MULTIDISCIPLINARY SCIENTIFIC JOURNAL
NÚCLEO DO CONHECIMENTO
REVISTA CIENTÍFICA MULTIDISCIPLINAR NÚCLEO DO CONHECIMENTO ISSN: 2448-0959
https://www.nucleodoconhecimento.com.br

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

REVIEW ARTICLE

COELHO, Taiane [1], KERPEL, Raquel [2]

COELHO, Taiane. KERPEL, Rachel. **Psychobiotics in the treatment of depression: a new look at mental health – a systematic search review.** Revista Científica Multidisciplinar Núcleo do Conhecimento. Year. 07, Ed. 05, Vol. 01, p. 125-152. May 2022. ISSN: 2448-0959, Access link: https://www.nucleodoconhecimento.com.br/nutrition/psychobiotics

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 the selection of studies published between 2005 and 2021. After selecting the

[1] Graduated in Nutrition; Certification in Nutritional Psychiatry (INCCOR-RJ). ORCID: 0000-0002-1588-5679.
[2] Advisor. Graduated in nutrition; PhD in collective health; Master in metabolism and dietetics; Professor in the field of nutrition. ORCID: 0000-0002-7556-2548.

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).

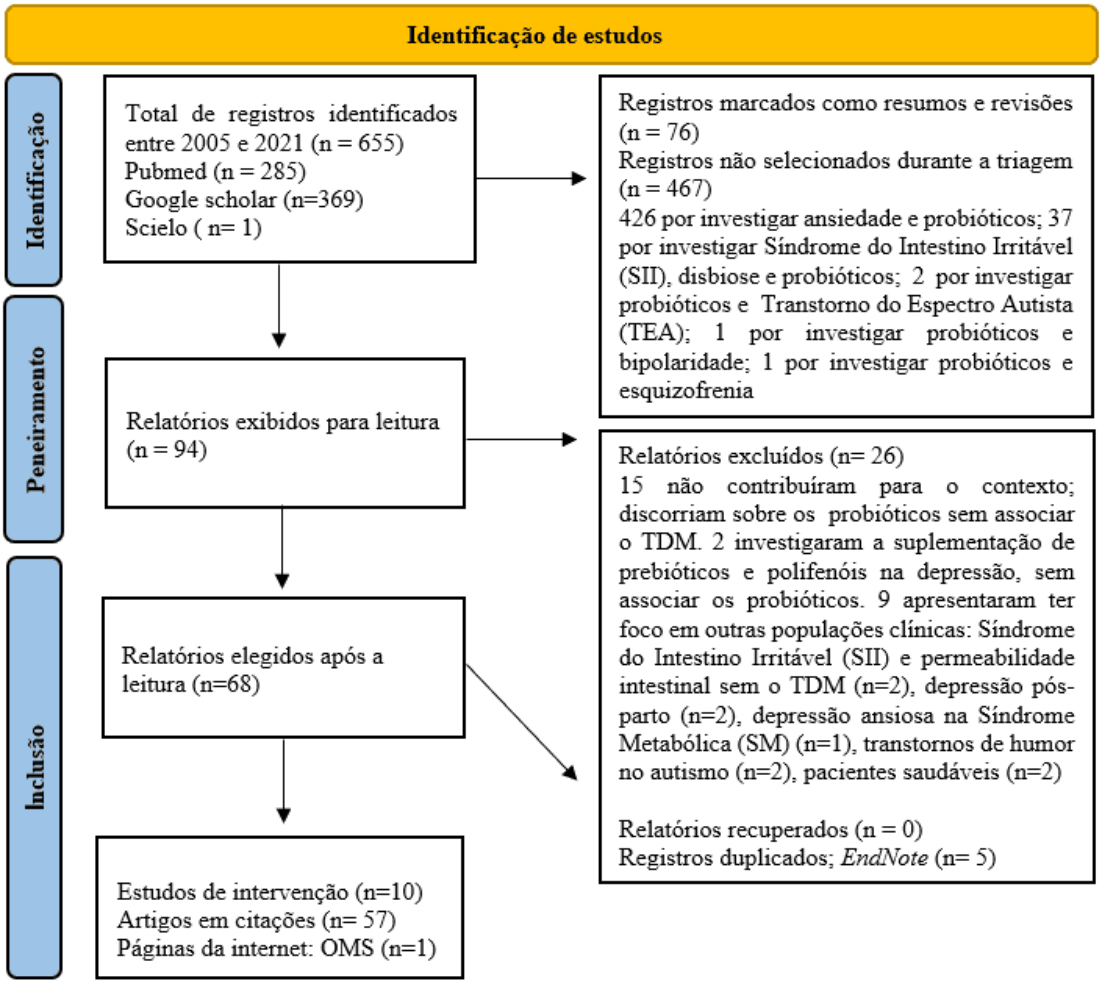
In view of the deepening of the search for psychobiotics, it is observed that review articles have more frequently reported preclinical studies, and there are still few reviews on studies that intervened in humans diagnosed with MDD (BERCIK; COLLINS; VERDU, 2012). ; CRYAN; O'MAHONY, 2011; HUANG; WANG; 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.

