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Review

MICROBIOTA DIVERSITY AND INFLAMMATION AS A NEW TARGET TO IMPROVE MOOD: PROBIOTIC USE IN DEPRESSIVE DISORDER

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SUMMARY

Background: *There is a lot of evidence for a bidirectional communication between the gut and brain. Dysbiosis and increase intestinal permeability may lead to a systemic low-grade inflammatory response or various neuroactive bacterial metabolite may cross gut barrier. Pro-inflammatory cytokines or bacterial metabolites such as short-chain fatty acid (SCFA) are known to pass through blood brain barrier and altered neurotransmitter metabolism or increase production of neurotoxic pathways. In this review we hypothesized that restoring the gut microbiota ecosystem could improve mental disorders. We reviewed literature for human evidence proving clinical relevance of probiotics intake in mental disorders.*

Subjects and methods: *We searched literature with keywords "depression" or "major depressive disorder" and "probiotic". We selected randomized control trial and we considered having both outcomes concerning impact on depressive symptoms but also on inflammation biomarkers, microbiota composition, cerebral nervous system or cognition.*

Results: *Seven out of fourteen randomized control trial reported significant improvement on depressive symptoms in patients taking probiotics. Besides improvement in depressive symptoms, we found decrease in inflammatory markers such as IL-6, decrease in serum kynurenine level, changes in microbiota diversity and abundance of species correlated to depressive disorder and higher cognitive performance.*

Conclusions: *Probiotic seems to be secure and more effective on depression when used in supplement to usual antidepressant and in mild to moderate depression. We highlighted positive impact on vulnerability factors prevent further worsening. Probiotics could have anti-inflammatory effect acting on inflammatory markers well known to have a role on pathogenesis of depression. A strong correlation between neuroactive metabolites and a relative abundance of microbiota bacterial species underlined importance to consider the gut-brain axis in mental disorders.*

Key words: *major depressive disorder – probiotic – inflammation – cognition - microbiota*

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INTRODUCTION

There is a lot of evidence for a bidirectional communication between the gut and brain via several pathways (Dubois et al. 2019). Researchers point out the role of intestinal flora in inflammation or endocrine systems and these systems are known to have a significant role in pathophysiology of mental disorders (Dubois et al. 2018). So, microbiota disturbances (dysbiosis) and increase intestinal permeability (leaky gut) may lead to a systemic low-grade inflammation or various neuroactive bacterial metabolite may cross gut barrier. Inflammation via pro-inflammatory cytokines and bacterial metabolites such as short-chain fatty acid (SCFA) are known to pass through blood brain barrier and altered neurotransmitter metabolism (such as serotonin), increase production of neurotoxic pathways (such as kynurenine axes) and oxidative stress. In this review we hypothesized that restoring the gut microbiota ecosystem could improve mental disorders symptoms by dampen systemic inflammation and decrease gut permeability preventing bacterial metabolites crossing by intestinal wall. This is already highlighted in animal models with fecal microbiota transplantation impacting behaviors. The aim of this study was to review the literature for human evidence proving clinical relevance of probiotics intake in mental disorders.

SUBJECTS AND METHODS

We searched on Pubmed, PsycINFO, PsycARTICLES, Sciencedirect and Embase articles with keywords "depression" or "major depressive disorder" and "probiotic". We selected only randomized control trial with individuals having a clinical diagnosis of major depressive disorder eventually assessed by a depression scale. We have excluded articles concerning healthy individuals or those with other mental or somatic disease objectified. After a first browse of the results, we considered articles congruent to our question and having both outcomes concerning impact on depressive symptoms but also on inflammation biomarkers, microbiota composition, cerebral nervous system or cognition. In sum, only 14 studies meet our criteria. We evoked for this review a possible interpretation and selection bias.

RESULTS

Seven studies (Akkasheh et al. 2016, Miyaoka et al. 2018, Kazemi et al. 2019, Lee et al. 2021, Tian et al. 2022, Schaub et al. 2022, Ullah et al. 2022) found significant decrease in depressive symptoms after probiotic intervention. Some of these studies also showed other outcomes such as improvement of appetite (Kazemi et

al. 2019), decrease in inflammatory markers such as hs-CRP (Akkasheh et al. 2016), decrease serum level of IL-6 (Lee et al. 2021), microbiota diversity or composition variation or higher production of bacterial metabolites such as SCFA (Lee et al. 2021, Tian et al. 2022, Schaub et al. 2022). Miyaoka et al. 2018 (Miyaoka et al. 2018) found in an open label randomized control trial that adding clostridium butyricum to usual antidepressant had

Table 1. Strains used during probiotic interventions, depressive symptoms at baseline, primary and secondary outcomes

