PSYCHOBIOLOGISTS IN THE TREATMENT OF DEPRESSION: A NEW LOOK AT MENTAL HEALTH – A SYSTEMATIC SEARCH REVIEW

REVIEW ARTICLE

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ABSTRACT

Major Depressive Disorder (MDD) is a multifactorial psychic disorder, conventionally treated with antidepressant medications. The symptoms caused by the depressive symptomatology itself and the side effects caused by the medications are some of the factors that negatively interfere in the adherence to pharmacological treatments. Currently, after probiotics have shown psychotropic effects, the scientific field has intensified efforts to understand whether probiotic supplementation serves as a treatment for psychiatric disorders. Therefore, the present study formulated the following question: can psychobiotics (probiotics) be denoted as a treatment for Major Depressive Disorder? Objective: to answer the guiding question through a review of studies that supplemented psychobiotics with the intention of treating Major Depressive Disorder. Methodology: for this review, a systematic search was designed, where, during the month of September 2021, the searches took place in the databases; Pubmed, Google Scholar, and Scielo, using the descriptors “probiotics AND depression AND dysbiosis” in English and Portuguese, and filters for

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the selection of studies published between 2005 and 2021. After selecting the materials, the duplicates were managed in *EndNote*, and the methodological quality of randomized trials was assessed using the *Risk of Bias-2* (ROB 2) tool. Results: there was a preference for 10 studies; preclinical (n=4), randomized (n=5) and open pilot (n=1), which met the inclusion criteria, and showed significant results on depression scores on psychiatric scales; demonstrating the decrease in anhedonia, cognitive reactivity, and insomnia in patients diagnosed with Major Depressive Disorder, in addition, significant changes were observed on factors that may be associated with the pathogenesis of depression, such as dysbiosis, and the inflammatory state in the face of the decrease of inflammatory biomarkers. Final considerations: according to the data review, the following answer was obtained for the guiding question: psychobiotics can be denoted as a treatment for Major Depressive Disorder. However, due to the need for a better understanding of the gut-brain axis and the mechanisms of action of psychobiotics, supplementation is recommended as an adjunctive therapy to antidepressant drugs. Therefore, studies with larger samples and longer intervention periods should be performed.

Keywords: Major Depressive Disorder, Probiotics, Dysbiosis.

1. INTRODUCTION

According to the World Health Organization (WHO, 2020) about 300 million people suffer from depressive disorders worldwide. This disorder has prevailed among men (5 to 12%) and women (10 to 25%), and occupies the second place in the burden of diseases that cause more damage in the economic and social sphere, and in the health field (MOTTA; MORÉE; NUNES, 2017; ZALAR; HALSBERGER; PETERLIN, 2018).

According to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-V), Major Depressive Disorder (MDD) is diagnosed when a person experiences at least 5 of the following symptoms for 2 weeks: depressed mood, anhedonia, excessive guilt, suicidal ideation, changes in appetite and sleep, psychomotor retardation, lack of
concentration and fatigue. Among these criteria, anhedonia or depressed mood (or both) must be present to be considered for diagnosis (BAPTISTA, 2018).

When diagnosed, the use of antidepressants is considered the first option for treatment, however, 30 to 40% of patients do not show significant responses, while 60 to 70% do not experience the expected remission of the disease (YUAN et al., 2020). In addition, it is also common for patients to give up pharmacological treatments, due to side effects and difficulties in following a routine (IBANEZ et al., 2014). Among other reasons, social stigma, lack of resources and trained professionals are also obstacles to treatment adherence (WHO, 2020).

As a result, the search for new therapies has had repercussions among researchers, rooting the term “gut-brain axis” in scientific language. The mechanisms of this axis have been widely studied after insights from research that evidenced that the gut and the brain have a bidirectional communication and a complex structure that links the central nervous system to the enteric nervous system and to multiple metabolic, inflammatory and endocrine pathways. Therefore, it is presumable that in these “underlying paths”, there are a number of factors to be examined (KONTUREK; BRZOZOWSKI; KONTUREK, 2011; MAYER, 2011).

