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Efficacy of Probiotics, Prebiotics, and Symbiotics for the Treatment of Depression: A meta-review

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ABSTRACT

Background. Recent research has highlighted the importance of nurturing and strengthening the intestinal microbiota due to its relationship with mental health, which has implications for the prevention and management of mental diseases such as depressive disorders. One opportunity to address this is supplementation with live microorganisms called probiotics or substances that promote their development called prebiotics, or both (symbiotics). **Objective.** This study aims to explore the existing literature on the efficacy of probiotics, prebiotics, and symbiotics for the treatment of depression symptoms and depression. **Method.** A meta-review of systematic reviews was conducted across various databases (Medline/PubMed, Web of Science, Scopus, Cinahl, and PsycInfo). Formulation of a research question and a comprehensive search strategy employing keywords and Boolean operators guided the identification of systematic reviews reporting quantitative synthesis, particularly meta-analysis of randomized controlled trials (RCT). Systematic reviews meeting these criteria were selected, and relevant findings were systematically extracted. **Results.** Thirteen systematic reviews with meta-analyses of RCT were selected. The evidence points towards the efficacy of prebiotics, probiotics, and symbiotics in depression treatment, albeit with a weak effect. Conditions optimizing the antidepressant efficacy of these supplements were identified, including their use as adjunctive therapy to pharmacological treatment, concurrent use of probiotics and prebiotics (or symbiotics), and the use of multi-strain formulations. **Discussion and conclusion.** Prebiotics, probiotics, and symbiotics are considered to demonstrate substantive evidence of their efficacy in the treatment of depression. Nevertheless, various research opportunities within this field have been identified.

Keywords: depression, probiotics, prebiotics, symbiotics, meta-analysis, psychological tests.

RESUMEN

Antecedentes. Investigaciones recientes han puesto de manifiesto la importancia de cuidar y fortalecer la microbiota intestinal debido a su relación con la salud mental, pudiendo tener implicaciones en la prevención y manejo de enfermedades como la depresión. Una oportunidad para lograr esto es la suplementación con microorganismos vivos llamados probióticos, el uso de sustancias que promueven su desarrollo (prebióticos) o ambos (simbióticos). **Objetivo.** Explorar la literatura existente sobre la eficacia de probióticos, prebióticos y simbióticos para el tratamiento de la sintomatología depresiva y de la depresión. **Método.** Se realizó una meta-revisión sistemática en diferentes bases de datos (*Medline/PubMed, Web of Science, Scopus, Cinahl, and PsycInfo*). Se formuló una pregunta de investigación y estrategia de búsqueda en estas bases de datos, utilizando palabras clave y operadores booleanos. Se seleccionaron las revisiones sistemáticas que reportaron síntesis cuantitativa como metaanálisis de ensayos controlados aleatorizados (ECA) y se extrajeron los hallazgos obtenidos en los mismos. **Resultados.** Se seleccionaron 13 revisiones sistemáticas con metaanálisis de ECA en las cuales se identificó evidencia de la eficacia de prebióticos, probióticos y simbióticos en el tratamiento de depresión, aunque con un efecto débil. Se reportaron algunas condiciones que pueden optimizar la eficacia antidepresiva de estos suplementos como: uso como terapia adjunta al tratamiento farmacológico, uso conjunto de probióticos y prebióticos (simbióticos) y uso de formulaciones multicepas. **Discusión y conclusión.** Se concluyó que los prebióticos, probióticos y simbióticos muestran evidencia de su eficacia en el tratamiento de la depresión, identificando varias oportunidades de investigación en este campo.

Palabras clave: depresión, probiótico, prebiótico, simbiótico, metaanálisis, pruebas psicológicas.

BACKGROUND

Although often overlooked or misinterpreted as mere sadness, depression is a multifaceted condition that manifests itself in various ways, affecting not only mood but also the physical health and daily functioning of afflicted individuals (Organización Panamericana de la Salud [OPS], 2017). Depression is not just a temporary state of sadness; it constitutes a persistent condition plunging those affected into a profound emotional abyss. It is often accompanied by feelings of hopelessness, loss of interest in previously pleasant activities, constant fatigue, difficulty concentrating, loss of appetite, disrupted sleep patterns, cognitive impairment, and feelings of worthlessness or guilt (American Psychiatric Association, 2016).

According to data provided by WHO in 2015, the prevalence of depression increased by 18.4% over ten years from 2005 to 2015. Current estimates suggest that nearly 322 million individuals worldwide suffer from depression. Its incidence is more pronounced among women than men, with a percentage difference of 1.5 %. Furthermore, depression manifests across all age groups, with a higher prevalence among women ages between 55 and 74 (OPS, 2017).

Treatment of depression includes psychotherapy and pharmacotherapy. The latter involves the use of antidepressant drugs, which work through various mechanisms of action, mainly regulating the monoaminergic system composed of the neurotransmitters serotonin (5HT), dopamine (DA), and norepinephrine (NA) (Pérez-Esparza et al., 2017). However, although this pharmacological treatment is highly effective, there is a group of patients in whom remission is not achieved, indicating the need for further investigation of alternative or adjuvant treatments.

In recent years, the importance of the intestinal bacterial flora (microbiota) in both physical and mental health has been identified, finding that disruptions to this flora may be associated with various chronic diseases, including mental health disorders such as depression and anxiety (Hou et al., 2022; Kumar et al., 2023). Moreover, a spectrum of intrinsic factors linked to the host can compromise the integrity of the intestinal bacterial flora, which can lead to dysbiosis. Some of these factors are genetic factors, chronic or infectious diseases, lifestyle habits such as unhealthy dietary patterns (unbalanced, high sugar content, and low fiber), and poor hygiene habits. Extrinsically, environmental factors, including exposure to xenobiotics such as drugs (particularly antibiotics), food additives, and other substances, have also been identified as contributors to *dysbiosis* (Hrncir, 2022).*dysbiosis* (Hrncir, 2022).*dysbiosis* (Hrncir, 2022). *dysbiosis* (Hrncir, 2022).

In this respect, treating depression and other mental health disorders could go beyond standard psychotherapeutic and pharmacological modalities and include therapeutic alternatives that restore and/or boost intestinal bacterial flora, such as a dietary regimen abundant in fruits, leafy green vegetables, fish, and polyphenols. Concurrently, the consumption of beneficial microorganisms, known as probiotics, of substances that promote their growth (prebiotics), or a combination of both (symbiotics), stands as a pertinent adjunct to these therapeutic strategies (Kumar et al., 2023).

