Depression is one of the most prevalent mental illnesses and is often associated with various other medical disorders. Since the 1980s, the primary pharmacological treatment has been antidepressants, but due to the recent discovery of the association between the gut microbiome and mental health, probiotics have been proposed as an adjunctive or alternate treatment. In this narrative review, we aim to provide a holistic perspective by synthesizing and evaluating existing evidence, discussing key biological mechanisms, exploring the history of probiotic use, and appreciating the influence of modern diet on mental health. Five online databases were searched for relevant studies up to December 2017. Systematic reviews that included randomized controlled trials assessing the efficacy of probiotics in the treatment of depressive symptoms were included. Seven systematic reviews met the inclusion criteria. Three of these reviews conducted meta-analyses, out of which, two concluded that probiotics improved depressive symptoms in the sample population. Out of the four reviews that conducted qualitative analysis, three reviews concluded that probiotics have the potential to be used as a treatment. Due to the differences in clinical trials, a definitive effect of probiotics on depressive symptoms cannot be concluded. Nonetheless, probiotics seem to potentially produce a significant therapeutic effect for subjects with pre-existing depressive symptoms. Further studies are warranted for definitive conclusions.

**Keywords:** depression, gut-brain axis, gut microbiota, probiotic, psychobiotic.


Depression is one of the most prevalent mental illnesses worldwide and is the fourth leading cause of global disease burden in women. It is often associated with major medical illnesses, such as cardiovascular disease, diabetes, and cancer, adding to their morbidity. Medications were first used as treatments for depression in 1958, and the first antidepressant medication to be marketed as such, imipramine, was introduced in 1959. Since the 1980s, pharmacological treatment with antidepressant medications has been a major modality of therapeutic intervention in the management of depressive disorders. From 1987 to 1997, antidepressant usage among populations diagnosed with major depressive disorder (MDD) increased from 37% to 74%. However, a large portion of patients that have been prescribed antidepressants do not meet the DSM criteria for MDD, as antidepressants are commonly prescribed for anxiety disorders, obsessive–compulsive disorder, and sub-threshold depression, among other disorders.

The ‘over-prescription’ of antidepressants has contributed to the common problem of polypharmacy. As a result, we are now seeing growing interest in non-pharmacological strategies for depression and other mental illnesses. An example of a non-pharmacological intervention is physical exercise, which has been used as treatment for a variety of mental illnesses, including depression, and there are multiple systematic reviews of randomized controlled trials (RCT) that have demonstrated its therapeutic effect. More recently, we have seen a growing focus in the literature on the role of gut bacteria on mental health.

There has been much discussion in the literature surrounding the association between depression, irritable bowel syndrome, and inflammatory bowel disease. One study in Canada looked at the National Population Health Survey from 1996–1997 and found that the population diagnosed with inflammatory bowel disease had threefold the rate of depression as the general public. This association could be related to changes in the gut microbiome that result from the disease process. However, this correlation could also be explained by the general burden of disease, the rise in inflammatory markers in the blood, or corticosteroid treatment.

In 2001, the World Health Organization published a report indicating the health benefits of probiotic supplements, and in 2005, the first paper was published that proposed the use of probiotics as an adjunctive treatment for MDD. Since then, the field has steadily grown with a recent spike in publications. In fact, over 90% of the articles published on the microbiome in PubMed were from 2010 onwards. There has been particular focus on the effect of gut microorganisms on the brain through the gut–brain axis. In 2013, the term ‘psychobiotic’ was born due to both the growing evidence in the literature for the use of probiotic supplements for mental health and the resulting media attention.

The evidence for the potential therapeutic benefits of probiotics for mental health was initially based on animal studies. One rat study found that *Bifidobacteria infantis* treatment significantly increased tryptophan, a serotonergic precursor, in the blood plasma (*P* < 0.005). It also decreased inflammatory markers, such as interferon (IFN)–γ, tumor necrosis factor (TNF)–α, and interleukin (IL)-6. This finding is consistent with the inflammatory model of depression.
Probiotic effects on depressive symptoms

that conceptualizes it as a disorder that involves an inflammatory response. A meta-analysis has shown that inflammatory markers, such as IL-6 and TNF-α, are significantly increased in depressed populations compared with control groups. Furthermore, peripheral levels of C-reactive protein (CRP) have repeatedly been shown to be associated with depression.