So far it is understood that within this communication the intestinal microbiota is one of the main intermediary factors. This fact makes it a priority for treatment to understand how gut microbes generate signaling over multiple pathways. In addition, it is also essential to consider that there are disparities in the composition of the microbiota between individuals and in different clinical populations. Thus, modulating and transplanting the microbiota are discussed as alternatives for the treatment of psychiatric diseases and disorders (BERCIK; COLLINS; VERDU, 2012; DORÉ et al., 2013; SMITS et al., 2013).

However, the gut microbiota is complex, comprising approximately 100 trillion living microorganisms that generate a relatively stable lifelong composition. This composition, although “stable”, can undergo changes called “dysbiosis state”, an imbalance often associated with a number of diseases (FORSYTHE et al., 2010;
RODRÍGUEZ et al., 2015). Several factors are considered to influence this state (of dysbiosis). According to David et al. (2014) and Wu et al. (2011) diet is one of them, while Goodrich et al. (2014) consider genetics, Yatsunenko et al. (2012) age, O'mahony et al. (2009) and Werbner et al. (2019) stress, and Markle et al. (2013) the influence exerted by different sex hormones.

Consequently, with the aim of rebalancing the microbiota, probiotics have been exponentially studied. Research has also employed the use of prebiotics, as prebiotics and probiotics work in synergism and soften the presence of harmful bacteria in the intestine providing important adjustments (VARAVALLO; THOMÉ; THESHIMA, 2008; TSAI et al., 2019).

Recently, in the field of psychiatry, probiotics have also become the target of research after it was evidenced that they produce “psychotropic effects”, and for this reason they were conceptualized as psychobiotics: “a living organism that, when ingested in adequate amounts, produces a health benefit of patients suffering from psychiatric illnesses” (DINAN; STANTON; CRYAN, 2013; DINAN; CRYAN, 2016).

In view of the deepening of the search for psychobiotics, it is observed that review articles have more frequently reported preclinical studies, and there are still few reviews on studies that intervened in humans diagnosed with MDD (BERCIK; COLLINS; VERDU, 2012); CRYAN; O'MAHONY, 2011; HUANG; WANG; HU, 2016; LIU; WALSH; SHEEHAN, 2019; YONG et al., 2020). Thus, new reviews analyzing the methodological quality of the most recent studies are vital for this growing area of research.

Therefore, the present study formulated the following question: can psychobiotics be denoted as a treatment for Major Depressive Disorder? Therefore, the objective was determined: to answer the guiding question through a review of studies that supplemented psychobiotics with the intention of treating Major Depressive Disorder. These supplements are administered both in the adjuvant form of antidepressant drugs, and in the autonomous form (that is, without the supplementation being combined with any antidepressant medication).
2. MATERIALS AND METHODS

This is a systematic search review (FERENHOF; FERNANDES, 2016). In which data were collected from the beginning to the end of September 2021, through three databases: Pubmed, Google Scholar, and Scielo, where filters were used to select studies published between the years 2005 and 2021. 2021, and terms provided by the Health Science Descriptors (DeCS/MeSH), in English: probiotics AND depression, probiotics AND depression AND dysbiosis, and in Portuguese: "probióticos e depressão, probióticos e depressão e disbiose". The steps of this process were described in the flowchart (Figure 1) below.
2.1 DETAILS OF SEARCHES AND DATA EXTRACTION

After the searches, a total of 655 articles were identified, where 94 of these articles were collected for reading, as they presented relevant information. Among them, 26 articles were selected for inclusion in the review. The remaining articles were excluded due to various reasons, such as not being relevant to the research question or not meeting the inclusion criteria. The flowchart steps were originally detailed by the authors of this review. Visit the link below for more information:

were excluded, as they did not contribute to the theoretical development, and investigated the use of probiotics without associating Major Depressive Disorder. Finally, 68 materials that were presented in Portuguese (n=65), English (n=2) and Spanish (n=1) were selected. Of these, 10 intervention studies contributed to data extraction, and 5 of them (randomized) had their methodological quality assessed using the Risk of Bias-2 (ROB-2) tool; provided free of charge by the Cochrane organization. Soon after, in the SCI Journal database (Science Journal Impact Factor), the Impact Factor (IF) of the journals that published the selected studies was verified (as shown in Table 3).