Authors	Strains	Depressive symptoms baseline	Depresive symptoms outcomes	Secondary outcomes
Akkasheh et al. 2016	L.acidophilus, L. casei, B.bifidum	Moderate to severe	8 weeks ↓ *BDI*	↓ hs-CRP
Romijn et al. 2017	L. helveticus, B. longum	Moderate to severe (> 2 ans) No AD	8 weeks NS	NS
Miyaoka et al. 2018	Clostridium butyricum	Moderate to severe Treatment-resistant	8 weeks + Usual AD ↓ *HAM-D* ↓ *BDI* *Responders = 70%* *Remission = 35%*	NS
Kazemi et al. 2019 Kazemi et al. 2020	L. helveticus, B.longum. + Prebiotic group	Mild to moderate	8 weeks ↓ BDI	↑ Appetite. ↓ KYN/TRP ratio.
Chahwan et al. 2019	B. bifidum, B. lactis, L.acidophilus, L. brevis, L. casei, L.salivarius, L. lactis, Lactococcus lactis	Mild to moderate.	8 weeks NS	↓ Cognitive reactivity.
Rudzki et al. 2019	L. plantarum.	Mild to moderate.	8 weeks + Usuual AD NS	↓ Kynurenine ↑ Cognitive performance
Reiter et al. 2020 Kreuzer et al. 2022 Reininghaus et al. 2020	B. bifidum, B. lactis, L. acidophilus, L. casei, L. paracasei, L.salivarius, L.plantarum, Lactococcus lactis	Mild to moderate	4 weeks NS	↑ Microbiota diversity ↑ Ruminococcus ↑ Coprococcus ↓ IL-6 gene expression
Lee et al. 2021	L. reuteri, B. adolescentis	Mild to moderate No history of AD or MDD	8 weeks ↓ *BDI-II (after 4 weeks)*	↑Bifidobacterium. ↑ Lactobacillus. ↓ Proteobacteria. ↑ SCFA ↑AA ↓ Serum IL-6
Tian et al. 2022	B. breve.	Mild to moderate	4 weeks + Usual AD ↓ *HDRS-24* ↓ *MADRS*	↑ Bifidobacterium. ↑ Lachnospiraceae ↑ Serum 5HT
Schaub et al. 2022	Streptococcus thermophilus, B. breve, B. longum, B. infantis, L. acidophilus, L. plantarum, L. paracasei, L. delbrueckii	Mild to moderate	4 weeks + follow-up (8 weeks) ↓ *HAM-D*	↑ Microbiota ↑ Lactobacillus *PLACEBO:* ↓ Prevotella. ↑Rumminicoccus. ↓ putamen
Ullah et al. 2022	L. helveticus, B. longum. + S-adenosyl methionine (SAM)	Subthreshold or mild to moderate depression	Cross-over trial (12 weeks) ↓ *HAM-D* ↓ *PHQ-9* Maintain until follow-up (6 weeks)	NS

Note: L = Lactobacillus; B = Bifidobacterium; AD = antidepressant; MDD = major depressive disorder; MDD = Major depressive disorder; BDI = Beck Depression Inventory; HAM-D/HDRS = Hamilton Depression Rating Scale; PHQ-9 = Patient Health Questionnaire; MADRS = Montgomery-Åsberg Depression Rating Scale; SCFA = Short-Chain Fatty Acid; AA = Amino-Acid; NS = no significative; KYN = kynurenine; TRP = Tryptophan

positive effect on treatment-resistant depression with 70% responders and 35% remissions. Tian et al. (2022) found a positive correlation between Bifidobacterium and Lachnospiraceae abundance and psychometric improvements. Main outcomes are reported in Table 1.

Strains used during probiotic interventions, depressive symptoms at baseline, primary and secondary outcomes. Although no improvement in depressive symptoms, Chahwan et al. (2019) found a greater reduction in cognitive reactivity towards sad mood in mild to moderate depressive disorder. Similarly, Rudzki et al. (2019) showed no improvement in depressive symptoms after a 8-week probiotic adjunctive treatment but highlighted higher cognitive performance with the attention and perceptivity test (APT) evaluating selective attention, sustained attention, vigilance, visual perception and visual scanning and the California verbal learning test (CVLT) evaluating episodic verbal learning and memory total. They also showed a decrease in serum kynurenine level. Based on the PROVIT study (Reiter et al. 2020, Reininghaus et al. 2020, Kreuzer et al. 2022) a monocentric, randomized, placebo-controlled trial investigates probiotics on depression, cognition, microbiome, blood parameters and gene expression, there is no evidence for improvement in depressive outcomes after a 4-week probiotic intervention. However, they found in this group an increase microbiota diversity and abundance of two species, Coprococcus and Ruminococcus gauvreauii as well as a decrease in IL-6 gene expression. Only one study found neither significant depressive nor secondary outcomes (Romijn et al. 2017). Population studied in this article reported high to moderate depression for more than two years and were free of any psychiatric medication for at least 4 weeks before the trial. Studies investigated adverse effect and tolerance of the medication (Romijn et al. 2017, Kazemi et al. 2019, Rudzki et al. 2019, Lee et al. 2021) and all of them reported no serious adverse event in taking probiotics and no significant difference comparing with placebo group. Adherence to the probiotic was good and there is also no difference in compliance.