Probiotics, found naturally in our digestive system and considered an essential part of the gut microbiota, may also be supplemented by specific live microorganisms that, when ingested as nutritional supplements, adapt to the intestinal environment, conferring benefits similar to naturally occurring probiotics. Conversely, prebiotics are selectively fermentable ingredients that cause specific changes in the composition and/or activity of the gastrointestinal micro-

Table 1
Searching Strategy across Various Databases

Medline (via Pubmed)
("probiotic s"[All Fields] OR "probiotical"[All Fields] OR "probiotics"[MeSH Terms] OR "probiotics"[All Fields] OR "probiotic"[All Fields] OR ("prebiotically"[All Fields] OR "prebiotics"[MeSH Terms] OR "prebiotics"[All Fields] OR "prebiotic"[All Fields])) AND ("review"[Publication Type] OR "systematic review"[Filter]) AND (("depressed"[All Fields] OR "depression"[MeSH Terms] OR "depression"[All Fields] OR "depressions"[All Fields] OR "depression s"[All Fields] OR "Depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields]) OR "Depressive disorder"[All Fields] OR "depressivity"[All Fields] OR "depressive"[All Fields] OR "depressively"[All Fields] OR "depressiveness"[All Fields] OR "depressives"[All Fields] OR "Depressive Symptoms"[All Fields] OR "Depressive Symptom"[All Fields] OR "Depressive disorder"[All Fields] OR "Depressive syndrome"[All Fields] OR "Depressive syndromes"[All Fields]) AND ("review"[Publication Type] OR "systematic review"[Filter])) AND (("systematic review"[Title/Abstract] OR "systematic reviews"[Title/Abstract]))

Web of Science (Clarivate)
((ALL=(Probiotics OR Prebiotics)) AND ALL=((Depression OR "Depressive Symptoms" OR "Depressive Symptom" OR "Depressive disorder" OR "Depressive syndrome" OR "Depressive syndromes"))) AND AB=(("systematic review" OR "systematic reviews"))

Scopus
(TITLE-ABS-KEY (probiotics OR prebiotics)) AND (TITLE-ABS-KEY (depression OR "Depressive Symptoms" OR "Depressive Symptom" OR "Depressive disorder" OR "Depressive syndrome" OR "Depressive syndromes")) AND (TITLE-ABS-KEY ("systematic review" OR "systematic reviews"))

Cinahl (via Ebsco)
TX (probiotics or prebiotics) AND TX (Depression OR "Depressive Symptoms" OR "Depressive Symptom" OR "Depressive disorder" OR "Depressive syndrome" OR "Depressive syndromes") AND AB ("systematic review" OR "systematic reviews")

PsycInfo (via Ovid)
((Probiotics or Prebiotics) and (Depression or "Depressive Symptoms" or "Depressive Symptom" or "Depressive disorder" or "Depressive syndrome" or "Depressive syndromes")).af. and ("systematic review" or "systematic reviews").md.

biota (Sarkar et al., 2016). Finally, symbiotics are selective formulations of probiotics and prebiotics.

The mechanism of action of probiotics is an extraordinary process owing to their multifaceted beneficial effects. These encompass the establishment of eubiosis within the intestinal microbiota, helping the host metabolism through immune system stimulation, inflammation regulation, and the production of metabolites, including short-chain fatty acids and neurotransmitters (Sikorska et al., 2023). A specific category within probiotics is psychobiotics, live microorganisms affording health benefits to individuals with mental illness when ingested in adequate doses. This is achieved through the production of neurotransmitters or their precursors, thereby influencing the microbiota-gut-brain axis (MGB) and modulating the hypothalamic-pituitary-adrenal (HPA) axis, consequently decreasing its activity. As such, certain probiotics may have positive effects on mood and cognitive function by modulating the gut microbiota and improving gut-brain communication (Dinan et al., 2013; Sikorska et al., 2023).

Several studies and systematic reviews have recently been published on the efficacy of probiotics, prebiotics, and/or symbiotics addressing depressive symptomatology or depression. This paper aims to present a meta-review outlining and summarizes the main findings in methodologically rigorous systematic reviews.

In regard to specific objectives, this meta-review seeks to describe the characteristics of published systematic reviews with quantitative synthesis, exploring subpopulations (classified by age group and health conditions) and treatment modalities (classified by length of treatment, monotherapy and add-on therapy), in which the effectiveness of probiotics, prebiotics, and symbiotics have been tested, to compare the efficacy between these different subpopulations and treatment modalities.

METHOD

A systematic review of systematic reviews — also known as a "meta-review" or "umbrella review" — (Aromataris et al., 2015; Smith et al., 2011) was conducted to analyze the efficacy of interventions based on probiotic, prebiotic, or symbiotic treatment for the management of depressive symptomatology and/or depression. A team comprising the six co-authors worked on the review. A review protocol was registered with the Research Registry platform and the identifying number was review registry1817 (Anguiano-Morán et al., 2024). A research question was formulated based on the identification of the components of the PICO strategy (population, intervention, comparison, and outcomes): P = healthy individuals with depressive symptomatology or diagnosed depression at various stages of evolution; I = treatment with probiotics, prebiotics, or symbiotics either as monotherapy or adjunctively to pharmacological treatment; C = administration of a placebo and/or standard pharmacological treatment; and O = evaluation of depression levels through self-reporting using psychometric depression scales. Only systematic reviews of Randomized Controlled Trials (RCT) reporting quantitative data synthesis (meta-analysis) were considered.

The research involved searches across databases such as *Medline (*via *PubMed)*, *Web of Science*, *Scopus*, *Cinahl (*via *Ebsco)*, *and PsycInfo (*via *Ovid)*, using keywords and Boolean operators. The specific search strategies for each database consulted are detailed in Table 1.

The Zotero bibliographic manager was used to manage the reference database and identify duplicate reviews, while the Rayyan online system was used to select studies through title and abstract by two reviewers. Inclusion criteria comprised having all the elements of the PICO strategy and publication in either English or Spanish. The full texts of the reviews selected through this process were acquired and analyzed by other two reviewers who carried out a painstaking selection considering the previous criteria, in addition to whether they included quantitative synthesis, and fulfilled certain quality considerations. A PRISMA flow diagram (Page et al., 2021) was generated to illustrate the search, screening, and article inclusion processes (Figure 1).

The quality of the selected reviews was assessed through the AMSTAR II instrument, which contains sev-

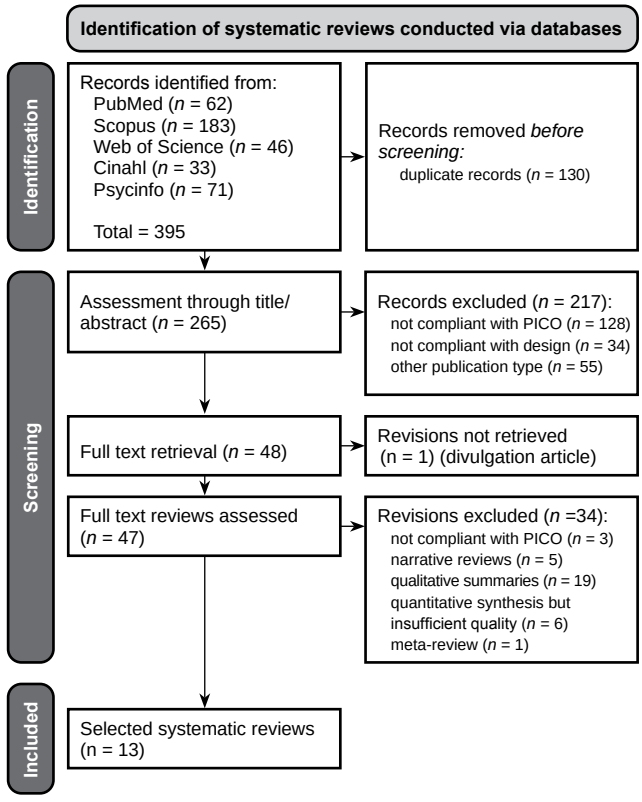

Figure 1. PRISMA Flow Diagram for the Search Process and Selection of Systematic Reviews.

en critical domains and nine non-critical domains. For each item, the answer could be "yes," "no," or "partly so." According to this instrument, overall confidence of the systematic reviews can be rated as the following: 1) "High," for no or one non-critical weakness; 2) "Moderate," for two or more non-critical weaknesses; 3) "Low," for one critical flaw with or without a non-critical weakness; and 4) "Very low," for two or more critical flaw with or without non-critical weakness (Shea et al., 2017).