Prior to the eligibility of the 10 studies, the following inclusion criteria were defined: full text presentation, analysis of the effects of probiotic supplementation in humans or rodents, both sexes, adults and elderly, diagnosed with depressive behaviors, and MDD as the DSM-IV/V criteria, finally, as non-inclusion criteria were defined: studies that analyzed other psychiatric disorders (example: anxiety, bipolarity).

3. RESULTS

From the perspective of new therapies, Logan and Katzman (2005) stated that probiotic supplementation is a valid proposal for studies, because, in view of their hypothesis, supplementation will serve as an adjuvant therapy for Major Depressive Disorder, since it has the ability to reduce inflammatory responses, improve nutritional status and alleviate oxidative stress.

Intervention studies in humans and in animal models corroborate this proposal, in the same way that the studies selected in this review showed effects of this nature. In preclinical studies, it was shown that there is a correlation between dysbiosis, intestinal permeability, and depressive behaviors (ARSENEAULT-BRÉARD et al., 2012; LI et al., 2019; QIU et al., 2021). In analysis, it is perceived that this relationship also involves metabolites derived from the microbiota and their potential influence on the formation of serotonin (5-HT); fundamental neurotransmitter for emotional homeostasis. Probiotic supplementation in rats had effects on the gut microbiota and increased 5-HT levels in the frontal cortex. These effects may be an
important contribution since depressive symptomatology is related to lower concentrations of serotonin in this area of the brain (LI et al., 2019). Other positive aspects were also observed on the intestinal epithelium through the proteins Zonulin and E-cadherin, and on the inflammatory state due to the decrease of pro-inflammatory cytokines (ARSENEAULT-BRÉARD et al., 2012; QIU et al., 2021). In addition to the effects on inflammatory pathways, the regulations generated on the expression of genes in nervous system receptors also seem to contribute to the antidepressant effect during supplementation. The species *L. helveticus* MCC1848 stood out by modulating the pattern of gene expressions (Drd3 and Htr1a) of NAC; area of the brain related to reward, suggesting reestablishment of the dopaminergic and serotonergic systems. As these findings are indicative that probiotics can contribute to treatment, however, it is necessary to investigate whether these effects also occur in humans (MAEHATA et al., 2019).

Supporting this search, Akkasheh et al. (2016) were one of the first to intervene in humans diagnosed with MDD and achieve positive results on the BDI (Beck Depression Inventory) scale after 8 weeks with *Lactobacillus* and *Bifidobacterium* supplementation. However, in this study probiotics were used as an adjunct treatment to an antidepressant medication, constituting a probability that the effects would take longer than 8 weeks to occur if they were not supplemented with the medication, so test durations should be studied more closely precision (ROMIJN et al., 2017).

In contrast, researchers have considered analyzing different strains, and intervention timeframes. In addition, there has been a focus on the co-supplementation of vitamins, minerals and probiotics, especially in mood changes (JAMILIAN et al., 2018; OSTADMOHAMMADI et al., 2019). However, this co-supplementation is still scarce in MDD, leading to greater interest in symbiotic supplementation, as they have already shown positive effects on the microbiota and mental health of healthy patients (GHORBANI et al., 2018). Still, Reininghaus et al. (2020) highlighted that the co-supplementation of vitamins and symbiotics can be an interesting path for the treatment of depression, since in their results expressive effects on inflammatory and
metabolic pathways were observed. According to the authors of this study, deepening the search by analyzing metabolic pathways may serve as a key to a better understanding of the course of diseases, and the interrelation between mental disorders and inflammatory processes. As seen in the favorable repercussions on psychiatric scales, and inflammatory biomarkers, the selected studies provide grounds for this perspective to be improved (CHAHWAN et al., 2019; GHORBANI et al., 2018; MAJEED et al., 2018; REITER et al., 2020; WALLACE; MILEV, 2021).