The effect of Lactobacillus rhamnosus on neurotransmission was looked at in a mouse study. They found that this bacterial strain regulated gamma-aminobutyric acid (GABA) expression selectively in the brain and ultimately reduced depression-related behavior in the treatment group. They compared results with mice that were vagotomized and found these effects to be absent. The authors concluded that the vagus nerve must play an important role in mediating the effects of the gut on the brain. These results were in line with those of another study that looked at direct vagus nerve stimulation (VNS) as an intervention for treatment-resistant depression, which reported that patients with low to moderate antidepressant resistance benefited from VNS.

Success in animal models has led researchers to investigate human populations for any link between gut bacteria and depression. One study compared gut bacteria in populations diagnosed with depression with a control group by analyzing the microbiota in their feces. They found a significant difference in fecal microbiota between the study and control groups. Specifically, they found Lachnoclostridium and Bacteroidales to be overrepresented (P = 0.02) and Bacteroides to be underrepresented (P = 0.05). The presence of one clade within Akotus was also associated with depression. They found that high and simple carbohydrate diets promoted its growth in the gut. Lastly, Oscilbacter was also associated with depression. A metabolic end product of this bacterial genus is valeric acid, a known neurochemical agent that binds to GABA-α receptors.

Probiotics present an exciting new direction for lifestyle prevention and treatment of depression. Both animal and human studies have shown promise for the potential benefit of probiotics on depression. The important next step is to investigate their effectiveness through more rigorous means. In the last decade, there have been several randomized trials published that have investigated the effect of probiotic supplements on depressive symptoms as well as several systematic reviews of these trials. Our study aims to gather and evaluate existing systematic reviews through a narrative review that describes the current state of the science. The narrative review will also provide important theoretical and contextual considerations to the topic of probiotics from biological and social perspectives. We believe that this is important given the rise in popularity of probiotics in popular culture.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed as a guideline for conducting and reporting this narrative review. No published protocol is available.

Search strategy

A literature search was conducted using electronic medical databases, including PubMed, Embase, PsycINFO, Medline, Cochrane Library, and Web of Science, from their inception to December 2017, to identify all relevant articles examining the use of probiotics as a therapeutic intervention for depressive symptoms. A comprehensive search was conducted using the following search terms: (probiotics OR Lactobacillus OR Bifidobacterium) AND (gut OR microbiome OR microbiota OR microflora) AND (depression OR depressive OR mental health OR mood). Results were filtered where possible to reviews and English-language studies. References of included studies were also reviewed for additional relevant articles that met the inclusion criteria.

Selection criteria

Study selection criteria were defined prior to the searches. Studies included in the review had to meet the following criteria: (i) systematic review with/without meta-analysis (narrative reviews and individual clinical trials were excluded); (ii) review included human populations (excluded if only animal trials were examined); (iii) clinical trials in systematic review included probiotics among the interventions investigated; (iv) review examined changes in depressive symptoms as either a primary or secondary outcome; (v) clinical trials in systematic review that assessed depressive symptoms must have been randomized controlled trials; and (vi) review must be in English and published in a peer-reviewed journal.

Study selection

Study selection was completed using the PRISMA process. A list of citations was compiled from the comprehensive literature search and all duplicates were removed. Titles and abstracts were then screened to exclude citations that were clearly irrelevant based on the selection criteria. If there was any doubt about inclusion, the article was included for the next stage of evaluation. All types of reviews made it past the initial round of screening for full-text verification. After the initial screening, all remaining full-text articles were screened to assess their eligibility for inclusion in this review.