Data extraction for the characteristics of the selected systematic reviews included study populations, interventions, comparators, and outcomes, participants enrolled in the studies, and the main outcomes obtained, both overall and by subgroup. Information on the heterogeneity reported as the I^2 statistic for overall and subgroup meta-analyses was also collected. According to this index, heterogeneity of effect estimates across trials can be described as small ($I^2 < 25\%$), moderate (I^2 between 26 and 74%), or substantial ($I^2 \geq 75\%$) (Higgins et al., 2003). Additionally, data on the risk of bias assessment reported in the systematic reviews was collected.

RESULTS

Flowchart

The diagram in Figure 1 shows the systematic review search and selection process. After the review process, 13 quantitative systematic reviews (meta-analyses) were selected.

Table 2
Evaluation of Quality of Selected Systematic Reviews

Systematic Review	*Items AMSTAR II*[a,b]																		*Confidence rating*[c]
	1	*2**	*3*	*4**	*5*	*6*	*7**	*8*	*9i **	*9ii **	*10*	*11i**	*11ii **	*12*	*13**	*14*	*15**	*16*	
Amirani et al., 2020	1	0	1	0.5	1	1	0	1	0.5	NA	0	1	NA	0	0	0	0	1	Very Low
Desai et al., 2021	1	1	1	1	1	1	0	1	1	NA	1	1	NA	0	1	1	0	1	Very Low
El Dib et al., 2021	1	1	1	1	1	1	0	1	1	NA	1	1	NA	0	1	1	0	1	Very Low
Goh et al., 2019	1	1	1	0.5	1	1	0	1	1	NA	0	1	NA	0.5	1	1	0	1	Low
Halemani et al., 2023	1	1	1	0.5	1	1	0	1	1	NA	0	1	NA	0	0	0	0	1	Very Low
Hofmeister et al., 2021	1	1	1	1	1	1	1	1	1	NA	0	1	NA	1	1	1	1	1	High
Huang et al., 2016	1	0	1	0.5	1	1	0	0.5	1	NA	0	1	NA	0	1	1	1	1	Low
Le Morvan et al., 2022	1	0	1	1	1	1	0	1	1	NA	1	1	NA	0	1	1	0	1	Low
Lin et al., 2023	1	1	1	1	1	1	0	1	1	NA	0	1	NA	1	1	0	1	1	Low
Liu et al., 2019	1	0	1	0.5	1	1	0	1	1	NA	0	1	NA	0	1	0	1	1	Very low
Nikolova et al., 2021	1	0	1	0.5	1	1	0	1	0.5	NA	0	1	NA	0	0	0	0	1	Very low
Zagórska et al., 2020	1	0	1	0.5	1	1	0	1	0.5	NA	0	1	NA	0	0	0	1	1	Very low
Zhu et al., 2022	1	1	1	0.5	1	1	0	0.5	1	NA	0	1	NA	1	1	1	1	1	Low

Notes:
[a]AMSTAR II instrument items: 1 = research question and inclusion criteria have PICO components (participants, intervention, comparison group, outcomes or results); 2 = review follows a previously established protocol; 3 = study design selection is justified; 4 = comprehensive literature search strategy; 5 = selection of duplicate studies; 6 = duplicate data extraction; 7 = listing and justification of excluded studies; 8 = describes included studies in detail; 9i = satisfactory technique for assessing risk of bias of RCT; 9ii = satisfactory technique for assessing risk of bias of nonrandomized interventional studies (RCT); 10 = reports sources of funding of studies included in review; 11i = if reporting meta-analyses, uses an adequate method of statistical pooling of RCT; 11ii = if reporting meta-analysis, uses an adequate statistical pooling method in RCT; 12 = assesses the impact of risk of bias on the meta-analysis; 13 = in the discussion, considers the impact of risk of bias on results; 14 = justifies and discusses any observed heterogeneity; 15 = assesses publication bias; 16 = reports conflicts of interest. Domains considered critical are shown with an asterisk (*).
[b]Evaluation of the items: no = 0; partial yes = .5; yes = 1; NA = not applicable.
[c]Rating is explained in the methods section.

Quality Analysis of Selected Systematic Reviews

Table 2 shows the quality analysis of the selected systematic reviews. Most systematic reviews had unsatisfactory results, with confidence being rated as "Low" or "Very low" and only one achieving a "High" (Hofmeister et al., 2021). In regard to the results for the critical items, some reviews did not report having a protocol registry before the review (item 2), others did not report the search strategies clearly (item 4), most failed to report the studies excluded or their justification for this (item 7), and still others did not provide a detailed discussion of the impact of the risk of bias in the selected studies on the findings (item 13), with several failing to report publication bias (item 15). The low frequency of compliance with item 7 was particularly striking; only one review reported the list of studies excluded and their justification (Hofmeister et al., 2021). Failure to comply with this item affected the overall results of the other reviews.

Characteristics of the Systematic Reviews Selected

Table 3 outlines the general characteristics and main results of the systematic reviews selected. In regard to the population of interest, these reviews included individuals with depressive symptomatology or a depressed population at various stages with or without other comorbidities. In regard to the intervention, most of the systematic reviews evaluated the efficacy of probiotics, although some also included the evaluation of prebiotics, symbiotics, and even paraprobiotics. These systematic reviews included studies using probiotics as monotherapy or adjunctive interventions to pharmacological treatment. Furthermore, the intervention encompassed both single and multiple strain therapies. Placebos or standard pharmacological treatment, whether separately or combined, were used as comparators. Depressive symptomatology was assessed using various psychometric scales.

Meta-analyses, as reported in these systematic reviews, evaluated effect size using metrics such as weighted mean difference (WMD), mean difference (MD), or standardized mean difference (SMD). Some systematic reviews opted for meta-analyses using various depression assessment scales (Amirani et al., 2020; El Dib et al., 2021) and intervention types (Liu et al., 2019), a combination of intervention types and populations (Hofmeister et al., 2021), or specific subpopulations (Desai et al., 2021). However, most systematic reviews involved an overall meta-analysis with subgroup analysis, explaining the factors influencing efficacy (Goh et al., 2019; Halemani et al., 2023; Huang et al., 2016; Le Morvan de Sequeira et al., 2022; Lin et al., 2023; Nikolova et al., 2021; Zagórska et al., 2020; Zhu et al., 2022).