The outcomes of pre-clinical studies (Chart 1), randomized trials and open pilot trials (Chart 2) are presented below.

Table 1 - Studies that performed interventions in animal models

<table>
<thead>
<tr>
<th>Author/ year/ country</th>
<th>Animals/ tests</th>
<th>CFU probiotics/duration</th>
<th>Results</th>
<th>Groups/placebo</th>
<th>Conflict of interest</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ArseneauL- Breárd et al. (2012)</td>
<td>40 Rats Sprague-Dawley Forced swimming, social interaction, passive avoidance</td>
<td>Probio'Stick L. helveticus B. longum 1 billion CFU Diluted in water (200ml) 14 days</td>
<td>↓ Depression ↓ Intestinal permeability ↓ IL-1β cytokine ↑ Social interaction</td>
<td>4 groups (n=10) Maltodextrin diluted in water (200ml)</td>
<td>Declare d not to contain The microbiota intervention of models of extra depression was not analyzed, common probiotics were supplemented, and only central metabolic signatures were recognized in the study</td>
<td>Thoracic surgery and myocardial infarction</td>
</tr>
<tr>
<td>Li et al. (2019)</td>
<td>50 Rats Wistar CUMS, forced swimming, sucrose preference</td>
<td>B. longum L.rhamnosus 1 x 10⁹ UFC Via probe 28 days</td>
<td>↓ Depression ↑ 5-HT/TPH2 frontal cortex ↓ Firmicutes and Tenericutes ↑ Weight control</td>
<td>5 groups (n = 10) Saline solution via tube</td>
<td>Declare d not to contain</td>
<td></td>
</tr>
</tbody>
</table>
Maehata et al. (2019)  
Japan  
48 Rats  
*C57BL / 6J (B6) and ICR*
  
Social interaction, sucrose preference, forced swimming  
  
*L. helveticus MCC1848 1 x 10⁹ UFC*  
Probiotic preparation was added to the formulated diet (AIN93G)  
7 days  
↓ Anhedonia  
3 groups (n=16)  
Diet formulated without the probiotic  
Declared not to contain  
An animal model that presents mild depression with less physical stress was used.

Qiu et al. (2021)  
China  
32 Rats  
*C57BL / 6J*
  
Sucrose preference, forced swimming  
*(LPS – depression induction injection)*  
  
*L. delbrueckii. subsp. bulgaricus 1 x 10⁹ UFC*  
Via probe  
7 days  
↓ Depression  
↓ Dysbiosis  
↓ Intestinal permeability  
↓ Super activation of microglia  
↓ TLR4 and NLRP3  
↑ IL-1β cytokine  
↑ ZO-1 and E-cadherin  
4 groups (n=8)  
Physiological serum via tube  
Declared not to contain  
No descriptions

Source: original elaboration organized by the authors of this review. Caption: ↑ increased, ↓ reduced. CFU Colony Forming Units, 5-HT Serotonin, TPH2 Tryptophan Hydroxylase 2, ZO-1 Zonula Occludens-1.

Table 2 - Studies that performed interventions in humans

<table>
<thead>
<tr>
<th>Author/ year/ country</th>
<th>Participants/age/ diagnosis/ scales</th>
<th>CFU supplementati on/ duration/drug</th>
<th>Results</th>
<th>Groups/place bo</th>
<th>Conflict of interests</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghorbani et al.</td>
<td>40 patients</td>
<td>Familact H ® Symbiotic</td>
<td>↓ Depression</td>
<td>2 groups</td>
<td>Declared not to contain</td>
<td>Small sample, short</td>
</tr>
</tbody>
</table>

