis. Hyperstimulation of the HHA axis seems to be an important factor in the pathophysiology of depression.<sup>24</sup> In this context, chronic administration of corticosterone (the main glucocorticoid hormone of rodents) is an accepted model to induce depressive-like behavior in rats and mice.<sup>25,26</sup> In addition, it has been shown that increased levels of cortisol in humans induced atrophy in the hippocampus and this has been implicated in the cognitive deficit of depressed patients.<sup>22</sup>

Studies also indicate that BDNF plays an important role in neuronal growth and proliferation, being their levels decreased in patients with MDD, as well as in animal models of depression.<sup>22,27,28</sup> The neurotrophic hypothesis, in sum, suggests that stress leads to reduced expression of this neurotrophin and, consequently, the atrophy of certain brain areas, mainly the hippocampus and prefrontal cortex.<sup>29</sup>

The inflammatory hypothesis also aims to explain the biochemical and molecular origins of depression. It has been reported a positive association between depression and cytokines increase, mainly interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-1beta (IL-1 $\beta$ ), and interferon-gamma (IFN- $\gamma$ ) and, also, acute-phase inflammatory proteins.<sup>30,31</sup> The inflammatory response is also capable of activating the HHA axis.<sup>22</sup> In addition, it also activates microglia, which are innate immune cells of the Central Nervous System (CNS)

responsive to pathogens and brain lesions.<sup>32,33</sup> In these situations, the microglial cells secrete neurotoxic factors such as TNF- $\alpha$ , IL-1 $\beta$  and nitric oxide (NO).<sup>34,35</sup> In this sense, microglial activation was observed in depressive patients who committed suicide.<sup>36</sup>

Thus, it has been suggested that the association of the various processes involved, such as those mentioned above, are part of MDD. That is, in sum, the hypotheses of depression are interconnected (Figure 1).

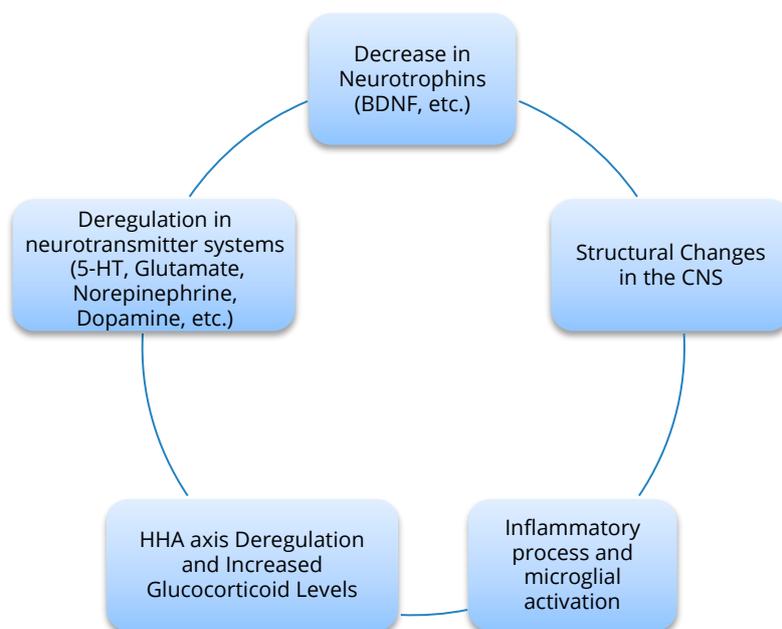


Figure 1 - Main events related to the development of MDD.

Source: the authors.

Abbreviations: BDNF: Neurotrophic factor derived from the brain; CNS: Central nervous system; HHA: hypothalamic-hypophysis-adrenal; 5-HT: 5-hydroxytryptamine.