Data extraction

Data extraction was completed using a data extraction form designed prior to the search. The following data items were extracted from the included systematic reviews: (i) publication date, or if unclear/publication date in the future, date published online; (ii) number of studies included in review and the number of studies that assessed depression or depressive symptoms in humans; (iii) whether a meta-analysis was conducted or not; (iv) if meta-analysis was conducted, its results; and (v) conclusions of the review. Data were then extracted from the individual trials assessing depression, and the extracted items included: (i) study sample characteristics; (ii) the probiotic strain used as intervention and duration; (iii) scales used to measure outcome; and (iv) results.

Quality assessment

Quality of included systematic reviews was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, a widely used tool that assesses methodological quality on five domains: limitations, inconsistency, indirectness, imprecision, and publication bias. On the basis of the quality of evidence, the GRADE system characterizes a systematic review’s recommendations as either strong or weak. No reviews were excluded based on ratings.

Data synthesis

A narrative synthesis of results was performed.

Results

Included systematic reviews

Figure 1 presents the literature search. A total of 566 titles and abstracts were initially retrieved from electronic database searches. After duplicates were removed, 410 citations remained. During the first round of screening, 366 clearly irrelevant citations were excluded, and 44 articles were included for full-text screening. Based on the pre-defined selection criteria, seven studies met the inclusion criteria and were included in this review. Reasons for exclusion at the full-text screening stage included: not a systematic review (n = 35) and effects of probiotics on depression were not assessed (n = 2).

Outcome measures

A variety of measurement techniques were used in individual clinical trials to measure the effect of probiotics on depressive symptoms. The scales used to measure effects of probiotics in the
The included clinical trials had varying study sample characteristics, duration of study, intervention species and strains, outcome measurements, and findings. Amongst the included studies, the clinical trial conducted by Akkasheh et al. was the only trial to assess effects of probiotics on subjects clinically diagnosed with MDD, whereas the other studies recruited subjects with irritable bowel syndrome, mild to moderate mood symptoms, rheumatoid arthritis, cancer, and/or healthy individuals. Akkasheh et al. conducted a double-blind, placebo-controlled RCT including 40 subjects with a diagnosis of MDD based on DSM-IV criteria whose age ranged between 20 and 55 years. Subjects were randomly allocated into two groups to receive either placebo (n = 20) or probiotic supplements consisting of the following freeze-dried strains: *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum* (n = 20) for 8 weeks. The researchers found that after 8 weeks of intervention, subjects who received probiotic supplements had significantly decreased Beck Depression Inventory total scores (−5.7 ± 6.4 vs −1.5 ± 4.8, P = 0.001) compared with those in the placebo group.

**Findings of reviews**

Table 1 shows the characteristics of the seven included systematic reviews, in order of publication date. Out of the seven systematic reviews, three conducted meta-analyses. The meta-analyses conducted by McKean et al. and Huang et al. showed that probiotic interventions have the ability to significantly decrease depressive symptoms in subjects (standardized mean difference [SMD] = 0.34 [favoring treatment, 95% confidence interval (CI) 0.07 to 0.61, P = 0.01] and SMD = −0.30 [favoring treatment, 95% CI: −0.51 to −0.09, P = 0.005], respectively).

Huang et al. further conducted subgroup analyses. A subgroup analysis based on health status showed probiotics to significantly decrease depressive symptoms in patients with MDD and in healthy subjects (SMD = −0.25 [favoring treatment, 95% CI: −0.47 to −0.03, P = 0.03] and SMD = −0.73 [favoring treatment, 95% CI: −1.37 to −0.09, P = 0.03], respectively). The second subgroup analyses conducted was based on age, and Huang et al. found probiotics to produce significant effects on subjects under the age of 60 years (SMD = −0.42 [favoring treatment, 95% CI: −0.72 to −0.13, P = 0.005]), but close to no effect on patients aged over 65 years (SMD = −0.18 [favoring treatment, 95% CI: −0.47 to −0.11, P = 0.22]).