RC: 119161  
Available in: [https://www.nucleodoconhecimento.com.br/nutrition/psychobiotics](https://www.nucleodoconhecimento.com.br/nutrition/psychobiotics)
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Location</th>
<th>Age (years)</th>
<th>TD</th>
<th>HAM-D/MADRS/CES-D</th>
<th>Dose/Supplements</th>
<th>Drug</th>
<th>Follow-up</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2018) Majeed et al.</td>
<td>India</td>
<td>40 patients</td>
<td>20–65</td>
<td>TDM, HAM-D, MADRS, CES-D</td>
<td>LactoSpore® 1 capsule/day B. coagulans MTCC 5856 (spores) 2 x 10⁹ UFC 90 days</td>
<td>Drug: not used</td>
<td>(n=20) Magnesium stearate contain supplementati on period</td>
<td></td>
</tr>
<tr>
<td>(2018) Chahwan et al.</td>
<td>Australia</td>
<td>71 patients</td>
<td>Mild/moderate to severe</td>
<td>TD18 years old + MINI, BDI-II, DASS-21 BAI, LEIDS-R</td>
<td>Ecologic® Barrier 2 sachet powder/day B. bifidum, B. lactis W51, B. lactis W52, L. acidophilus, B. breve, L. casei, L. salvari, L. lactis, L. lactis W58, 1 x 10¹⁰ UFC 8 weeks</td>
<td>Drug: not used</td>
<td>2 groups (n=34 probiotics, n=37 placebos) Declare d not to contain The high attrition rate can be attributed to the weekly visits. In the post-trial (week 9) participants were absent</td>
<td></td>
</tr>
</tbody>
</table>
| (2020) Reininghaus et al. | Australia | 61 patients | 18–75         | TDM | OMNI-BIOTIC® STRESS Symbiotic 1 sachet powder/day | ↓ Depression ↑ Regulation in the IL-17 | Drug: not used | 2 groups (n=28 probiotics, n=33 placebos) Identical Declare d not to contain Small sample, smokers between the two groups, short period of supplementatio n, and hospital diet may have
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Country</th>
<th>Age</th>
<th>Probiotics</th>
<th>Pathway</th>
<th>Drug</th>
<th>Placebo</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reiter et al. (2020)</td>
<td>61 patients 18 – 75 years old</td>
<td>Austria</td>
<td>TDMHAM – D, BDI-II, SCL-90</td>
<td>B. bifidum, B. lactis W51, B. lactis W52, L.acidophilus, L. casei, L.paracasei, L.plantarum, L. salivarius, L. lactis ≥ 2.5 × 10^9 UFC</td>
<td>↑ Regulation of metabolic pathways (KEGG)</td>
<td>Participants' conventional antidepressants</td>
<td>OMNi-BIOTIC® STRESS Symbiotic1 sachet powder/day</td>
<td>2 groups (n=28 probiotics, n=33 placebos)</td>
</tr>
<tr>
<td>Wallace and Milev et al. (2021)</td>
<td>10 patients 18 – 75 years old</td>
<td>Canada</td>
<td>TDM CAN-BIND</td>
<td>B. longum, L. helveticus</td>
<td>↓ Depression</td>
<td>There was no placebo group</td>
<td>CEREBIOME® 1 sachet powder/day</td>
<td>Declared not to contain</td>
</tr>
<tr>
<td>MADRS, QIDS-SR16, SHAPS</td>
<td>$3 \times 10^9$ UFC</td>
<td>8 weeks</td>
<td>group</td>
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<tr>
<td>Drug: not used</td>
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Source: original elaboration organized by the authors of this review. Caption: ↑ increased, ↓ reduced. All human studies selected both sexes male ♂ and female ♀.

UFC Colony Forming Units. IBS Irritable Bowel Syndrome. Scales: BAI Beck Anxiety Inventory, BDI Beck Depression Inventory, CAN-BIND Canadian Network for Integration of Biomarkers in Depression, CES-D Center for Epidemiological Studies Depression Scale, HAM-D Hamilton Rating Scale for Depression, LEIDS-R Leiden Depression Sensitivity Index - Revised, MADRS Depression Rating Scale – Montgomery - Asberg, MINI Mini International Neuropsychiatric Interview, QIDS-SR16 Rapid Inventory of Depressive Symptomatology, SCL-90 Symptom Rating Scale-90 -R-SCL-Revisited, SHAPS Snaith-Hamilton Pleasure Scale.