Figure 1 - Flowchart search design (PRSMA 2020)



Source: the flowchart steps were originally detailed by the authors of this review. Visit

to learn more about the PRISMA flow diagram: PAGE, J. Matthew, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. System Rev, vol. 10, no. 89, Apr. 2021. Available at: https://doi.org/10.1186/s13643-021-01626-4 Accessed on: 09/01/2021. Link to access flow diagram: http://prisma-statement.org/prismastatement/flowdiagram.aspx

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 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

Author/ year/ country	Animals/ tests	CFU probiotics/duration	Results	Groups/placebo	Conflict of interests	Limitations
Arseneault-Breárd *et al.* (2012) Canada	40 Rats *Sprague-Dawley* Forced swimming, social interaction, passive avoidance	Probio'Stick *L . helveticus* *B . longum* 1 billion CFU Diluted in water (200ml) 14 days	↓Depression ↓ Intestinal permeability ↓ IL-1β cytokine ↑ Social interaction	4 groups (n=10) Maltodextrin diluted in water (200ml)	Declared not to contain	Thoracic surgery and myocardial infarction
Li *et al.* (2019) China	50 Rats *Wistar* CUMS, forced swimming,	*B. longum* *L.rhamnosus* 1 x 10 ^{9} UFC Via probe 28 days	↓ Depression ↑ 5 –HT/TPH2 frontal cortex ↓ *Firmicutes*	5 groups (n = 10) Saline solution via tube	Declared not to contain	The microbiota intervention of models of extra depression was not

	sucrose preference		*and Tenericutes* ↑ Weight control			analyzed, common probiotics were supplemented, and only central metabolic signatures were recognized in the study
Maehata *et al.* (2019) Japan	48 Rats *C57BL / 6J (B6) and ICR* Social interaction, sucrose preference, forced swimming	L. helveticus MCC1848 1 x 10 ^{9} 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)	Lac L. delbrueckii. subsp. *bulgaricus* 1 x 10 ^{9} 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

Author/ year/ country	Participants/age/ diagnosis/ scales	CFU supplementation/ duration/drug	Results	Groups/placebo	Conflict of interests	Limitations
Ghorbani *et al.* (2018) Irã	40 patients 18 – 65 years old TD moderate HAM-D	Familact H ® Symbiotic 2 capsules/day *L. casei, L. rhamnosus, L. acidophilus, L. bulgaricus, B. breve, B. longum* 3x 10^8, 2 x 10^9, 2 × 10^8, 1 × 10^9 UFC 6 weeks Drug: (Fluoxetine hydrochloride) for 10 weeks	↓ De-pression	2 groups (n=20) Magnesium stearate	Declared not to contain	Small sample, short supplementation period
Majeed *et al.* (2018) Índia	40 patients 20 – 65 years old TDM HAM-D, MADRS, CES-D	LactoSpore ® 1 capsule/day *B. coagulans* MTCC 5856 *(spores)*2 × 10^9 UFC90 daysDrug: not used	↓Depression ↓ Insomnia ↓ Symptoms ↓*Myelopero-oxidase*	2 groups (n=20) Identically formulated pill without the probiotic	Stated that this work was sponsored and supported by Sabinsa Corporation NJ 08520, USA	Small sample
Chahwan *et al.* (2019) Australia	71 patients Mild/ moderate to severe TD18 years old +MINI, BDI-II, DASS-21 BAI, LEIDS-R	Ecologic ® Barrier 2 sachet powder/day *B. bifidum, B. lactis W51, B. lactis W52, L. acidophilus, B. breve, L. casei, L. salvarius, L. lactis, L. lactis* W58,1 × 10^{10} UFC 8 weeks Drug: not used	↓ De-pression ↓ Cognitive reactivity	2 groups (n=34 probiotics, n=37 placebos) Corn starch and maltodextrin	Declared not to contain	The high attrition rate can be attributed to the weekly visits. In the post-trial (week 9) participants were absent
Reininghaus *et al.* (2020)	61 patients	OMNi-BiOTiC ® STRESS	↓ De-pression	2 groups (n=28 probiotics,	Declared not to contain	Small sample, smokers between the two

Australia	18 – 75 years old TDM HAM – D, BDI-II, SCL-90	Symbiotic 1 sachet powder/day *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 Added D-biotin (125 mg) 28 days Drug: participants' conventional antidepressants	↑ Regulation in the IL-17 pathway ↑ Regulation of metabolic pathways (KEGG) ↑ *R. gauvreauii* and *Coprococcus*	n=33 placebos) Identical drink without the probiotic, added biotin for ethical reasons		groups, short period of supplementation, and hospital diet may have influenced the results. There was discontinuity; initial allocation (n=82)