## IM and MDD

Studies in humans and animals demonstrate that the IM may perform modulatory functions in depression. According to Winter and collaborators (2018), the IM may be able to produce different humorous chemical substances that would enter the brain and affect their functions.<sup>37</sup> Another hypothesis is that the brain affected by depression induces changes in the microbiome through the HHA axis and the immune system, leading to intestinal symptomatology that, consequently, would exacerbate the symptoms of depression.<sup>37</sup>

According to Sherwin and collaborators (2016), biological mechanisms that support neuropsychiatric conditions, such as depression, include deficits in serotonergic neurotransmission, BDNF changes, immune activation, and HHA axis dysregulation, being all processes that can be regulated by some bacteria residing in the intestine.<sup>11</sup>

## **BDNF and IM in MDD**

BDNF is fundamental for brain plasticity, memory, neurogenesis, and neuronal health, being verified its increase in the treatment of depression.<sup>38</sup> On the other hand, low levels of this neurotrophin were associated with MDD.<sup>39,40</sup>

Recently, studies have suggested that IM influences the expression of BDNF. BDNF messenger RNA (mRNA) in the hippocampus and IM were decreased with chronic administration of antibiotics in adolescent rats.<sup>41</sup> Germ-free mice also exhibit reduced expression of hippocampal BDNF compared to normally colonized mice.<sup>42</sup>

The bacterial composition is related to changes in BDNF levels. In this sense, Jiang et al. (2015) demonstrated that bacteria of the genus *Clostridium* were negatively associated with the serum concentrations of this neurotrophin.<sup>43</sup> Furthermore, Liang et al. (2015) with probiotic supplementation of *Lactobacillus helveticus* in rodents, showed increased levels of BDNF mRNA in the hippocampus and at the same time reduced the type-depression and anxiety behavior.<sup>44</sup> Moreover, O'Leary and colleagues (2018) observed that vagotomy decreased the expression of BDNF mRNA in the hippocampus and was associated with changes in the development of immature neurons in mice.<sup>45</sup> The results of this study suggest that the activity of the vagus nerve influences the neurogenesis through the BDNF, being this one of the pathways of the microbiota-gut-brain (MGB) axis.

## **Serotonin and the metabolism of tryptophan interlocking IM and depression**

Serotonin, or 5-hydroxytryptamine (5-HT), is an excitatory neurotransmitter of the CNS, but also synthesized and released by intestinal enterochromaffin cells. Approximately 90% of 5-HT is synthesized in the Gastrointestinal Tract (GIT), being

involved in the regulation of intestinal secretions, gastrointestinal motility (contraction and relaxation of smooth muscle), and pain perception.<sup>46,47</sup> In the CNS, serotonergic signaling is involved in pathways implicated in the regulation of mood and cognition.<sup>48</sup> Its biosynthesis occurs from the essential amino acid tryptophan, not so much CNS as not Enteric Nervous System (ENS).<sup>49</sup>

Most of the tryptophan digested (about 90%) is metabolized in kynurenine by the tryptophan dioxygenase and indoleamine 2,3-dioxygenase (IDO) enzymes, while only 3% is converted to serotonin.<sup>50,51</sup> The remainder is degraded in indole and its derivatives by IM.<sup>52</sup> The action of these enzymes can be triggered by the increase of proinflammatory cytokines and corticosteroids, which generate more kynurenine, implying the reduction of serotonin.<sup>50</sup> The activation of the kynurenine pathway in the brain is related to symptoms of depression, such as persistent sadness, anhedonia, and decreased energy levels.<sup>53</sup> Bradley and colleagues (2015) reported that patients with MDD presented activation of the kynurenine pathway.<sup>54</sup>

kynurenine can be metabolized in two distinct products, one being neurotoxic (such as quinolinic acid) and another neuroprotective (such as kynurenic acid).<sup>38</sup> Already been demonstrated that patients with MDD who had attempted suicide presented increased levels of quinolinic acid in the cerebrospinal fluid (approximately 300% higher) when compared to non-depressive individuals.<sup>55</sup> Naslund and collaborators (2013) found that the inhibition of tryptophan hydroxylase (an important enzyme in serotonin biosynthesis) decreased serotonin in the rat brain, which presented anxiety behavior, demonstrating that peripheral tryptophan could interfere with brain activity.<sup>56</sup> In this sense, reduction of plasma tryptophan was associated with the reestablishment of depressive symptoms in individuals who successfully responded to SSRI antidepressants.<sup>57,58</sup>