According to data extraction, an evaluative analysis of the risk of bias of randomized studies was performed in 5 domains of the ROB-2 tool (Figure 2), resulting in the graph (Figure 2.1) below.

Figure 2 – Analysis of the risk of bias in randomized trials

(supplement) x comparator (placebo): 5 domains (D). Colors: red; high risk of bias, yellow; some concerns, green; no risks.

Figure 2.1 - Percentages of risk of bias in graph


Next, the 10 selected studies and their interventions (marked with an X) are presented together, and in chronological order.

Table 3 - Interventions applied in the set of studies

<table>
<thead>
<tr>
<th>N</th>
<th>Author/year</th>
<th>Title, journal/country, journal: Impact Factor (IF)</th>
<th>Probiotics</th>
<th>Antidepressant</th>
<th>Prebiotics</th>
<th>Vitamin(s)</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Arseneault-Breárd et</td>
<td>Combination of Lactobacillus</td>
<td>X</td>
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<tr>
<td><strong>II</strong></td>
<td>Maehata et al. (2019)</td>
<td>Heat-killed Lactobacillus helveticus strain MCC1848 confers resilience to anxiety or depression-like symptoms caused by subchronic social defeat stress in mice. Japan.</td>
<td><strong>Biosci Biotech Bioch.</strong></td>
<td>FI – WSG: 1.516, Index H: 116, FI – Scopus: 1,986</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IV</strong></td>
<td>Qiu et al. (2021)</td>
<td>Lactobacillus delbrueckii alleviates depression-like behavior through inhibiting toll-like receptor 4 (TLR4) signaling in mice.</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Authors</td>
<td>Title</td>
<td>Available in</td>
<td>Impact Factor (IF)</td>
<td>Index H</td>
<td>Scopus</td>
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</tr>
<tr>
<td>IX</td>
<td>Reiter et al. (2020)</td>
<td>Interleukin-6 Gene Expression Changes after a 4-Week Intake of a</td>
<td>Available in: <a href="https://www.nucleodoconhecimento.com.br/nutrition/psychobiotics">https://www.nucleodoconhecimento.com.br/nutrition/psychobiotics</a></td>
<td>N/D</td>
<td>24</td>
<td>188</td>
<td></td>
</tr>
</tbody>
</table>
Multispecies Probiotic in Major Depressive Disorder: Preliminary Results of the PROVIT Study. Austria. *Nutrients*. FI – WSG: 4.546, Index H: 115, FI – Scopus: 5.929


Source: original elaboration organized by the authors of this review. Caption: FI Impact Factor, H Index – Google Scholar, N/A Not Defined, WSG Web of Science Group.

**4. DISCUSSION**

According to the World Health Organization (WHO, 2020) depressive disorder has been presented as a worrying condition for the 21st century, as it reflects on the increasing rates of suicide. The scientific field has constantly reiterated on this topic, and intensified efforts to develop new treatments that can contribute to the improvement of depressive symptoms through intestinal modulation (KELLY *et al*., 2016; YONG *et al*., 2020).

However, in the literature, preclinical studies that supplemented psychobiotics predominate, and obtained significant results on dysbiosis, intestinal permeability and brain neurochemistry (ARSENEAULT-BRÉARD *et al*., 2012; CRYAN; O’MAHONY, 2011; LI *et al*., 2019; ; MAEHATA *et al*., 2019; QIU *et al*., 2021; YONG *et al*., 2020). Fortunately, this scenario is changing, and human studies are increasingly being encouraged, recognizing that probiotics benefit the microbiota and multiple endocrine, inflammatory and neural pathways. However, this heterogeneity of action
demands a greater understanding of the “enteric-gut-brain microbiome” (DINAN; CRYAN, 2016; CRYAN; O’MAHONY, 2011; HEMARAJATA; VERSALOVIC, 2013).