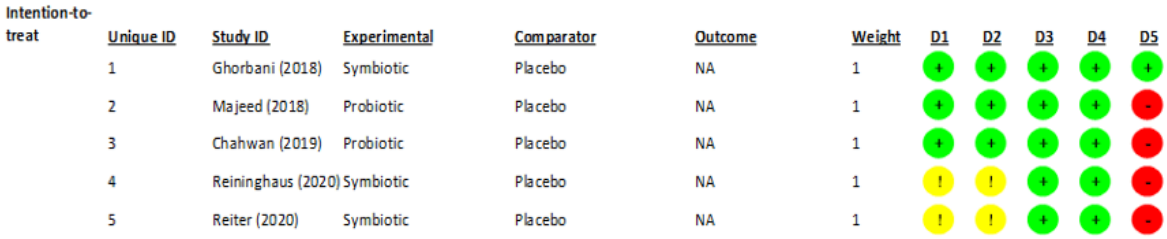
Reiter *et al.*(2020) Austria	61 patients 18 – 75 years old TDM HAM – D, BDI-II, SCL-90	OMNi-BiOTiC ® STRESS Symbiotic1 sachet powder/day *B. bifidum*, *B. lactis* W51, *B. lactis* W52, *L.acidophilus, L. casei*, *L.paracasei, L.plantarum*, *L. salivarius, L. lactis* ≥ 2,5 × 10^9 UFC 4 weeks Drug: participants' conventional antidepressants	↓Depression ↓ IL-6 cytokine	2 groups (n=28 probiotics, n=33 placebos) Identical drink without the probiotic, added biotin for ethical reasons	Declared not to contain	Effects of different medications, short period of supplementation, age and gender difference of participants can influence the microbiota. There was discontinuity; initial allocation (n=82)
Wallace and Milev *et al.* (2021)	10 patients 18 – 75 years old	CEREBIOME ® 1 sachet powder/day *B. longum, L.*	↓Depression ↓ Anhedonia ↑ sleep quality	There was no placebo group	Declared not to contain	Small sample, 70% were women, short period of supplementation, and the method was non-blind without placebo

Canada	TDM CAN-BIND, MADRS, QIDS-SR16, SHAPS	*helveticus* 3 x 10^9 UFC 8 weeks Drug: not used				group

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 – Montgamarey - 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.

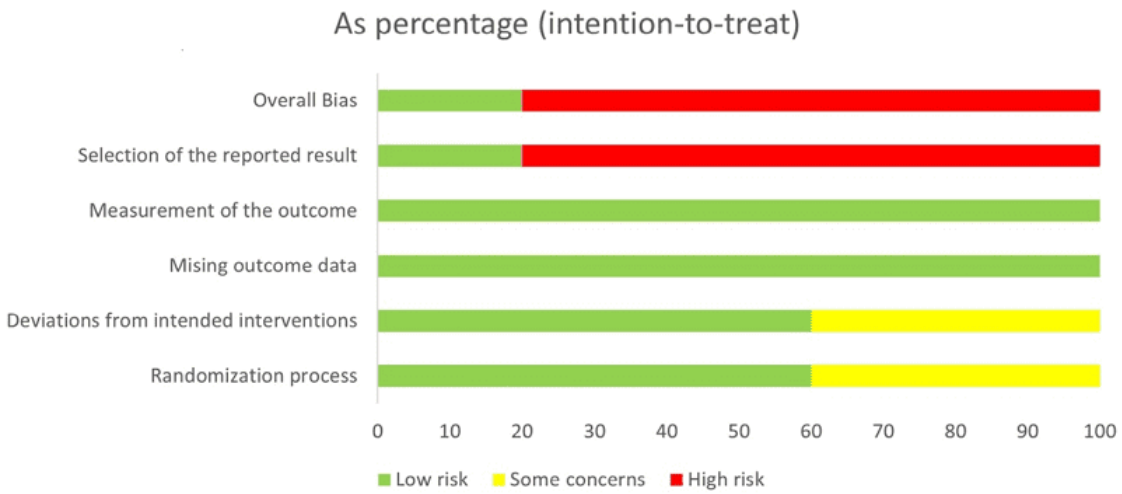
Figure 2 – Analysis of the risk of bias in randomized trials



Source: original results obtained from the evaluative analysis of the authors of this review. Access to learn more about the Risk of Bias-2 (ROB-2) tool: STERNE, Jonathan A. C., et al. RoB 2: a revised tool to assess the risk of bias in randomized trials. BMJ, vol. 366, no. l4898, Aug. 2019. Available at: https://doi.org/10.1136/bmj.l4898 Accessed: 11/06/2021. Tool download link:

https://www.riskofbias.info/ Captions: intent to treat: Study ID: experiment (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



Source: original results obtained from the evaluative analysis of the authors of this review. Access to learn more about the Risk of Bias-2 (ROB-2) tool: STERNE, Jonathan A. C., et al. RoB 2: a revised tool to assess the risk of bias in randomized trials. BMJ, vol. 366, no. l4898, Aug. 2019. Available at: https://doi.org/10.1136/bmj.l4898 Accessed: 11/06/2021. Tool download link: https://www.riskofbias.info/ Caption: graph topics: in percentages (intention to treat): general bias, outcome selection, outcome measurement, missed outcomes, deviations from intended intervention, process of randomization. Colors: red; high risk of bias, yellow; some concerns, green; no risks.