Efficacy of Probiotics

The assessment of probiotic efficacy was examined across 13 selected systematic reviews, focusing on the treatment of depressive symptomatology and depression itself.

Within the healthy population, probiotic efficacy was evaluated in three reviews (Goh et al., 2019; Huang et al., 2016; Zagórska et al., 2020). Only Huang et al. (2016) demonstrated a statistically significant meta-analysis from four studies (n = 325, *SMD*: -.25; $CI_{95\%}$: -.47, -.03).

Five reviews evaluated probiotic efficacy in populations with depressive symptomatology, predominantly associated with chronic diseases (Goh et al., 2019; Hofmeister et al., 2021; Le Morvan de Sequeira et al., 2022; Lin et al., 2023; Zhu et al., 2022). Statistically significant meta-analyses were observed in three reviews: 1) Hofmeister et al. (2021) with 35 studies (n = 2,988, *SMD*: .31; $CI_{95\%}$: .15, .46); 2) Le Morvan de Sequeira et al., (2022) with 11 studies (n = 830, *SMD*: -.30; $CI_{95\%}$: -.51, -.09); and 3) and Lin et al. (2023) with eight studies (n = 412, *SMD*: -2.00; $CI_{95\%}$: -3.41, -.59).

Eight systematic reviews found statistical significance in populations diagnosed with varying stages of depression that involved probiotic treatment as monotherapy or as an adjunct intervention to pharmacological treatment (Amirani et al., 2020; El Dib et al., 2021; Hofmeister et al., 2021; Le Morvan de Sequeira et al., 2022; Liu et al., 2019; Nikolova et al., 2021; Zagórska et al., 2020; Zhu et al., 2022). Some of the most outstanding reviews, such as Hofmeister et al. (2021) with nine studies (n = 544, *SMD*: .78; $CI_{95\%}$: .19, 1.37); Zhu et al. (2022) with ten studies (n = 541, *SMD*: .46; $CI_{95\%}$: .22, .70); and Liu et al. with 25 studies (*SMD*: -.24; $CI_{95\%}$: -.36, -.12), had substantial sample sizes. Two reviews evaluated probiotic efficacy in monotherapy (Lin et al., 2023; Nikolova et al., 2021) yet reported no statistically significant differences compared to the placebo in their meta-analyses.

In the population with major depressive disorder (MDD), probiotic efficacy was evaluated through a subgroup analysis as part of a systematic review (Goh et al., 2019) including three studies, and was statistically significant (n = 144, *SMD*: -.75; $CI_{95\%}$: -1.09, -.41). Another review (Huang et al., 2016) included one study focusing on this population, which was statistically significant (n = 40, *SMD*: -.73; $CI_{95\%}$: -1.37, -.09).

Regarding the analysis of probiotic efficacy across various age categories, four reviews implemented subgroup analyses within their meta-analyses (Amirani et al., 2020; Huang et al., 2016; Lin et al., 2023; Zhu et al., 2022). Two reviews established 40 years as the threshold, creating two age groups (< 40 years and ≥ 40 years): 1) Amirani et al. (2020) included studies involving patients with depression and found statistically significant evidence in both age groups, while 2) Lin et al. (2023)included patients with depressive symptomatology and depression, only finding statistically significant evidence in the ≥ 40 years old

Table 3
Summary of Selected Systematic reviews with meta-analysis

Selected systematic review	*Population(s)*[a,b]	*Intervention(s)*[c]	*Comparator(s)*	*Instrument used*	*Results of meta-analyses of RCT*
Amirani et al., 2020	Population with moderate to major depression (MDD) (*n* = 180)	Probiotics or Symbiotics (Monotherapy or Therapy in addition to active treatment with pharmacotherapy and/or psychotherapy) Probiotic (genera): Lactobacillus Bifidobacterium Duration: six to 12 weeks	Placebo Active treatment (pharmacological or psychotherapy) Placebo + Active treatment	HAMD BDI	**HAMD:** Overall analysis: meta-analysis of four studies (*n* = 180; Con:90; Int:90) was significant (*WMD*: -9.60; CI_{95}: -10.8, -9.11). I^2 = 99.7% Subgroup analysis by age. Age < 40 years: Meta-analysis of two studies was significant (*WMD*: -1.69; CI_{95}: -2.37, -1.02). I^2 = 81.0% Age ≥ 40 years: meta-analysis of two studies was significant (*WMD*: -18.10; CI_{95}: -18.80, -17.41). I^2 = 98.8% **BDI:** Overall analysis: meta-analysis of three studies (*n* = 154; Con:76; Int:78) was not statistically significant (*WMD*: -11.17; CI_{95}: -24.99, 2.65). I^2 = 99.1%
Desai et al., 2021	Pregnant women and postpartum (perinatal) (*n* = 545)	Probiotics Probiotic (genera): Lactobacillus Bifidobacterium Duration: prenatal: 12-36 weeks; postnatal: up to 24 weeks postpartum	Placebo	EPDS	**EPDS:** Meta-analysis of 2 studies (*n* = 545; Con:263; Int:282) was not significant (*MD*: -.46; CI_{95}: -2.16, 1.25). I^2 = 74.0%
El Dib et al., 2021	Population with depression (with or without other morbidities) (*n* = 375)	Probiotics or Symbiotics (Monotherapy or Therapy in addition to active treatment with pharmacotherapy and/or psychotherapy) Probiotic (genera): Lactobacillus Bifidobacterium Bacillus coagulans Clostridium butyricum Enterococcus faecalis Duration: three to 24 weeks	Placebo Active treatment (pharmacological or psychotherapy) Placebo + Active treatment	BDI DASS-Depression MADRS	**BDI:** Meta-analysis of three studies (*n* = 156; Con:127; Int:129) was significant (*MD*: -3.20; CI_{95}: -5.91, -.49). I^2 = 21% **DASS**: Meta-analysis of two studies (*n* = 221; Con:110; Int:111) was not significant (*MD*: 2.01; CI_{95}: -.80, 4.82). I^2 = 0% **MADRS:** Meta-analysis of two studies (*n* = 119; Con:59; Int:60) was not significant (*MD*: -2.41, CI_{95}: -10.55, 5.72). I^2 = 87%

Table 3
Summary of Selected Systematic reviews with meta-analysis (continued)