The different results in biomarkers and in the scores of psychiatric scales corroborate this statement, as it makes it clear that the mechanisms of action vary according to the gender and species of the supplemented probiotic. To date, the most investigated mechanisms are bacteria of the _Lactobacillus_ and _Bifidobacterium_ genera, which have been shown to be largely safe, including in the treatment of depressive disorders (IVANOV; HONDA, 2012; VIZCAÍNO _et al._, 2016; ZAWISTOWSKA-ROJEK; TYSKI, 2018; ).

However, diet and nutritional factors also have value in this investigation (DASH _et al._, 2015; HOLSCHER, 2017; LEDOCHOWSKI _et al._, 2000; LIU; CAO; ZHANG, 2015; SUZUKI, 2020; SKONIECZNA-ŻYDECKA _et al._, 2018). According to Logan and Katzman (2005), improving nutritional status and promoting anti-inflammatory effects is eminent to achieve greater success in relieving depressive symptoms.

In view of this, it is worth noting that the co-supplementation of a symbiotic and vitamin B7 (D-biotin) showed competences to regulate both metabolic and inflammatory pathways, and benefit the intestinal microbiota of patients with MDD. In addition, the outcomes of this co-supplementation showed increases in the concentrations of _Ruminococcus gauvreauii_ and _Coprococcus;_ which are predominantly related to an increase in quality of life, however, did not express any effect on intestinal permeability. Even so, considering the results, Reininghaus _et al._ (2020) concluded that there is an important connection between diet quality, gut microbiota, and mental health, encouraging new studies to include analysis of metabolic pathways alongside investigations of inflammatory pathways.

To date, the greatest interest is in understanding brain activity and inflammatory responses in dysbiosis and psychiatric disorders (LEVY _et al._, 2017; TILLISCH _et al._, 2013; TRAN _et al._, 2019). It is believed that pro-inflammatory cytokines play an important role in the pathogenesis of depression, and with that, Interleukin-6 (IL-6) has gained focus. In contrast, the immune system responses are carried out in
cascades and encompass a wide systemic interaction, thus, there is a need for more investigations on the subtypes of inflammation in the different degrees of depression (REITER et al., 2020). Accordingly, it is essential to extend the analysis to other types of probiotic strains, and to observe the integrity of innate immune responses, as this is also an interface to be scrutinized (MAJEED et al., 2018).

Both prebiotic and probiotic supplementation have demonstrated ability to act on immunity and various diseases (DIDARI et al., 2015; SLAVIN, 2013; VIZCAÍNO et al., 2016; ZALAR; HALSBERGER; PETERLIN, 2018). Thus, in these supplements, the disparities of the microbiota of each individual must be considered. For example, in depressed patients, the “depression microbiota” is usually found, with a predominance of bacteria from the phylum Firmicutes, Bacteroidetes and Actinobacteria. This diversity that makes up the microbiota has stimulated the taxonomic analysis of resident intestinal bacteria from different clinical populations in order to compare them and understand their responses (GOODMAN et al., 2011; NEISH, 2009; SARTOR, 2008; ZHENG et al., 2016).

Eventually, there are studies that expose microbiota disparities during probiotic supplementation. Chahwan et al. (2019) in their study analyzed the differences in the composition of the microbiota between individuals diagnosed with mild, moderate and severe depression, and showed that there was no significant difference between them, in the comparison between non-depressed and depressed individuals, there was a predominance of Ruminococcus gnavus in those diagnosed with severe depression. In this study, side effects such as nausea and drowsiness were also observed during Lactobacillus and Bifidobacterium supplementation. Like this one, another study also described side effects in subjects in the placebo and probiotic group, despite this, both studies achieved good adherence to treatments (CHAHWAN et al., 2019; GHORBANI et al., 2018). Compared to the study by Majeed et al. (2018) Bacillus coagulans MTCC 5856 supplementation did not cause side effects and attenuated precisely the gastrointestinal symptoms and insomnia of patients diagnosed with MDD and Irritable Bowel Syndrome.
Faced with this issue, it is important to emphasize that gastrointestinal symptoms are commonly reported in intestinal microbiota disturbances, and in psychiatric disorders. And, therefore, this relationship has directed the attention of researchers to the supplementation of symbiotics in health in general (CARDING et al., 2015; MAJEED et al., 2018; O’HARA; SHANAHAN, 2006). For, probiotics and symbiotics have already shown positive effects on mental health, inflammatory responses, and gastrointestinal symptoms linked to MDD (GHORBANI et al., 2018; MAJEED et al., 2018; REININGHAUS et al., 2020; REITER et al., 2020).