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

N	Author/year	Title, journal/country, journal: Impact Factor (IF)	Probiotics	**Antidepressant**	**Prebiotics**	**Vitamins**	**Side effects**
I	Arseneault-	Combination	X				

	Breárd *et al.* (2012)	of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 reduces post-myocardial infarction depression symptoms and restores intestinal permeability in a rat model. Canada. Br J Nutr. FI – WSG: 3.334, Index H: 188, FI – Scopus: 4.105					
II	Li *et al.* (2019)	Effects of regulating gut microbiota on the serotonin metabolism in the chronic unpredictable mild stress rat model. China. Neurogastroenterol Motil. FI – WSG: 3,008, Index H: 42, FI – Scopus: 3,65	X		x		
III	Maehata *et al.* (2019)	Heat-killed *Lactobacillus helveticus* strain MCC1848 confers resilience to anxiety or depression-like symptoms caused by subchronic social defeat stress in mice. Japan. Biosci Biotech Bioch. FI – WSG: 1.516, Index H: 116, FI – Scopus: 1,986	X				

IV	Qiu *et al.*(2021)	*Lactobacillus delbrueckii* alleviates depression-like behavior through inhibiting toll-like receptor 4 (TLR4) signaling in mice. China. **Ann** Transl Med. FI – WSG: 3.297, Index H: 48, FI – Scopus: N/D	X				
V	Ghorbani *et al.* (2018)	The Effect of Synbiotic as an Adjuvant Therapy to Fluoxetine in Moderate Depression: A Randomized Multicenter Trial. Iran. Arch Neurosci. FI – N/D	X	X	x		x

VI	Majeed *et al.* (2018)	*Bacillus coagulans* MTCC 5856 for the management of major depression with irritable bowel syndrome: a randomized, double-blind, placebo controlled, multi-centre, pilot clinical study. India. Food Nutr Res. FI – WSG: 0,756, Index H: 24, FI – Scopus:1.259	X				
VII	Chahwan *et al*. (2019)	A randomized, triple-blind, placebo-controlled trial of probiotics for depressive symptoms. Australia. J Affect Disord. FI – WSG: 3.892, Index H: 188, FI – Scopus: 5,104	X				x

VIII	Reininghaus *et al*. (2020)	PROVIT: Supplementary Probiotic Treatment and Vitamin B7 in Depression—A Randomized Controlled Trial. Austria**.** Nutrients. FI – WSG: 4.546 , Index H: 115, FI – Scopus: 5,929	X	X	X	X	
IX	Reiter *et al.*(2020)	Interleukin-6 Gene Expression Changes after a 4-Week Intake of a 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	X	X	X	X	
X	Wallace and Milev (2021)	Tolerability of Probiotics on Depression: Clinical Results From an Open-Label Pilot Study. Canada. Front Psychiatry. FI – WSG: 4.157, Index H: N/D, FI – Scopus: 7.864	X				

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.

REFERENCES

AKKASHEH, Ghodarz *et al*. Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial. **Nutrition**, Estados Unidos, vol. 32, n.3, p.315-20, mar. 2016. Disponível em: doi:10.1016/j.nut.2015.09.003 Acesso em: 01/09/2021.

ARSENEAULT-BRÉARD, Jessica *et al*. Combination of Lactobacillus helveticus R0052 and Bifidobacterium longum R0175 reduces post-myocardial infarction

depression symptoms and restores intestinal permeability in a rat model. **The British Journal of Nutrition**, Canadá, vol. 107, n. 12, p. 1793-9, jun. 2012. Disponível em: doi:10.1017/S0007114511005137 Acesso em: 13/09/2021.

BAPTISTA, Makilim Nunes. Avaliando “depressões”: dos critérios diagnósticos às escalas psicométricas. **Avaliação Psicológica**, Brasil, vol. 17, n. 3, p. 301-310, set. 2018. Disponível em: http://dx.doi.org/10.15689/ap.2018.1703.14265.03 Acesso em: 01/09/2021.

BERCIK, P.; COLLINS, S.M.; VERDU, E.F. Microbes and the gut-brain axis. **Neurogastroenterol Motil**, Canadá, vol. 24, n.5, p. 405-13, mai. 2012. Disponível em: https://doi.org/10.1111/j.1365-2982.2012.01906.x Acesso em: 01/09/2021.

CARDING, Simon *et al.* Dysbiosis of the gut microbiota in disease. **Microbial Ecology in Health and Disease**, Reino Unido, vol. 26, p. 26191, fev. 2015. Disponível em: doi: 10.3402/mehd.v26.26191 Acesso em: 02/09/2021.

CHAHWAN, Bahia *et al*. Gut feelings: A randomised, triple-blind, placebo-controlled trial of probiotics for depressive symptoms. **Journal of Affective Disorders**, Austrália, vol. 253, p. 317-326, jun. 2019. Disponível em: doi:10.1016/j.jad.2019.04.097 Acesso em: 13/09/2021.

CRYAN, J. F.; O’MAHONY, S. M. The microbiome-gut-brain axis: from bowel to behavior. **Neurogastroenterology and Motility**, Irlanda, vol. 23, n.3, p. 187-92, mar. 2011. Disponível em: doi:10.1111/j.1365-2982.2010.01664.x Acesso em: 01/09/2021.