Selected systematic review	*Population(s)*[a,b]	*Intervention(s)*[c]	*Comparator(s)*	*Instrument used*	*Results of meta-analyses of RCT*
Goh et al., 2019	Healthy population (*n* = 1,035) Population with various clinical diagnoses (T2D, IBS, CVD, fibromyalgia). (*n* = 722) Population with MDD (*n* = 144)	Probiotics or Symbiotics (Monotherapy or Therapy in addition to active treatment with pharmacotherapy and/or psychotherapy) Probiotics (genera): Lactobacillus Bifidobacterium S. thermophilus Conventional Yogurt Duration: four to 24 weeks	Placebo Active treatment (pharmacological or psychotherapy) Placebo + Active treatment	Diverse scales assessing depressive symptoms	**Various scales of depressive symptoms:** *Overall analysis:* meta-analysis of 24 studies (*n* = 1,901; Con:871; Int:1,030) was significant (*SMD*: -.31; CI_{95}: -.56, -.07). I^2 = 82% *Subgroup analysis by type of population* MDD: Meta-analysis of three studies (*n* = 144; Con:76, Int:68) was significant (*SMD*: -.75; CI_{95}: -1.09, -.41). I^2 = 0% Population with other clinical diagnoses: Meta-analysis of seven studies (*n* = 722, Con:357, Int:365) was not significant (*SMD*: -.26; CI_{95}: -.70, .17). I^2 = 84% Healthy population: Meta-analysis of 14 studies (*n* = 1,035; Con:438; Int:597) was not significant (*SMD*: -.25; CI_{95}: -.60, .11). I^2 = 82% *Subgroup analysis by type of intervention:* Only one strain: Meta-analysis of 11 studies (*n* = 1,070; Con:469; Int:601) was not significant (*SMD*: -.01; CI_{95}: -.30, .27). I^2 = 71% Multiple strains: Meta-analysis of 13 studies (*n* = 831; Con:402; Int:429) was significant (*SMD*: -.57; CI_{95}: -.96, -.18). I^2 = 85%
Halemani et al., 2023	Pregnant women before delivery (prenatal) (*n* = 298) Women after delivery (postnatal) (*n* = 518)	Probiotics (genera): Lactobacillus Bifidobacterium S. thermophilus	Placebo	Diverse scales assessing depressive symptoms	**Various scales of depressive symptoms:** *Overall analysis:* meta-analysis of four studies (*n* = 816; Con:414; Int:402) was not significant (*SMD*: -.10; CI_{95}: -.29, .09). I^2 = 43% *Subgroup analysis by perinatal period* Prenatal: Meta-analysis of two studies (*n* = 298; Con:155, Int:143) not significant (*SMD*: -.05; CI_{95}: -.24, .35). I^2 = 40% Postnatal: Meta-analysis of two studies (*n* = 518, Con:259, Int:259) was significant (*SMD*: -.22; CI_{95}: -.40, -.05). I^2 = 0%
Hofmeister et al., 2021	Population with no depression (*n* = 3,417) Population suffering from depression (*n* = 817)	Probiotics Prebiotics Symbiotics Paraprobiotics Fecal microbiota transplant (Monotherapy or therapy in addition to active treatment with pharmacotherapy and/or psychotherapy) Probiotics (genera): Lactobacillus, Bifidobacterium, Bacillus, Clostridium, Lactococcus, Streptococcus, Weisella Duration: four - 52 weeks	Placebo	Diverse scales assessing depressive symptoms	**Various scales of depressive symptoms:** *Probiotics in people without depression:* meta-analysis of 35 studies (*n* = 2,988; Con:1,569; Int: 1419) was significant (*SMD*: .31; CI_{95}: .15, .46). I^2 = 74.4% *Probiotics in people with depression:* Meta-analysis of nine studies (*n* = 544; Con:271; Int:273) was significant (*SMD*: .78; CI_{95}: .19, 1.37). I^2 = 89.9% *Prebiotics in people without depression:* Meta-analysis of two studies (*n* = 184; Con:92; Int:92) was not significant (*SMD*: .13; CI_{95}: -.23, .48). I^2 = .0% *Prebiotics in people with depression:* Meta-analysis of three studies (*n* = 122; Con:68; Int:54) was significant (*SMD*: .39; CI_{95}: .04, .73). I^2 = 26.6% *Symbiotics in people without depression:* Meta-analysis of six studies (*n* = 307; Con:156; Int:151) was significant (*SMD*: .68; CI_{95}: .36, 1.00). I^2 = 44.0% *Symbiotics in people with depression*: One study (*n* = 40; Con:20; Int:20) was **not** significant (*SMD*: .63; CI_{95}: 00, 1.27). *Paraprobiotics:* One study was not significant. *Fecal transplant in people without depression*: One study (*n* = 49; Con:23; Int:26) **not** significant (*SMD*: -.16; CI_{95}: -.72, .40)

Table 3
Summary of Selected Systematic reviews with meta-analysis (continued)

Selected systematic review	*Population(s)*[a,b]	*Intervention(s)*[c]	*Comparator(s)*	*Instrument used*	*Results of meta-analyses of RCT*
Huang et al., 2016	Healthy population (*n* = 325) Population with MDD (*n* = 40)	Probiotics or Symbiotics (Monotherapy or Therapy in addition to active treatment with pharmacotherapy and/or psychotherapy) Probiotic (genera): Lactobacillus Bifidobacterium Lactococcus S thermophilus,	Placebo Active treatment (pharmacological or psychotherapy) Placebo + Active treatment Placebo	Diverse scales assessing depressive symptoms	**Various scales of depressive symptoms:** *Overall analysis*: meta-analysis of five studies (*n* = 365, Con: 182, Int: 183) was significant (*SMD*: -.30; CI_{95}: -.51, -.09). I^2 = 0% *Subgroup analysis by age group:* Under 60: Meta-analysis of four studies (*n* = 180) was significant (*SMD*: -.43; CI_{95}: -.72, -.13). I^2 = 0% Over 65: 1 study (*n* = 185) was not significant (*SMD*: -.18; CI_{95}: -.47, .11). I^2 = Not applicable *Subgroup analysis by health level:* Healthy: *meta*-analysis of four studies (*n* = 325) was significant (*SMD*: -.25; CI_{95}: -.47, -.03). I^2 = 0% MDD: 1 study (*n* = 40) was significant (*SMD*: -.73; CI_{95}: -1.37, -.09). I^2 = Not applicable
Le Morvan de Sequeira et al., 2022	No diagnosis of depression (healthy or with other morbidities such as T2D, insomnia, fibromyalgia, obesity, stress) ("Healthy"). (*n* = 830) Population with diagnosed depressive disorder (*n* = 262)	Probiotics or Symbiotics (Monotherapy or Therapy in addition to active treatment with pharmacotherapy and/or psychotherapy) Probiotic (genera): Lactobacillus Bifidobacterium Duration: four-24 weeks	Placebo Active treatment (pharmacological or psychotherapy) Placebo + Active treatment	Various scales assessing depressive symptoms	**Various scales of depressive symptoms:** Overall analysis: meta-analysis of 15 studies (*n* = 1,092; Con:541; Int:551) was significant (*SMD*: -.37; CI_{95}: -.55, -.20). I^2 = 48% *Subgroup analysis by treatment duration* 4-8 weeks: Meta-analysis of nine studies (*n* = 475) was significant (*SMD*: -.40; CI_{95}: -.64, -.16). I^2 = 39% 9-24 weeks: Meta-analysis of six studies (*n* = 617) was significant (*SMD*: -.34; CI_{95}: -.61, -.07). I^2 = 59% *Subgroup analysis by type of intervention* Single Strain: Meta-analysis of seven studies (*n* = 653) was significant (*SMD*: -.32; CI_{95}: -.61, -.03). I^2 = 66% Multi-strain: Meta-analysis of eight studies (*n* = 439) was significant (*SMD*: -.43; CI_{95}: -.62, -.23). I^2 = 4% *Subgroup analysis by type of population* No diagnosis of depression, healthy or with other morbidities ("Healthy"): Meta-analysis of eleven studies (*n* = 830) was significant (*SMD*: -.30; CI_{95}: -.51, -.09). I^2 = 51% Population with diagnosed depressive disorder: Meta-analysis of four studies (*n* = 262) was significant (*SMD*: -.58; CI_{95}: -.82, -.33). I^2 = 0% *Subgroup analysis by depression scale* BDI: Meta-analysis of 11 studies (*n* = 649) was significant (*SMD*: -.41; CI_{95}: -.59, -.23). I^2 = 25% HADS-D: Meta-analysis of three studies (*n* = 364) was not significant (*SMD*: -.19; CI_{95}: -.57, .19). I^2 = 58% HAM-D: Meta-analysis of three studies (*n* = 206) was not significant (*SMD*: -.30; CI_{95}: -.74, .14). I^2 = 60%