The most recent meta-analysis, conducted by Ng et al., showed probiotics to provide no significant decrease in depressive symptoms in subjects when compared to placebo (SMD = −0.128 [favoring treatment, 95% CI: −0.261 to 0.00463, P = 0.059]). Ng et al. further conducted a subgroup analysis based on mental health status and concluded that although the data suggested that probiotics had no significant effect on the whole group of subjects, probiotics could produce significant improvements in the moods of individuals diagnosed with MDD or mild to moderate anxiety and/or depression (SMD = −0.684 [favoring treatment, 95% CI: −1.296 to −0.0712, P = 0.029]) when compared to effects on healthier individuals (SMD = −0.09999 [favoring treatment, 95% CI: −0.235 to 0.348, P = 0.146]). In other words, this analysis found that probiotics were associated with a moderate improvement effect in the symptoms of subjects classified as meeting criteria of MDD but not in the nominal (dimensional) scores of depressive symptoms for subjects not classified as having MDD.

**Clinical trials**

Supplementary Table S1 shows characteristics of all the individual trials that have assessed probiotic interventions on depressive symptoms included in the systematic reviews. All individual studies were randomized controlled trials. Out of the grand total of 63 included trials, there were 25 unique clinical studies conducted.

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**Fig.1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) scheme of retrieved literature.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Publication date</th>
<th>No. studies assessing depression in humans/total no. studies included</th>
<th>Meta-analyses conducted (Yes/No)</th>
<th>Results of meta-analysis</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ng et al.32 (2018)</td>
<td>March 2018 Published online: November 2017</td>
<td>12/12</td>
<td>Yes, including 10/12 studies</td>
<td>No significant difference in mood symptoms between treatment and placebo groups post-intervention. SMD = −0.128 (95%CI −0.261 to 0.00463, P = 0.059) [Favoring treatment] Separate subgroup analysis: Probiotics produced significant improvements in the moods of individuals with pre-existing depressive symptoms, SMD = −0.684 (95%CI −1.296 to −0.0712, P = 0.029) but had insignificant effects in healthy individuals, SMD = −0.0999 (95%CI −0.235 to 0.0348, P = 0.146)</td>
<td>Meta-analysis of 10 randomized controlled trials found that probiotic supplementation had overall insignificant effects on mood. Subgroup analyses found statistically significant benefit in individuals with pre-existing mood symptoms, while the effects tended to be insignificant in healthy individuals. Although generally safe and palatable, it cannot be recommended that probiotics replace antidepressant medications as the primary treatment for depressed patients. Results suggest that a probiotic intervention may have an advantageous effect on mental health by reducing psychological symptoms, including anxiety, depression, and perceived stress in healthy adult volunteers.</td>
</tr>
<tr>
<td>McKean et al.30 (2017)</td>
<td>April 2017</td>
<td>7/7</td>
<td>Yes</td>
<td>Meta-analysis showed that supplementation with probiotics resulted in significantly reduced preclinical psychological symptoms of anxiety, depression, and stress in healthy individuals. SMD = 0.34 (95%CI 0.07 to 0.61, P = 0.01) [Favoring treatment]</td>
<td></td>
</tr>
<tr>
<td>Wallace et al.33 (2017)</td>
<td>2017 (month unknown) Published online: February 2017</td>
<td>8/10</td>
<td>No</td>
<td>—</td>
<td>Treatment with probiotics may improve symptoms associated with MDD. Despite extensive preclinical data, the clinical effects of probiotics on mental health have yet to be studied comprehensively in a sample of depressed patients. Further research is warranted to determine probiotics’ efficacy for alleviating depressive symptoms. According to the qualitative analyses of current studies, probiotics can improve depressive symptoms.</td>
</tr>
<tr>
<td>Wang et al.21 (2016)</td>
<td>October 2016</td>
<td>12/38</td>
<td>No</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Publication date</td>
<td>No. studies assessing depression in humans/total no. studies included</td>
<td>Meta-analyses conducted (Yes/No)</td>
<td>Results of meta-analysis</td>
<td>Conclusions</td>
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<tr>
<td>Pirbaglou et al. <a href="2016">34</a></td>
<td>September 2016</td>
<td>10/10</td>
<td>No</td>
<td>—</td>
<td>Despite limitations and/or inconsistencies in current findings, it appears that probiotic supplementation had a positive impact on reducing anxiety and depressive symptoms in several studies. Findings must be regarded as tentative until future trials address the intricacies of the gut–brain axis.</td>
</tr>
<tr>
<td>Huang et al. <a href="2016">31</a></td>
<td>August 2016</td>
<td>5/5</td>
<td>Yes</td>
<td>Meta-analysis showed that probiotics significantly decreased the Depression scale score in all subjects, $\text{SMD} = -0.30$ (95%CI $-0.51$ to $-0.09$, $P = 0.005$) [Favoring treatment] Separate subgroup analysis: Probiotics produced significant improvements on population aged under 60 years, $\text{SMD} = -0.43$ (95%CI $-0.72$ to $-0.13$, $P = 0.005$), while it had no effect on people aged over 65 years, $\text{SMD} = -0.18$ (95%CI $-0.47$ to 0.11, $P = 0.22$). Probiotics had an effect on both the healthy population, $\text{SMD} = -0.25$ (95%CI $-0.47$ to $-0.03$, $P = 0.03$) and patients with MDD, $\text{SMD} = -0.73$ (95%CI $-1.37$ to $-0.09$, $P = 0.03$)</td>
<td>This systematic review supports the potential role of probiotics in reducing the risk of depression. The findings suggest an important role for probiotics in reducing the risk of depression in non-depressed individuals.</td>
</tr>
<tr>
<td>Romijn et al. <a href="2015">35</a></td>
<td>October 2015</td>
<td>8/10</td>
<td>No</td>
<td>—</td>
<td>There is very limited evidence for the efficacy of probiotic interventions in psychological outcomes. There were far more negative findings than positive findings in all areas assessed. However, due to variability in study designs, bacterial strains used, and placebo product used, interpreting the results of these trials cohesively is problematic.</td>
</tr>
</tbody>
</table>