DASH, Sarah *et al*. The gut microbiome and diet in psychiatry: focus on depression. **Current Opinion in Psychiatry**, Austrália, vol. 28,1, n. 1, p. 1-6, jan. 2015. Disponível em: doi:10.1097/YCO.0000000000000117 Acesso: 02/09/2021.

DAVID, Lawrence A., *et al*. Diet rapidly and reproducibly alters the human gut microbiome. **Nature**, Estados Unidos, vol. 505, n. 7484 p. 559-63, jan. 2014. Disponível em: doi:10.1038/nature12820 Acesso em: 01/09/2021.

DIDARI, Tina *et al.* Effectiveness of probiotics in irritable bowel syndrome: Updated systematic review with meta-analysis. **World Journal of Gastroenterology**, Irã, vol. 21, n. 10, p. 3072-84, mar. 2015. Disponível em: doi:10.3748/wjg.v21.i10.3072 Acesso em: 02/09/2021.

DINAN, Timothy G.; STANTON, Catarina; CRYAN, John F. Psychobiotics: a novel class of psychotropic. **Biological Psychiatry**, Irlanda, vol. 74, n. 10, p. 720-6, nov. 2013. Disponível em: doi:10.1016/j.biopsych.2013.05.001 Acesso em: 01/09/2021.

DINAN, Timothy G.; CRYAN, John F. Mood by microbe: towards clinical translation. **Genome Medicine**, Irlanda, vol. 8, n. 1, p. 36, abr. 2016. Disponível em: doi:10.1186/s13073-016-0292-1 Acesso em: 01/09/2021.

DORÉ, Joël *et al.* Hot topics in gut microbiota. **United European Gastroenterol J**, França, vol. 1, n. 5, p. 311-318, out. 2013. Disponível em: doi:10.1177/2050640613502477 Acesso em: 01/09/2021.

FERENHOF, Helio Aisenberg; FERNANDES, Roberto Fabiano. Desmistificando a revisão de literatura como base para redação científica: método SSF. **Revista ACB**; Biblioteconomia em Santa Catarina – SC, Florianópolis, Brasil, vol. 21, n. 3, p. 550-563, ago./nov. 2016. Disponível em: file:///C:/Users/Usuario/Downloads/1194-6369-1-PB.pdf Acesso em: 01/09/2021.

FORSYTHE, Paul *et al*. Mood and gut feelings. **Brain, Behavior, and Immunity**, Canadá, vol. 24, n. 1, p. 9-16, jan. 2010. Disponível em: doi:10.1016/j.bbi.2009.05.058 Acesso em: 01/09/2021.

GHORBANI, Zeinab *et al.* The Effect of symbiotic as an Adjuvant Therapy to fluoxetine in Moderate Depression: A Randomized Multicenter Trial. **Arch Neurosci**,

Irã, vol. 5, n.2, p.60507, abr. 2018. Disponível em: doi: 10.5812/archneurosci.60507 Acesso em: 13/09/2021.

GOODMAN, Andrew L., *et al.* Extensive personal human gut microbiota culture collections characterized and manipulated in gnotobiotic mice. **Proceedings of the National Academy of Sciences of the United States of America**, Estados Unidos, vol. 108, n.15, p. 6252-7. abr. 2011. Disponível em: doi:10.1073/pnas.1102938108 Acesso em: 01/09/2021.

GOODRICH, Julia K., *et al.* Human genetics shape the gut microbiome. **Cell**, Estados Unidos, vol. 159, n. 4, p. 789-99, nov. 2014. Disponível em: doi:10.1016/j.cell.2014.09.053 Acesso em: 01/09/2021.

GRENHAM, Sue *et al* Brain-gut-microbe communication in health and disease. **Front Physiol**, Irlanda, vol. 2 p. 94, dez. 2011. Disponível em: https://doi.org/10.3389/fphys.2011.00094 Acesso em: 01/09/2021.

HEMARAJATA, Peera; VERSALOVIC, James. Effects of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. **Therapeutic Advances in Gastroenterology**, Estados Unidos, vol. 6, n. 1, p. 39-51. jan. 2013. Disponível em: doi:10.1177/1756283X12459294 Acesso em: 02/09/2021.

HOLSCHER, Hannah D. Dietary fiber and prebiotics and the gastrointestinal microbiota. **Gut Microbes**, Estados Unidos, vol. 8, n. 2, p. 172-184, mar. 2017. Disponível em: doi:10.1080/19490976.2017.1290756 Acesso em: 02/09/2021.

HUANG, Ruixue; WANG, Ke; HU, Jianan. Effect of Probiotics on Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. **Nutrients**, China, vol. 8, n. 8, p. 483, ago. 2016. Disponível em: https://doi.org/10.3390/nu8080483 Acesso em: 01/09/2021.

IBANEZ, Grazielle *et al.* Adesão e dificuldades relacionadas ao tratamento medicamentoso em pacientes com depressão. **Rev Bras Enferm**, Brasil, vol. 67, n.

4, p. 556-562, ago. 2014. Disponível em: https://doi.org/10.1590/0034-7167.2014670409 Acesso em: 01/09/2021.