IM proves to have importance in the metabolism of tryptophan, considering that the plasma concentrations of this amino acid in conventionally created mice (with germs) are 40% lower when compared to germ-free mice.<sup>59</sup> *Lactobacillus* spp., for example, can synthesize and metabolize tryptophan, resulting in immunological regulation and protection of the intestinal mucosa.<sup>60</sup> Certain intestinal bacteria may decrease the activity of enzymes responsible for the degradation of tryptophan or even degrade directly through

tryptophanases.<sup>61</sup> They may also synthesize it, as some express tryptophan synthase.<sup>62</sup>

It has also been demonstrated that germ-free mice have increased concentrations of serotonin and 5-hydroxyindoleacetic acid (5-HIAA, the main catabolic product of serotonin) in the hippocampus, increased plasma tryptophan, and decreased expression of hippocampal BDNF.<sup>16</sup> On the other hand, plasma levels of serotonin were decreased in germ-free mice compared to conventional mice.<sup>59</sup> These differences in serotonin levels still need to be explained through molecular mechanisms.<sup>63</sup>

Studies have also shown that germ-free mice have higher serotonin transporter (SERT) expression, suggesting its regulation by IM.<sup>64</sup> Altered expression of SERT leads to interruption of serotonin transmission and, in this context, data indicate an association between the interruption of serotonin signaling, intestinal inflammation and consequent alteration in intestinal motility and the development of the depressive syndrome.<sup>65,64</sup>

Finally, Kelly and collaborators (2016) observed that the FMT of patients with MDD for rodents with IM deficiency-induced signs of depressive symptoms, as well as changes in tryptophan metabolism.<sup>18</sup> This suggests that the microbiota may influence the onset of depression.

In an attempt to restore depleted or unbalanced IM, for clinical purposes in MDD, transferring fecal material from a healthy donor to the depressed one may in the future be feasible. In this perspective, when the mechanisms of the MGB axis are better understood, FMT can assist in the treatment of depression.<sup>66</sup>

## Inflammation and MGB axis in MDD

The expression of the proinflammatory cytokines (IL-1 $\beta$ , IL-6, TNF- $\alpha$ , IFN- $\gamma$ ) and C-reactive protein has been observed in depression.<sup>67-69</sup> However, the pathways by which cytokines act in MDD are not well understood.

A hypothesis supports the idea that with greater intestinal permeability, parts of the cell wall of gram-negative bacteria, such as lipopolysaccharide (LPS) endotoxin, and other forms of residues, toxins, and even whole bacteria, can be translocated into the

bloodstream, triggering the production of cytokines by innate immune cells (eg, macrophages) through the activation of toll-like receptors 4.<sup>70</sup> Translocation of intestinal LPS may be a trigger for peripheral and central inflammation.<sup>71</sup> In this perspective, administration of LPS endotoxin in healthy humans resulted in increased salivary cortisol, plasma noradrenaline, and proinflammatory cytokines, being associated with depressive behaviors.<sup>72</sup>

In a study involving 112 patients diagnosed with MDD and 28 normal volunteers, Maes and collaborators (2012) demonstrated increased levels of antibodies against LPS (IgM and IgA) in the peripheral blood of patients.<sup>73</sup> These findings suggest an increase in intestinal permeability in MDD, which allows bacterial products and cytokines to enter the systemic circulation, cross the blood-brain barrier (BBB), promoting changes in the brain and the behavior.<sup>74,75</sup> In the CNS, cytokines may act on receptors expressed in the microglial cells. In general, the onset of depression has intense inflammation in the brain or activation of microglia<sup>76</sup>, being the microglial disorder one of the hypotheses of depression. In studies with models of the absence of complex microbiota (such as germ-free mice), there was lower microglial activity after LPS administration.<sup>77</sup>

Another hypothesis concerning MDD is that stress alters the composition of IM, resulting in positive regulation of proinflammatory pathways mediated by NLRP3 inflammasome (also known as NALP3). Signaling involving NLRP3 may result in the expansion of bacterial species with proinflammatory effects and, consequently, reduce the levels of monoamines and neuroactive compounds available in the CNS.<sup>78</sup> In addition, the activation of NLRP3 is related to an increase in the symptoms of depression and intestinal dysbiosis.<sup>78</sup> In this sense, a therapeutic alternative would be to reduce the activity of NLRP3 through the administration of bacteria with immunoregulatory and anti-inflammatory properties.<sup>79-81</sup>

In the state of inflammation, altered levels of neurotransmitters, such as serotonin, are also detected in the intestine.<sup>82-84</sup> Changes in intestinal motility coming from this serotonergic dysregulation could stimulate the depressive state, however, more research is needed to prove it.