CI, confidence interval; MDD, major depressive disorder; SMD, standardized mean difference (Cohen’s D).
Quality assessment

Table 2 presents the quality assessments of the included systematic reviews based on the GRADE system.23 As all included trials were RCT, assessment began at high quality of evidence, and was rated down based on five domains: limitations, inconsistency, imprecision, indirectness, and publication bias. Wallace et al.33 and Romijn et al.35 did not assess the methodological quality of their included studies comprehensively enough, and were rated down accordingly. McKean et al.30 conducted a meta-analysis and provided a pooled estimate of studies with high heterogeneity ($I^2 = 67\%$). It appears to have been possible for McKeen et al.30 to conduct separate subgroup analyses. However, they did not do so, resulting in very serious inconsistency. Publication bias was suspected in four studies30,31,33,35 because the systematic reviews did not comment on whether the bias was evaluated or not. A high-quality level means that we can be confident that the true effect lies close to that of the estimate of the effect, while a very low-quality level means we have very little confidence in the effect estimate.35 The studies rated as having high quality were Ng et al.,32 Wang et al.,21 and Huang et al.;31 the study by Pirbaglou et al.34 was rated as moderate quality; and the studies rated as very low quality were McKeen et al.,30 Wallace et al.,21 and Romijn et al.35

Discussion

In this section, we summarize and evaluate reviewed studies, briefly discuss theoretical and known biological explanatory mechanisms, and present our findings and their implications from a holistic perspective.