IVANOV, Ivaylo I; HONDA, Quênia. Intestinal commensal microbes as immune modulators. **Cell host & microbe**, Estados Unidos, vol. 12, n. 4, p. 496-508, out. 2012. Disponível em: https://doi.org/10.1016/j.chom.2012.09.009 Acesso em: 02/09/2021.

JAMILIAN, Mehri *et al*. The effects of probiotic and selenium co-supplementation on parameters of mental health, hormonal profiles, and biomarkers of inflammation and oxidative stress in women with polycystic ovary syndrome. **Journal of Ovarian Research**, Irã, vol. 11, n. 1, p. 80, set. 2018. Disponível em: https://doi.org/10.1186/s13048-018-0457-1 Acesso em: 01/09/2021.

KELLY, John R., *et al.* Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat. **Journal of Psychiatric Research**, Irlanda, vol. 82, p. 109-118, nov. 2016. Disponível em: https://doi.org/10.1016/j.jpsychires.2016.07.019 Acesso em: 02/09/2021.

KONTUREK, Peter C.; BRZOZOWSKI, T.; KONTUREK, S. J. Stress and the gut: pathophysiology, clinical consequences, diagnostic approach and treatment options. **Journal of Physiology and Pharmacology**, Alemanha, vol. 62, n. 6, p. 591-599, dez. 2011. Disponível em: https://www.jpp.krakow.pl/journal/archive/12_11/pdf/591_12_11_article.pdf Acesso em: 01/09/2021.

LEDOCHOWSKI, M., *et al.* Carbohydrate malabsorption syndromes and early signs of mental depression in females. **Digestive Diseases and Sciences**, Áustria, vol. 45, n. 7, p. 1255-9, jul. 2000. Disponível em: doi:10.1023/a:1005527230346 Acesso em: 02/09/2021.

LEVY, Maayan *et al.* Dysbiosis and the immune system. **Nature Reviews. Immunology**, Israel, vol. 17, n. 4, p. 219-232, mar. 2017. Disponível em: doi:10.1038/nri.2017.7 Acesso em: 02/09/2021.

LI, Huawei *et al.* Effects of regulating gut microbiota on the serotonin metabolism in the chronic unpredictable mild stress rat model. **Neurogastroenterol Motil**, China, vol. 31, n. 10, p. 13677, jul. 2019. Disponível em: doi: 10.1111/nmo.13677 Acesso em: 13/09/2021.

LIU, Richard T.; WALSH, Rachel F.L.; SHEEHAN, Ana E. Prebiotics and probiotics for depression and anxiety: A systematic review and meta-analysis of controlled clinical trials. **Neurosci Biobehav Rev**, Estados Unidos, vol. 102, p. 13-23, abr. 2019. Disponível em: doi:10.1016/j.neubiorev.2019.03.023 Acesso em: 01/09/2021.

LIU, Xiaofei; CAO, Shangqing; ZHANG, Xuewu. Modulation of Gut Microbiota-Brain Axis by Probiotics, Prebiotics, and Diet. **J Agric Food Chem**, China, vol. 63, n. 36, p. 7885-7895, set. 2015. Disponível em: doi:10.1021/acs.jafc.5b02404 Acesso em: 02/09/2021.

LOGAN, Alan C.; KATZMAN Martin. Major depressive disorder: probiotics may be an adjuvant therapy. **Med Hypotheses**, Estados Unidos, vol. 64, n. 3, p. 533-538, out. 2005. Disponível em: doi:10.1016/j.mehy.2004.08.019 Acesso em: 02/09/2021.

MAEHATA, Hazuki *et al.* Heat-killed *Lactobacillus helveticus* strain MCC1848 confers resilience to anxiety or depression-like symptoms caused by subchronic social defeat stress in mice. **Bioscience, Biotechnology, and Biochemistry**, Japão, vol. 83, n. 7 p. 1239-1247, mar. 2019. Disponível em: doi:10.1080/09168451.2019.1591263 Acesso em: 13/09/2021.

MAJEED, Muhammed *et al.* *Bacillus coagulans* MTCC 5856 for the management of major depression with irritable bowel syndrome: a randomised, double-blind, placebo controlled, multi-centre, pilot clinical study. **Food & Nutrition Research**, Índia, vol. 62, jul. 2018. Disponível em: doi:10.29219/fnr.v62.1218 Acesso em: 13/09/2021.

MARKLE, Janet G. M., *et al.* Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. **Science**, Canadá, vol. 339, n. 6123, p. 1084-8, jan. 2013. Disponível em: doi: 10.1126/science.1233521 Acesso em: 01/09/2021.

MAYER, Emeran A. Gut feelings: the emerging biology of gut-brain communication. **Nature Reviews**. **Neuroscience**, Estados Unidos, vol. 12, n. 8, p. 453-66, jul. 2011, Disponível em: doi:10.1038/nrn3071 Acesso em: 01/09/2021.