## Deregulation of the HHA axis and IM in MDD

HHA axis dysregulation, together with increased plasma levels of proinflammatory cytokines, are common in depression.<sup>85,86</sup> In this sense, bacterial translocation, that is, the displacement of bacteria and/or their products (eg endotoxins) from the lumen of the GIT to mesenteric lymph nodes and other organs<sup>87</sup>, increases cytokines in the blood and consequently generates stress that sensitizes the HHA axis to the activation, generating depressive behavior.<sup>88-91</sup> Weerth (2017) indicates that changes in HHA axis activity, induced by environmental stressors, may be involved with intestinal dysbiosis, intestinal permeability, and low-grade inflammation, which in turn influence CNS actions.<sup>92</sup>

Sudo and colleagues (2004) observed that germ-free mice exhibited an exaggerated response of the HHA axis with stress induction, presenting an increase in ACTH and corticosterone levels when compared to normal IM animals.<sup>15</sup> This response was reversed through colonization with *Bifidobacterium infantis* in neonatal animals.<sup>15</sup> This beneficial effect of recolonization did not occur after vagotomy, suggesting that the vagus nerve is an important communication pathway between probiotics and the brain.<sup>12</sup> In the same study by Sudo et al. (2004), the recolonization of IM with probiotics did not reverse the exaggerated response of the HHA axis in adult mice, indicating the existence of critical neurodevelopment windows. These time-specific windows indicate that IM would affect the CNS early in life, interfering in the brain and behaviors of the future life.<sup>15</sup>

Dysregulation of the HHA axis has been identified in mood disorders, with dysbiosis being one of the factors that could alter it. In this context, considering that IM imbalance stimulates inflammation and that certain bacteria can trigger the release of proinflammatory cytokines, the reduction of inflammatory pathways may be a potential strategy to normalize the hypothalamic-pituitary-adrenal structures.

## Composition of IM in MDD

It is estimated that IM comprises  $10^{13}$  to  $10^{14}$  microorganisms (10 times the number of cells in the body), being composed of approximately 75% Firmicutes and Bacteroidetes.<sup>93-95</sup> However, it is

recognized that approximately two-thirds of the microbiota is not common among most humans.<sup>94</sup> It is generally accepted that the stability of the intestinal community and the diversity of species are characteristic of a healthy microbiota.<sup>38</sup> Kelly et al. (2016) observed lower amount and microbial diversity in the gut of patients with depressive disorder.<sup>18</sup> The same study reveals that the transfer of fecal material from depressive patients to mice results in behavioral signs (increased anhedonia and anxiety-like behaviors) and physiological (alterations in the tryptophan metabolism) characteristic of the depressive syndrome. However, this discussion is not yet fully defined.

Jiang and collaborators (2015) reported a greater fecal microbial diversity in patients with MDD. Bacteroidetes were increased in depressive patients (mainly the genera *Parabacteroides* and *Alistipes*).<sup>43</sup>

According to a study in which an IM depletion of adult rats was induced through the administration of antibiotics, a decrease in both Firmicutes and Bacteroidetes was demonstrated, as well as an increase in the type-depressive behaviors.<sup>96</sup> In humans, the use of antibiotics was related to depression in the first year of life.<sup>97</sup>

Although the compositional results of IM are sometimes conflicting, depression shows to be associated with changes in the abundance of certain bacterial genera. In addition, the inconsistent data may be due to the composition of the microbiome being influenced by age, genetics, metabolism, diet, geography, health status, stress, and medications.<sup>98-100</sup>

Changes in the abundance of some bacterial genera were observed. However, considering the high interindividual variability of the normal microbiota, large samples are necessary to obtain more significant findings.<sup>101</sup>