Summary of reviewed studies

The purpose of this part of the study was to gather and evaluate published systematic reviews assessing the effect of probiotics on depressive symptoms. There are both positive and negative findings. Although the most recently published study, by Ng et al.,32 found the overall effect of probiotics to be statistically insignificant for a combined dataset of both depressed and healthy individuals, further subgroup analysis conducted suggests that probiotics can produce significant improvements in the moods of individuals with pre-existing depressive symptoms. These results differ significantly from the findings of a previous meta-analysis conducted by Huang et al.,31 which collected data from five randomized clinical trials and found the effects of probiotics on mood to be statistically significant in both depressed and healthy individuals. A possible explanation for this conclusion can be attributed to Huang et al.,31 only including one clinical trial conducted on depressed patients. Ng et al.32 used the same five trials reviewed by Huang et al. in addition to five other trials added to the meta-analysis – including two new studies in individuals with mild to moderate depressive symptoms – and two more studies for the narrative review. Additionally, the study by Ng et al.32 was evaluated to be of high quality of evidence; therefore, we can be confident of its results.25

The meta-analysis conducted by McKeen et al.30 had positive findings, concluding that probiotics can significantly reduce psychological symptoms of anxiety, depression, and stress in healthy individuals. However, their meta-analysis had a high level of heterogeneity. The heterogeneity may be explained by the differences in probiotic strains used, duration of intervention, and differences in gut microbiome characteristics of study participants. Perhaps further subgroup analyses could have explained the heterogeneity and produced more conclusive results. This study was also suspected of publication bias; therefore, its conclusions cannot be received with confidence.23

Wallace et al.33 conducted a qualitative synthesis of 10 clinical trials and categorized its results as: (i) effects on moods; (ii) effects on stress and anxiety; and (iii) effects on cognition. For the purposes of this review, trials assessed under effects on mood and effects on stress and anxiety were included due to the high level of correlation between depression, stress, and anxiety.26,27 A majority of the studies found positive results, with probiotics having the most significant effects on symptoms of anxiety that are comorbid with depression.33 Due to the review’s inadequate assessment of methodological quality of the included clinical trials, its conclusions cannot be received with a high level of confidence.25

Wang et al.21 intended to assess effects of probiotics on the central nervous system (CNS) on humans and animals, and included a total of 38 unique studies for qualitative synthesis. Fifteen of these studies included humans, 12 of which assessed depressive symptoms. According to their qualitative analyses, they concluded that *Bifidobacterium longum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Lactobacillus helveticus*, *Lactobacillus rhamnosus*, and *Lactobacillus casei* were most effective in improving symptoms.

The systematic review conducted by Pirbaglou et al.34 consisted of trials assessed in more recent reviews with the exception of one.36 They concluded that probiotic supplementation had a positive impact on reducing anxiety and depressive symptoms, and had a moderate quality of evidence. In contrast, the study by Romijn et al.35 was

<table>
<thead>
<tr>
<th>Reference (study design)</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>Ng et al.,32 (RCT)</td>
<td>No serious</td>
<td>No serious</td>
<td>No serious</td>
<td>No serious</td>
<td>Undetected</td>
<td>(+)(+)(+)(+)</td>
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<td></td>
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<td>indirectness</td>
<td>imprecision</td>
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<td>No serious</td>
<td>Very serious</td>
<td>No serious</td>
<td>No serious</td>
<td>Suspected</td>
<td>(+)(+)(+)</td>
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<tr>
<td></td>
<td>limitations</td>
<td>inconsistency</td>
<td>indirectness</td>
<td>imprecision</td>
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<tr>
<td>Wallace et al.,33 (RCT)</td>
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<td>No serious</td>
<td>No serious</td>
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<td>(+)(+)(+)</td>
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<td></td>
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<td>imprecision</td>
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<tr>
<td>Wang et al.,21 (RCT)</td>
<td>No serious</td>
<td>No serious</td>
<td>No serious</td>
<td>No serious</td>
<td>Undetected</td>
<td>(+)(+)(+)(+)</td>
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<td></td>
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<td>Pirbaglou et al.,34 (RCT)</td>
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<td>(+)(+)(+)(+)</td>
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<tr>
<td></td>
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<tr>
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<td>Undetected</td>
<td>(+)(+)(+)(+)</td>
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<td>High</td>
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<td>Romijn et al.,35 (RCT)</td>
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<td>No serious</td>
<td>No serious</td>
<td>No serious</td>
<td>Suspected</td>
<td>(+)(+)(+)</td>
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<td>inconsistency</td>
<td>indirectness</td>
<td>imprecision</td>
<td></td>
<td>Very Low</td>
</tr>
</tbody>
</table>

GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
conducted when the use of probiotics as an intervention was still a recent innovation. They noted that there were more negative findings than positive findings. However, as the use of probiotics for the treatment of depression was a novel field and there was a lack of evidence at the time of the study, its conclusions are to be received with low confidence.23

Although there are differences in conclusions amongst studies, the more recent high-quality evidence suggests that probiotics can produce significant effects in individuals with pre-existing depressive symptoms, whereas the effect on mood symptoms is less significant in healthier populations. Discrepancies between findings can possibly be explained by differences in sample characteristics, differences in microbiome features, variety of probiotic strains used as an intervention and its duration of use, and other baseline characteristics. Despite the differences, there is good evidence from the literature to shed light on the psychological health benefits of probiotics and the link between gut microbiota and neuropsychiatric function.

The gut–brain axis

The gut–brain axis possesses bidirectional communication.57 The brain affects the quantity and quality of fauna in the gut through modulating immune responses to the microorganisms in the intestines. These bacterial colonies in turn produce neurochemical substances that directly or indirectly affect the brain. This axis achieves benefits for both the CNS of the host and the microorganisms themselves. The host is able to utilize neurochemicals produced by gut bacteria for neural communication, mood stabilization, and social and exploratory behavior.58 Indirectly, gut bacteria benefit from the increased social interaction that occurs as a direct consequence of the metabolites they have produced for the brain, as it increases their ability to spread through the human population.58

More than just social interaction, Bercik et al.59 found that the specific makeup of gut fauna may also contribute to personality characteristics. Germ-free mice that were previously daring became timid and apprehensive after being colonized with the gut bacteria of a mouse that was also timid and shy. Conversely, germ-free mice that were previously reclusive became exploratory and daring after being introduced to gut bacteria from exploratory mice.

Gut bacteria have also been demonstrated to play a role in how we cognitively and affectively interpret the world. A team of researchers randomized females to a diet of fermented milk products with probiotics (FMPP) twice a day or a diet of non-fermented milk products twice a day.60 After a month of diet, they were given an emotional faces attention task, and a functional magnetic resonance imaging scan was conducted before and after. They found that subjects on the FMPP diet had decreased neuronal reactivity to the emotional stimulus compared to the control group, indicating higher emotional resilience.

On a more physiological level, there seems to be a connection between the hypothalamic–pituitary–adrenal axis (stress regulation) and gut bacteria. Germ-free mice and normal mice were exposed to a stressful environment and measurements of stress hormones were taken.61 Germ-free mice showed a markedly increased stress response as compared to the normal mice. Furthermore, the researchers found that they could normalize the stress response of the germ-free mice by probiotic treatments.

Further effects of gut microbiota on the brain include blood–brain barrier (BBB) integrity.62 Germ-free mice show a decreased expression of occludin – an important protein for tight junctions between cells – in the frontal cortex, striatum, and hippocampus. A dysfunctional BBB can expose the brain to toxic substances that can result in a variety of neurological, neurovascular, and mental illnesses. When germ-free mice were given Clostridium tyrobutyricum or Bacteroides thetaiotaomicron, there was decreased permeability in the BBB.62

As described earlier, the gut–brain axis is bidirectional. Until now, we have described the effect of gut bacteria on the brain. But there is also evidence that suggests the brain/mind may alter the gut microbiota. In psychiatric disorders, there is an increase in Lactobacillus and a decrease in Prevotella.52 In MDD, there is an increase in Enterobacteriaceae and Alistipes and a decrease in Faecalibacterium and Ruminococcus.62 The direction of causality is not conclusive in these findings. However, Su et al.63 found that after exposure to weaning stress in piglets, there was a reduction in Lactobacillus. This suggests a brain-to-gut direction of causality rather than gut-to-brain direction. The finding of Lactobacillus reduction in response to stress has been reported across species, including primates, mice, and humans.64