Table 3
Summary of Selected Systematic reviews with meta-analysis (continued)

Selected systematic review	*Population(s)*[a,b]	*Intervention(s)*[c]	*Comparator(s)*	*Instrument used*	*Results of meta-analyses of RCT*
Lin et al., 2023	Population with depression (basic psychiatric symptoms) (*n* = 364) Population with depressive symptoms related to other diseases (MS, T2D/CVD, fibromyalgia, PCOS, MI). (*n* = 412)	Probiotics (monotherapy) Probiotics (genera): Bacillus Lactobacillus Bifidobacterium Lactococcus Streptococcus termophilus C. butyricum	Placebo	IBC / BDI-II DASS-21	**BDI:** *Overall analysis:* Meta-analysis of 13 studies (*n* = 776; Con:379, Int: 397) was significant (*MD*: -1.98; CI_{95}: -3.14, -.82). I^2 = 76% *Subgroup analysis by age* Age < 40 years: Meta-analysis of 6 studies (*n* = 402) was not significant (*MD*: -.40; CI_{95}: -1.52, .71). I^2 = 30% Age ≥ 40 years: Meta-analysis of 7 studies (*n* = 374) was significant (*MD*: -2.80; CI_{95}: -4.17, -1.43). I^2 = 59% *Subgroup analysis by treatment duration* ≤ 8 weeks: Meta-analysis of 6 studies (*n* = 376) was significant (*MD*: -3.28; CI_{95}: -5.55, -1.00). I^2 = 57% > 8 weeks: Meta-analysis of 7 studies (*n* = 400) was significant (*MD*: -1.20; CI_{95}: -2.35, -.05). I^2 = 74% *Subgroup analysis by type of population* Depression (basic psychiatric symptoms): Meta-analysis of 5 studies (*n* = 364) was not significant (*MD*: -1.66; CI_{95}: -3.33, .02). I^2 = 0% Depressive symptoms related to other illnesses: Meta-analysis of 8 studies (*n* = 412) was significant (*MD*: -2.00; CI_{95}: -3.41, -.59). I^2 = 85%
Liu et al., 2019	Population suffering from depression	Prebiotics, Probiotics or Symbiotics (Monotherapy or Therapy in addition to active treatment with pharmacotherapy and/or psychotherapy). Probiotic (genera) Bifidobacterium Bacillus Duration: eight days to 45 weeks	Placebo Active treatment (pharmacological or psychotherapy) Placebo + Active treatment	Diverse scales assessing depressive symptoms	**Various scales of depressive symptoms:** *Prebiotics - Overall analysis* Meta-analysis of five studies was not significant (*SMD*: -.08; CI_{95}: -.30, .51). I^2 = Not reported *Probiotics - Overall analysis* Meta-analysis of 25 studies was significant (*SMD*: -.24; CI_{95}: -.36, -.12). I^2 = 48.2%
Nikolova et al., 2021	Population with moderate to major depression (MDD) (*n* = 404)	Probiotic or Symbiotic (Monotherapy or Therapy in addition to active treatment with pharmacotherapy and/or psychotherapy). Probiotic (genera): Lactobacillus Bifidobacterium C. butyricum Duration: 8 weeks	Placebo Active treatment	Diverse scales assessing depressive symptoms	**Various scales of depressive symptoms:** *Overall analysis*: meta-analysis of 7 studies (*n* = 404; Con:202, Int: 202) was significant (*SMD*: .58; CI_{95}: .19, .97). I^2 = 73 % *Subgroup analysis by type of intervention:* Add-on therapy to pharmacotherapy: Meta-analysis of 5 studies (*n* = 254) was significant (*SMD*: .83; CI_{95}: .49, 1.17). I^2 = 40 % Monotherapy**:** Meta-analysis of 2 studies (*n* = 150) was not significant (*SMD*: -.02; CI_{95}: -.34, .30). I^2 = 0 %

Table 3
Summary of Selected Systematic reviews with meta-analysis (continued)

Selected systematic review	*Population(s)*[a,b]	*Intervention(s)*[c]	*Comparator(s)*	*Instrument used*	*Results of meta-analyses of RCT*
Zagórska et al., 2020	Healthy population Population suffering from depression	Probiotic or Symbiotic (Monotherapy or Therapy in addition to active treatment with pharmacotherapy and/or psychotherapy). Probiotic (genera): Lactobacilus Bifidobacterium	Placebo Active treatment (pharmacological or psychotherapy) Placebo + Active treatment	Diverse scales assessing depressive symptoms	**Various scales of depressive symptoms:** *Overall analysis:* meta-analysis of 16 studies was significant (*SMD*: -.35; CI_{95}: -.59, -.12). I^2 = 79 % *Subgroup analysis by health level:* Healthy: Meta-analysis of 11 studies was not significant (*SMD*: -.16; CI_{95}: -.34, .02). I^2 = 56 % Depressed: Meta-analysis of five studies was significant (*SMD*: -.87; CI_{95}: -1.66, -.09). I^2 = 90 %
Zhu et al., 2022	Population without depression (with or without other morbidities) (*n* = 804) Population suffering from depression (*n* = 541)	Probiotic or Symbiotic (Monotherapy or Therapy in addition to active treatment with pharmacotherapy and/or psychotherapy). Probiotic (genera): Lactobacilus Bifidobacterium Weisella cibaria	Placebo Active treatment (pharmacological or psychotherapy) Placebo + Active treatment	Diverse scales assessing depressive symptoms	**Various scales of depressive symptoms:** *Overall analysis*: meta-analysis of 19 studies (*n* = 1,345) was significant (*SMD*:0.19; CI_{95}: .01, .37). I^2 = 59.67 % *Subgroup analysis by health level:* Without depression (healthy or other morbidities): meta-analysis of nine studies (*n* = 804) was not significant (*SMD*: -.10; CI_{95}: -.23, .02). I^2 = 0 % With depression: Meta-analysis of 10 studies (*n* = 541) was significant (*SMD*: .46; CI_{95}: .22, .70). I^2 = 47.33 % *Subgroup analysis by age* Age < 60 years: Meta-analysis of 12 studies (*n* = 827) was significant (*SMD*: .36; CI_{95}: .14, .58). I^2 = 57.51 % Age ≥ 60 years: Meta-analysis of seven studies (*n* = 518) was not significant (*SMD*: -.13; CI_{95}: -.31, .04). I^2 = 0 % *Subgroup analysis by duration of treatment (Tx).* < 8 weeks: Meta-analysis of nine studies (*n* = 519) was significant (*SMD*: .30; CI_{95}: .12, .47). I^2 = 27.62 % < 8 weeks: Meta-analysis of 10 studies (*n* = 826) was not significant (*SMD*: .08; CI_{95}: -.20, .35). I^2 = 67.65 % *Subgroup analysis by type of treatment (Tx).* Single-strain: Meta-analysis of 10 studies (*n* = 671) not significant (*SMD*: .18; CI_{95}: -.19, .55). I^2 = 78.79 % Multi-strain: Meta-analysis of nine studies (*n* = 674) was significant (*SMD*: .17; CI_{95}: .01, .32). I^2 = 0 %