## Bacterial compounds and MDD

The influence of IM on neuropsychiatric disorders, including depression, may be related to the ability of the microbiota to synthesize neuroactive and immunomodulatory compounds, such as short-chain fatty acids (SCFAs) and important neurotransmitters. The species *Lactobacillus brevis*, *Bifidobacterium dentium*, and *Bifidobacterium infantis* seem to synthesize the neurotransmitter GABA.<sup>102</sup> Other bacteria, including *Lactobacillus lactis* subspecies

*cremoris*, *Lactobacillus lactis* subspecies *lactis*, *Lactobacillus plantarum*, *Streptococcus* spp., *Escherichia* spp., *Enterococcus* spp. appear to synthesize serotonin, while *Bacillus* spp. produce dopamine and noradrenaline in the gut.<sup>103,104</sup>

Based on another study, a higher concentration of *Oscillibacter* was observed in patients with MDD. This genus produces valeric acid (a SCFAs), which is similar to GABA.<sup>105,106</sup> Regarding the neurotransmitter GABA, it has already been demonstrated that there is a dysfunction in the GABAergic system in depression.<sup>107</sup>

Although reports of the potential of bacteria compounds influence the brain, remains unclear if they directly reach the sites in the CNS or only induce central responses via long-distance activities via the vagal and/or spinal nerves.<sup>109,108</sup> Further studies are needed to determine if these neurotransmitters and neuroactive molecules derived from IM alter neurotransmitter systems in the CNS.

## Probiotics in the treatment of MDD

Probiotics are live microorganisms that, when administered in appropriate doses, confer health benefits.<sup>110</sup> Experimental studies have shown that the probiotic *Lactobacillus helveticus* increased concentrations of BDNF and serotonin in the hippocampus and reduced depression.<sup>44</sup> In another study, the administration of *Lactobacillus plantarum* in germ-free mice increased the serotonin and dopamine levels in the striatum, but did not show significant effects on depression behaviors.<sup>111</sup>

In patients with MDD, administration of eight weeks of strains of *Lactobacillus acidophilus*, *Lactobacillus casei* and *Bifidobacterium bifidum* strains reduced depression scores as well as serum C-reactive protein levels and attenuated oxidative stress.<sup>112</sup> Similarly, administration of *Lactobacillus helveticus* and *Bifidobacterium longum* ( $\geq 10 \times 10^9$  CFU/5g) for 8 weeks improved depression scores (BDI).<sup>113</sup>

Probiotics may also reduce inflammation and, consequently, increase the integrity of the intestinal barrier, thereby preventing bacterial translocation.<sup>114,115</sup> Desbonnet et al. (2010) showed that Sprague-Dawley rats treated for 14 days with *Bifidobacterium infantis* had significant decreases in cytokines (IFN- $\gamma$ , TNF- $\alpha$ , and IL-6) and 5-hydroxyindolacetic acid concentration (serotonin metabolite), as

well as marked increases in plasma concentrations of tryptophan and kynurenic acid.<sup>13</sup> In the maternal separation model, this probiotic restored basal noradrenaline concentrations, normalized the immune response, and decreased the depressive behavior<sup>13</sup>.

Probiotics have been shown to be a potentially beneficial intervention in depressive syndrome. In addition, they have a more favorable safety and tolerability profile, with no serious adverse effects in the short and medium-term and with lower latency than typical antidepressants. However, the probiotic strain, dosage and duration of treatment used varied significantly. Therefore more studies are needed to identify these variables.

## Conclusion

The accumulation of evidence, especially in experimental animals, supports the hypothesis that IM plays an important role in depression. Dysbiosis appears to be associated with HHA axis dysregulation, BDNF reduction, alteration of neurotransmitters and tryptophan metabolism, and stimulation of inflammatory pathways. These possible mechanisms also involve MDD.

Although it is not clear whether changes in IM are the cause or consequence of depression, the lines of evidence open windows to better understand MDD. A deeper assessment of the MGB axis, in order to elucidate its mechanisms, becomes necessary to unravel all microbiota-depression connections.

Targeting MDD studies to the MGB axis opens options for antidepressant treatments, including transfers of healthy microbiota to patients and manipulation of the composition of the microbiota with bacteria that produce neuroactive and immunomodulatory substances.

Lastly, it is noted that the administration of probiotics as primary and/or adjunctive treatment, preventive or even after pharmacological therapy, seems promising.

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