Some of the key chemicals produced or impacted by gut bacteria that have effects on the brain are tryptophan, short-chain fatty acids, and equol.62 Tryptophan is essential in the release of serotonin. Clostridium sporogenes and Ruminococcus gravis are responsible for decarboxylating tryptophan, producing tryptamine.65 This compound releases serotonin from the enterochromaffin cells. It has been demonstrated in mice that the gut microbiota can respond to stress by upregulating this process and increasing the amount of serotonin released.66

Short-chain fatty acids that are produced by gut bacteria are used to regulate appetite. Equol is an estrogen produced through metabolizing daidzein (a compound found in soy isoflavone) in the gut by the microbiota.62 This is found to boost cognitive functions, such as memory, and protect against cerebral ischemia.62

Modern living and the rise of depression

Depression has arguably been on the rise since the early 20th century.67 There are many factors that can account for this change that range from political to philosophical, for instance, the two World Wars and rise of totalitarian regimes, along with the increased sense of individual nihilism that pervaded the Western social conscience as a consequence of modernist and postmodernist thinkers. A newer contribution to the explanation may be related to the role of the microbiome in the gut–brain axis. The nature, variety, and density of bacterial species in the gut could have been affected by significant changes in the food industry that occurred in the 20th century, as well as an increased use of antibiotics and an increase in overall hygiene. Based on comparisons with the Hadza of Tanzania, a hunter–gatherer tribe that is unaffected by these social changes, the civilization human being has markedly decreased diversity in gut microbiota.57 Microbiota diversity is essential in providing the microbiome with the ability to adapt to changes in the environment.57 A lack of diversity renders the gut susceptible to diseases and alteration based on environmental changes. We believe it is possible that changes in our gut microbiome that may have resulted from hyper-sanitation and modern dietary styles have contributed to the rise in depression throughout the decades, despite an overall improvement in the quality of living.57 Studies that explore the impact of dietary and lifestyle changes on the microbiome and, by direct or indirect extension, mental health in general and depression in particular, are needed and may have major public health implications.

Conclusions and further directions

Gut microbiota are likely to play a role in CNS functioning and clinical interventions (such as the use of probiotics) or societal trends and lifestyle changes that modify gut bacterial content are likely to be relevant to the treatment of depressive symptoms. Due to the differences in sample characteristics, probiotic intervention combinations, durations of trials, outcome scales, and results, a definitive beneficial effect of probiotics on depressive symptoms cannot be concluded from the literature reviewed in this study. Probiotics do seem likely to produce therapeutic effects in individuals with depressive symptoms; however, further research must be conducted to reach definitive conclusions. Larger, longer-duration RCT are warranted to assess whether probiotics can cause a stable effect. Such studies should include samples of participants that are matched with controls for baseline characteristics, including microbiome features, to confirm the role of probiotics on psychiatric symptoms. Additionally, studies need
to assess benefits of specific strains as effects may be strain-specific, as well as explore the potential therapeutic uses of fecal microbiota transplantation in the management of mental illness.

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Author contributions
I.N. performed the literature search, the selection of studies for inclusion, the extraction of data from selected studies, the quality assessment, interpretation of findings, and drafted and revised the paper. Z.R. performed the literature search, interpreted the findings, and drafted and revised the paper. Y.A. conceptualized the paper, interpreted the findings, and reviewed and revised the paper. M.A. conceptualized the paper, interpreted the findings, and reviewed and revised the paper.

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13. Evensen A, Ceylan ME. The gut-brain axis: The missing link in depression, the extraction of data from selected studies, the quality assessment, interpretation of findings, and drafted and revised the paper. Z.R. performed the literature search, interpreted the findings, and drafted and revised the paper. Y.A. conceptualized the paper, interpreted the findings, and reviewed and revised the paper. M.A. conceptualized the paper, interpreted the findings, and reviewed and revised the paper.


Supporting information
Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:
Table S1. Characteristics of all individual trials included in systematic reviews assessing depressive symptoms, including study sample, probiotic strains used as intervention, duration of study, scales used to measure outcomes, and results