MOTTA, Cibele Cunha Lima; MORÉE, Carmen Leontina Ojeda Ocampo; NUNES, Carlos Henrique Sancineto da Silva. O atendimento psicológico ao paciente com diagnóstico de depressão na Atenção Básica. **Cienc Saúde Colet**, Brasil, vol. 22, n. 3, p. 911-920, mar. 2017. Disponível em: https://doi.org/10.1590/1413-81232017223.27982015 Acesso em: 01/09/2021.

NEISH, Andrew S. Microbes in gastrointestinal health and disease. **Gastroenterologia**, Estados Unidos. vol. 136, n. 1, p. 65-80, jan. 2009. Disponível em: doi:10.1053/j.gastro.2008.10.080 Acesso em: 02/09/2021.

O'HARA, Ann M.; SHANAHAN, Fergus. The gut flora as a forgotten organ. **EMBO Reports**, Irlanda, vol. 7, n. 7, p. 688-93, jul. 2006. Disponível em: doi:10.1038/sj.embor.7400731 Acesso em: 02/09/2021.

O'MAHONY, Siobhain M., *et al.* Early life stress alters behavior, immunity, and microbiota in rats: implications for irritable bowel syndrome and psychiatric illnesses. **Biological Psychiatry**, Irlanda, vol. 65, n. 3, p. 263-7, fev. 2009. Disponível em: doi:10.1016/j.biopsych.2008.06.026 Acesso em: 02/09/2021.

ORGANIZAÇÃO MUNDIAL DA SAÚDE (OPAS/OMS). **Folha Informativa – Depressão**. (Brasil, 2020). Disponível em: https://www.paho.org/pt/topicos/depressao Acesso em: 01/09/2021.

OSTADMOHAMMADI, Vahidreza *et al*. Vitamin D and probiotic co-supplementation affects mental health, hormonal, inflammatory and oxidative stress parameters in women with polycystic ovary syndrome. **Journal of Ovarian Research**, Irã, vol. 12,

n. 1, p. 5, jan. 2019. Disponível em: doi:10.1186/s13048-019-0480-x Acesso em: 02/09/2021.

QIU, Xiangjie *et al. Lactobacillus delbrueckii* alleviates depression-like behavior through inhibiting toll-like receptor 4 (TLR4) signaling in mice. **Annals of Translational Medicine**, China, vol. 9, n. 5 p. 366, mar. 2021. Disponível em: doi:10.21037/atm-20-4411 Acesso em: 13/09/2021.

REININGHAUS, Eva Z., *et al.* PROVIT: Supplementary Probiotic Treatment and Vitamin B7 in Depression-A Randomized Controlled Trial. **Nutrients**, Áustria, vol. 12, n. 11, p. 3422, nov. 2020. Disponível em: doi:10.3390/nu12113422 Acesso em:13/09/2021.

REITER, Alexandra *et al*. Interleukin-6 Gene Expression Changes after a 4-Week Intake of a Multispecies Probiotic in Major Depressive Disorder-Preliminary Results of the PROVIT Study. **Nutrients**, Áustria, vol. 12, n. 9, p. 2575, ago. 2020. Disponível em: doi:10.3390/nu12092575 Acesso em: 13/09/2021.

RODRÍGUEZ, Juan Miguel *et al.* The composition of the gut microbiota throughout life, with an emphasis on early life. **Microbial Ecology in Health and Disease**, Espanha, vol. 26, n. 26050, fev. 2015. Disponível em: doi:10.3402/mehd.v26.26050 Acesso em: 01/09/2021.

ROMIJN, Amy R., *et al.* A double-blind, randomized, placebo-controlled trial of Lactobacillus helveticus and Bifidobacterium longum for the symptoms of depression. **The Australian and New Zealand Journal of Psychiatry**, Nova Zelândia, vol. 51, n. 8, p. 810-821, ago. 2017. Disponível em: doi:10.1177/0004867416686694 Acesso em: 01/09/2021.

SARRIS, Jerome *et al.* Nutritional medicine as mainstream in psychiatry. **The Lancet. Psychiatry**, Estados Unidos, vol. 2, n. 3, p. 271-4, fev. 2015. Disponível em: doi:10.1016/S2215-0366(14)00051-0 Acesso em: 02/09/2021.

SKONIECZNA-ŻYDECKA, Karolina *et al.* Faecal Short Chain Fatty Acids Profile is Changed in Polish Depressive Women. **Nutrients**, Polônia, vol. 10, n. 12, p. 1939, dez. 2018. Disponível em: doi:10.3390/nu10121939 Acesso em: 02/09/2021.

SLAVIN, Joanne. Fiber and prebiotics: mechanisms and health benefits. **Nutrients**, Estados Unidos, vol. 5, n. 4, p. 1417-35, abr. 2013. Disponível em: doi:10.3390/nu5041417 Acesso em: 02/09/2021.

SMITS, Loek P., *et al.* Therapeutic potential of fecal microbiota transplantation. **Gastroenterology**, Holanda, vol. 145, n. 5, p. 946-53, set. 2013. Disponível em: doi:10.1053/j.gastro.2013.08.058 Acesso em: 02/09/2021.

SARTOR, R Balfour. Microbial influences in inflammatory bowel diseases. **Gastroenterology**, Estados Unidos, vol. 134, n. 2, p. 577-94, fev. 2008. Disponível em: doi:10.1053/j.gastro.2007.11.059 Acesso em: 02/09/2021.