However, in this review, studies that supplemented symbiotics and benefited inflammatory pathways maintained their participants' conventional psychotropic medications (REININGHAUS et al., 2020; REITER et al., 2020). Thus, of the six studies in humans, only three showed the effects of probiotics in their autonomous form, that is, without using drugs (CHAHWAN et al., 2019; MAJEED et al., 2018; WALLACE; MILEV, 2021). Among them, one of the most recent studies analyzed the effects of probiotics in 10 antidepressant drug-naive patients. Thus, Wallace and Milev (2021) obtained positive results on depressive symptomatology within 4 to 8 weeks, however, during the design of this study, participants remained non-blind, and there was no placebo group for comparisons.

However, it is necessary to consider that despite the results, most studies are independent of the choice of administration; whether with or without medication, described limitations and presented risks of bias. This fact proposes new studies with better designed research designs, and a greater understanding of the communication and response system of the gut-brain axis. After all, it is possible that so far research has presented only the tip of an “iceberg” that will occupy the scientific field for some time, but which in a way has already revealed promising prospects for the area of nutritional psychiatry (GRENHAM et al., 2011; SARRIS et al., 2015).

5. FINAL CONSIDERATIONS

According to the data review, and citations organized in this study, it is possible to take a look at the guiding question: “can psychobiotics be denoted as a treatment for
Major Depressive Disorder?” And to conclude unanimously: studies suggest that psychobiotics can be denoted as a treatment for Major Depressive Disorder, since the psychotropic effects in which they produce were effective in reducing patients' depressive symptoms within 4 to 8 weeks, as observed in the outcomes of psychiatric scales validated for this analysis.

In addition to depressive symptoms, other important factors for the rebalancing of mental health were simultaneously optimized, such as sleep quality and the reduction of inflammatory responses, which came to stand out within the theme, generating the science that a conjecture of looks to be carried out so that this treatment can be made possible. Therefore, it is essential to consider supplements: that each individual has disparities in their microbiota, at the same time that the composition of the intestinal microbiota is closely linked to inflammatory responses. However, it is possible that the different subtypes of inflammation do not appear on the analysis of a single inflammatory biomarker, being, therefore, pertinent to take these perspectives for future investigations, since the regulation of the inflammatory state has had repercussions as one of the access routes for the relief of depressive symptoms. From this, the importance of covering investigations evaluating inflammatory and metabolic pathways in the face of nutritional factors is connected to this line of thought, since, according to the evidence, a deeper look into this aspect can also be important for further discussions.

In addition, the scientific field expresses that a greater understanding of the gut-brain axis and the mechanisms of different probiotic strains is necessary, in view of this, the supplementation of psychobiotics is recommended as an adjuvant therapy of antidepressant drugs.

Finally, through the extraction of data, and the evaluative analysis of the methodological quality of the randomized studies, carried out in this review, the following guidelines were formalized for the subsequent studies: the methodological design must be better planned, so that the studies futures have a lower risk of bias in the domains: general bias, selection of results, deviations in the intended intervention, and randomization process. In addition, in view of the limitations
described, it is essential that future studies carry out interventions with longer testing periods, in larger samples, considering the supplementation of psychobiotics in an adjuvant and autonomous form, so that it becomes possible to distinguish the effects of probiotics and the effects of antidepressants. Because, given the improvement of studies, it is likely that more lights will be turned on within the discussions on mental health, and thus, the knowledge obtained so far on the gut-brain axis will become increasingly clear.

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