Notes:
[a]Population included in meta-analyses evaluating the efficacy of probiotics (or prebiotics, symbiotics, etc.) in the management of depression
[b]Disease/diagnosis acronyms: MDD: major depressive disorder; IBS: irritable bowel syndrome; IBS: irritable bowel syndrome; T2D: Type 2 diabetes; CVD: cardiovascular disease; MS: multiple sclerosis; PCOS: polycystic ovary syndrome; MI: myocardial infarction
[c]The active treatment with pharmacotherapy by the participants included various pharmacological groups
[d]Treatment with probiotics could use one or more species and strains
acronyms of psychometric scales to assess depressive symptomatology: BDI: Beck Depression Inventory; HAM-D Hamilton Depression Scale; MADRS: Montgomery-Asberg Depression Rating Scale; DASS: Depression, Anxiety and Stress Scale. Other psychometric scales to assess depressive symptoms that were used in the selected systematic reviews are: HADS: Hospital Anxiety and Depression Scale; SDS: Self-rating Depression Scale, EPDS: Edinburgh Postnatal Depression Scale, among others
[e]Meta-analyses reported evaluating the efficacy of probiotics (or prebiotics, symbiotics, etc.) in the management of depression
[f]Acronyms of aspects to describe results: RCT: Randomized Controlled Trials; *MD*: mean difference; *WMD*: weighted mean difference; *SMD*: standardized mean difference; Con: participants in control group; Int: participants in intervention group; CI_{95}: confidence interval (95%)

age group. The remaining two reviews (Huang et al., 2016 and Zhu et al., 2022) established 60 years as the threshold, creating two age groups (< 60 years and ≥ 60 years). both reviews only found statistically significant evidence in the age group of 60 years old.

Additional subgroup analyses considered factors that could influence probiotic treatment efficacy, including the number of strains in the formulation and treatment duration. Regarding the number of strains, three reviews categorized two treatment types: one strain and two or more strains (multi-strain) (Goh et al., 2019; Le Morvan de Sequeira et al., 2022; Zhu et al., 2022). Statistically significant evidence for one-strain treatment was found in Le Morvan de Sequeira et al., 2022, while all three reviews reported statistically significant evidence for multi-strain treatment.

Three reviews analyzed treatment duration (Le Morvan de Sequeira et al., 2022; Lin et al., 2023; Zhu et al., 2022) and established an eight-week threshold, creating two groups with different durations (< 8 weeks and ≥ 8 weeks). while each review found statistically significant evidence for the < 8-week duration group, only two reported statistically significant evidence for the ≥ 8-week duration group (Le Morvan de Sequeira et al., 2022; Lin et al., 2023).

Two reviews evaluated probiotic efficiency in pregnant women with perinatal depressive symptomatology or depression (Desai et al., 2021; Halemani et al., 2023). Desai et al. (2021)collectively evaluated probiotic efficacy in perinatal depression (prenatal and postnatal), with no statistically significant differences being found from the comparison group. However, Halemani et al. (2023) found no statistically significant evidence in a subgroup analysis of two prenatal studies although they did find statistically significant evidence in two postnatal studies (n = 518, *SMD*: -.22; $CI_{95\%}$: -.40, -.05).

Efficacy of Prebiotics

Prebiotic efficacy was assessed in two reviews (Hofmeister et al., 2021; Liu et al., 2019). Liu's review found no evidence of statistically significant efficacy, whereas Hofmeister found evidence of probiotic efficacy in individuals with depression in a meta-analysis of three studies (n = 122, *SMD*: .39; $CI_{95\%}$: 04, .73).

Efficacy of Symbiotics

The efficacy of symbiotics has only formally been evaluated by Hofmeister et al., 2021. This review reported evidence of statistically significant efficacy in individuals without depression through a meta-analysis of six studies (n = 307, *SMD*: .68; $CI_{95\%}$: .36, 1.00).

Efficacy of Paraprobiotics

One systematic review formally evaluated the efficacy of paraprobiotics (Hofmeister et al., 2021). However, the authors only included one study that reported no evidence of statistically significant efficacy.

Risk of Bias and Heterogeneity assessments

Table 4 summarizes information on the population included in the studies of the selected systematic reviews, the number of studies included, the risk of bias assessment, as well as the heterogeneity assessment (I^2) for the reported overall meta-analyses, as well as the actions undertaken to reduce this heterogeneity.

Concerning the risk of bias analysis, the vast majority of reviews (11) reported the results in detail, only two reviews did not (Amirani et al., 2020; Zagórska et al., 2020). The majority (10) of these 11 reviews that did present the details of the analysis reported at least one study that was evaluated as having a "high risk of bias" in one of the evaluation categories. The evaluation category in which the highest frequency of evaluations with "high risk of bias" was usually reported was "Incomplete outcome data" (attrition bias).

In regard to the evaluation of heterogeneity, out of a total of 20 overall meta-analyses reported in the 13 selected systematic reviews, three (15%) overall meta-analyses reported "low" heterogeneity, eight (40%) overall meta-analyses reported "Moderate" heterogeneity, and seven (35%) overall meta-analyses reported "Substantial" heterogeneity. This high frequency of substantial heterogeneity could be because most of the reviews included studies with populations of different groups (with a variety of age categories and health conditions such as healthy, diagnosed with chronic diseases and varying levels of depression). They also included different treatment modalities (prebiotic, probiotic or symbiotic, of various durations, single-strain/multi-strain, monotherapy/add-on therapy). Most reviews performed subgroup analyses that may have decreased the overall heterogeneity, as shown in the I^2 reported for subgroup meta-analyses (Table 3). In addition, some studies performed sensitivity analyses to exclude studies that could affect heterogeneity or had a risk of bias issues.