SUZUKI, Takuya. Regulation of the intestinal barrier by nutrients: The role of tight junctions. **Animal Science Journal Nihon Chikusan Gakkaiho**, Japão, vol. 91, n. 1, p. 13357, dez. 2020. Disponível em: doi:10.1111/asj.13357 Acesso em: 02/09/2021.

TILLISCH, Kirsten *et al.* Consumption of fermented milk product with probiotic modulates brain activity. **Gastroenterology**, Estados Unidos, vol. 144, n. 7, p. 1394-401; 1401.e1-4, mar. 2013. Disponível em: doi:10.1053/j.gastro.2013.02.043 Acesso em: 02/09/2021.

TRAN, Nhan *et al.* The gut-brain relationship: Investigating the effect of multispecies probiotics on anxiety in a randomized placebo-controlled trial of healthy young adults. **Journal of Affective Disorders**, Estados Unidos, vol. 252, p. 271-277, abr. 2019. Disponível em: doi:10.1016/j.jad.2019.04.043 Acesso em: 02/09/2021.

TSAI, Yu-Ling *et al.* Probiotics, prebiotics and amelioration of diseases. **Journal of Biomedical Science**, Taiwan, vol. 26, n. 1, p. 3, jan. 2019. Disponível em: doi:10.1186/s12929-018-0493-6 Acesso em: 01/09/2021.

VARAVALLO, Maurilio Antonio; THOMÉ, Julia Nigro; TESHIMA, Elisa. Aplicação de bactérias probióticas para profilaxia e tratamento de doenças gastrointestinais. **Semina: Cienc Biol Saúde**, Brasil, vol. 29, n. 1, p. 83-104, jun. 2008. Disponível em: http://dx.doi.org/10.5433/1679-0367.2008v29n1p83 Acesso em: 01/09/2021.

VIZCAÍNO, Ricnia *et al.* Usos clínicos de los probióticos. **Arch Venez Pueric Pediatr**, Venezuela, vol. 79, n. 1, p. 029-040, mar. 2016. Disponível em: http://ve.scielo.org/scielo.php?script=sci_arttext&pid=S000406492016000100007&lng=es&nrm=iso Acesso em: 01/09/2021.

WALLACE, Caroline J. K.; MILEV, Roumen V. The Efficacy, Safety, and Tolerability of Probiotics on Depression: Clinical Results From an Open-Label Pilot Study. **Front Psychiatry**, Canadá, vol. 12 p. 618279, fev. 2021. Disponível em: doi: 10.3389/fpsyt.2021.618279 Acesso em: 13/09/2021.

WERBNER, Michal *et al.* Social-Stress-Responsive Microbiota Induces Stimulation of Self-Reactive Effector T Helper Cells. **MSystems**, Israel, vol. 4, n. 4, p. 00292-18, mai. 2019. Disponível em: doi:10.1128/mSystems.00292-18 Acesso em: 01/09/2021.

WU, Gary D., *et al*. Linking long-term dietary patterns with gut microbial enterotypes. **Science**, Estados Unidos, vol. 334, n. 6052, p. 105-8, set. 2011. Disponível em: doi:10.1126/science.1208344 Acesso em: 01/09/2021.

YATSUNENKO, Tanya *et al*. Human gut microbiome viewed across age and geography. **Nature**, Estados Unidos, vol. 486, n. 7402, p. 222-7, mai. 2012. Disponível em: doi:10.1038/nature11053 Acesso em: 02/09/2021.

YONG, Shin Jie *et al.* Antidepressive Mechanisms of Probiotics and Their Therapeutic Potential. **Frontiers in Neuroscience**, Malásia, vol. 13, p. 1361, jan. 2020. Disponível em: doi:10.3389/fnins.2019.01361 Acesso em: 01/09/2021.

YUAN, Ziqi *et al*. Application of antidepressants in depression: A systematic review and meta-analysis. **Journal of Clinical Neuroscience**, China, vol. 80, p. 169-181, ago. 2020. Disponível em: doi:10.1016/j.jocn.2020.08.013 Acesso em: 01/09/2021.

ZALAR, Bojan; HALSBERGER, Alexandre; PETERLIN, Borut. The Role of Microbiota in Depression – a brief review. **Psychiatria Danubina**, Eslovênia, vol. 30, n. 2, p. 136-141, jun. 2018. Disponível em: doi:10.24869/psyd.2018.136 Acesso em: 01/09/2021.

ZAWISTOWSKA-ROJEK, Anna; TYSKI, Stefan. Are Probiotic Really Safe for Humans? **Polish Journal of Microbiology**, Polônia, vol. 67, n. 3, p. 251-258, set. 2018. Disponível em: doi:10.21307/pjm-2018-044 Acesso em: 02/09/2021.

ZHENG, P., *et al.* Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. **Molecular Psychiatry**, China, vol. 21, n. 6, p. 786-96, jun. 2016. Disponível em: doi:10.1038/mp.2016.44 Acesso em: 02/09/2021.

Sent: March, 2022.

Approved: May, 2022.