DISCUSSION

In this literature review based specifically on RCT findings, we highlighted that probiotics could be used as a secure supplement therapeutic strategy in major depressive disorder. Several authors reported statistically significant improvement of depression score in individuals following probiotic treatment. Why this antidepressant-like effect failed to be demonstrated in some studies is not entirely explain and future research are necessary. We hypothesized that heterogeneity in inclusion criteria, variations in depressive severity at baseline, probiotic composition and dosage and treatment duration influenced outcomes. Firstly, probiotics may be administrated with or without other treatment. According to our review, it seems that probiotics are less effective on depressive symptoms when used as unique or primary treatment than in supplement to usual therapy such as SSRIs. Length of probiotic intervention varies between 4 weeks or 8 weeks based on the standard antidepressant treatment duration. Secondly, characteristics of depression before probiotic intervention seems to determine effect. Probiotics may be more effective in less severe depressive symptoms. Some studies including only mild to moderate depressed individuals found positive outcomes. Some authors evoked more impact if depression is more "inflammatory" as probiotics suspected having an anti-inflammatory effect but this concept is not actually define in clinical practice. Some authors found no direct effect on mood but objective improvement on cognition, reactivity (negative thinking reactivation by minor triggers) (Barnhofer & Chittka 2010) or appetite with probiotic treatment. Which are vulnerability markers leading to worsen quality of life and mood and acting on this could be prevent further worsening or promote symptomatology alleviation. Third, some trial used a unique bacterial strain while others used a multistrains mixture. There could be a variability regarding efficacity depending on strain composition. As described below, there is evidence for correlations between some bacteria strain and blood biomarkers levels, gene activity or microbiota diversity changes. However, determining which bacterial strain is the most effective in mental health remains complicated and more evidence are needed. Several studies found significant difference concerning microbiota diversity and species abundance. In some trial the increase abundance of *Bifidobacterium* or *Lactobacillus* may reflect that probiotics have well been ingested and reached correctly intestinal microbiota. Evidences found higher abundance of species known to be depleted in depression such as for example Coprococcus, an acid butyric producer (Sanada et al. 2020). There are some evidences that this increase is positively correlates with psychometric improvement of depressive disorder. Moreover, it was also demonstrated a decrease in some strains suspected to be higher in depressed patients such as *Proteobacteria* or *Enterobacteriaceae*. Furthermore, we found some interesting results regarding microbiota evolution in individuals receiving a placebo. Authors observed fewer healthy strains such as *Prevotella* and more ones known to be increase in depressive people. For example, an increase of *Ruminoccocus* known to be pro-inflammatory. So, it seems that taking probiotic help to maintain a healthy bacterial diversity having an impact on species living there. As we described in the results, higher level of amino-acids and SCFA such as butyric acid are found in stool samples of depressed patients receiving probiotic treatment. A strong correlation between metabolites and a relative abundance of

bacterial species are found. For example, butyric acid levels and abundance of *Faecalibacterium*. Given evidences for lower levels of anti-inflammatory, butyrate-producing bacteria in MDD, these outcomes support the assumption that probiotics may have an antidepressant effect and links between inflammatory, gut microbiota and mental health. Evidence concerning amino-acids profile in patients with depression are more divergent. Deviating results concerning inflammatory blood markers are found. Some trials conclude to a decrease in interleukine-6 (IL-6) levels after probiotics intake. As we described in the results, Reiter et al. (2020) demonstrated a decrease IL-6 gene expression with probiotic. These results support the notion that probiotics could have an anti-inflammatory effect, reducing level of pro inflammatory cytokine. And the notion that probiotic impact pathogenesis of depression, acting on a biomarker well known to be elevated in major depressive disorder (Lamers et al 2019). Some authors found no significant difference in term of inflammation between probiotic and placebo group. But some of them demonstrated a potential signature of a lower inflammation given a reduced level of kynurenine with a decreased kynurenine/tryptophan ratio. As a reminder, inflammation induces the use of tryptophan to produce neurotoxic kynurenine instead of serotonin. Findings highlighted how possibly probiotics impact CNS in depression. By increase serotonin level reaching the brain or by reducing kynurenine, a neurotoxic metabolite. Improvement of cognitive performance correlate to kynurenine decrease with probiotic underlined the role of gut-brain axis in mental disorders. This role is also noted with evidence of a significant decrease in right and left putamen activation after probiotic intake.

CONCLUSION

Several randomized control trial reported significant improvement on depressive symptoms in patients taking probiotics. They seem to be more effective on depression when used in supplement to usual antidepressant and in mild to moderate depression. Significant variations concerning microbiota diversity and abundance of species correlate to depressive disorder are found. Improvement of cognitive performance is objectified and probiotics possibly impact cerebral nervous system by a decrease level of pro inflammatory cytokines or neurotoxic kynurenine but also by increase serotonin level crossing through the brain blood barrier.

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Contribution of individual authors:

All authors make substantial contributions to conception and design and or acquisition of data and or analysis or interpretation of data.

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