DISCUSSION AND CONCLUSION

The present meta-review offers a comprehensive overview of systematic reviews investigating the efficacy of probiotics, prebiotics, and symbiotics to improve depressive symptoms across diverse depression levels and age groups. It is the first meta-review to synthesize key findings from recent systematic reviews of this issue.

Table 4
Summary of Risk of Bias and Heterogeneity Assessments in Selected Systematic Reviews

Systematic review	*Population for each overall meta-analysis*[a]	*n*[b]	*RoB tool*[c]	*Notes regarding RoB assessment*[d]	*n*[e]	*Overall heterogeneity (I^2)*	*Heterogeneity classification*[f]	*Actions taken to reduce heterogeneity*
Amirani et al., 2020	Depression/HAMD Depression/BDI	7	Cochrane (for RCT)	Does not report the results of the risk of bias assessment	4 3	99.7 % 99.1 %	Substantial Substantial	No subgroup meta-analysis was reported No sensitivity analysis was reported
Desai et al., 2021	Pregnant women	2	Cochrane (for RCT)	One study (50%) was reported having one high risk of bias classified as "Other bias"	2	74.0 %	Moderate	A small number of studies were included to perform a subgroup meta-analysis No sensitivity analysis was reported
El Dib et al., 2021	Depression/BDI Depression/DASS-D Depression/MADRS	5	Cochrane (for RCT)	Three studies (60 %) had at least one "definitely high risk" in the "Incomplete outcome data"	3 2 2	21 % 0 % 87 %	Small Small Substantial	Nor subgroup meta-analysis was reported A sensitivity analysis was reported
Goh et al., 2019	Healthy/CC/ Depression	24	Cochrane (for RCT)	Six studies (32%) were reported as having one high risk of bias classified as "Other bias"	24	82 %	Substantial	Subgroups analysis by clinical condition (healthy, major depressive disorder, and other clinical diagnosis) A sensitivity analysis was reported
Halemani et al., 2023	Pregnant women	4	Cochrane (for RCT)	One study (33 %) was reported with a high risk of bias ("Selection of the reported result")	4	43 %	Moderate	Subgroups analysis by clinical condition (prenatal or postnatal) No sensitivity analysis was reported
Hofmeister et al., 2021	No depression/ Probiotics Depression/ Probiotics No depression/ Prebiotics Depression/ Prebiotics No depression / Symbiotics Depression/ Symbiotics	56	Cochrane (for RCT)	24 studies (~43 %) were classified as High risk in the Overall risk of bias assessment. The most frequent category in them was "Bias from missing outcome data"	35 9 2 3 6 1	74.4 % 89.9 % 0.0 % 26.6 % 44.0 % --	Substantial Substantial Small Moderate Moderate	It does not perform subgroup analysis A sensitivity analysis was performed
Huang et al., 2016	Healthy/Depression	5	Cochrane (for RCT)	No study had a high risk of bias evaluation in the different categories.	5	0 %	Small	Subgroups analysis by age group (under 60, over 65 years), and health status (with/without depression) A sensitivity analysis was reported
Le Morvan et al., 2022	Healthy/Depression	15	Cochrane (for RCT)	Six studies (46%) had one high risk of bias (four studies in "Deviations from the intended interventions" and two studies in "Missing outcome data")	15	48 %	Moderate	Subgroups analysis by treatment duration (4-8 weeks and 9-24 weeks), type of treatment (single strain or multi-strain), type of population (with/ without depression), and depression scale (BDI, HADS-D, HAM-D) No sensitivity analysis was reported

Table 4
Summary of Risk of Bias and Heterogeneity Assessments in Selected Systematic Reviews (continued)

Systematic review	*Population for each overall meta-analysis*[a]	*n*[b]	*RoB tool*[c]	*Notes regarding RoB assessment*[d]	*n*[e]	*Overall heterogeneity (I^2)*	*Heterogeneity classification*[f]	*Actions taken to reduce heterogeneity*
Lin et al., 2023	Depression / DS	13	Cochrane (for RCT)	Two studies (15 %) had one high risk of bias ("Incomplete outcome data" and "selective reporting study, each)	13	76 %	Substantial	Subgroup analysis by age (< 40, ≥ 40), treatment duration (≤ 8 and > 8 weeks), and population (with/without depression). A sensitivity analysis was reported
Liu et al., 2019	Depression/ Prebiotics Depression/ Probiotics	30	Cochrane (for RCT)	40 % of studies were reported as having one high risk of bias ("Incomplete outcome data")	5 25	(Not reported) 42.8 %	--- Moderate	It does not report subgroup analysis Reports a sensitivity analysis, excluding studies with different designs (using symbiotics, or different types of probiotics)
Nikolova et al., 2021	Depression	7	SIGN	Only one study (14 %) was reported with an overall assessment classified as high risk of bias	7	73 %	Moderate	Subgroups analysis by type of intervention (monotherapy or Add-on therapy) No sensitivity analysis was reported
Zagórska et al., 2020	Healthy/Depression	16	Jadad scale	Does not report the results of the risk of bias assessment in detail	16	79 %	Substantial	Subgroup analysis by type of population (healthy or depressed) No sensitivity analysis was reported
Zhu et al., 2022	Healthy/Depression	19	Cochrane (for RCT)	Four studies (27%) were assessed as having at least one high risk of bias ("Incomplete outcome data").	19	59.7 %	Moderate	Subgroup analysis by population (with/without depression), age (< 60, ≥60), treatment duration (< 8 and < 8 weeks), and type of treatment (single strain or multi-strain) A sensitivity analysis was reported

Notes:
[a]The target population in each overall meta-analysis is described. Acronyms for population: CC: chronic conditions; DS: depressive symptoms. Acronyms for subgroups: BDI: Beck Depression Inventory; HAM-D Hamilton Depression Scale; MADRS: Montgomery-Asberg Depression Rating Scale
[b]n = number of studies included in meta-analysis
[c]Tool used to evaluate risk of bias (RoB). Acronyms: SIGN: Scottish Intercollegiate Guidelines Network
[d]Notes regarding the risk of bias assessment for the studies included in meta-analysis
[e]n = number of efficacy comparisons included in each subgroup meta-analysis (this could be different from the number of studies since one study could have more than one group of population, interventions, or outcomes)
fClassification explained in methods section

Thirteen systematic reviews exploring probiotics as an alternative approach to alleviating depressive symptoms were included. Most of these systematic reviews were rated as poor. Some of the factors contributing to this result were the absence of protocol registration, insufficient clarity in reporting the studies excluded and funding sources, and lack of sensitivity analysis concerning the risk of bias.

Main findings

In general terms, the meta-review found evidence confirming the efficacy of prebiotics, probiotics, or symbiotics in addressing depressive symptomatology or diagnosed depression across varying clinical stages. As expected, reviews that included studies involving healthy individuals showed non-statistically significant evidence of treatment efficacy or minimal effect sizes (evaluated as *MD* or *SMD*).

Prebiotics efficacy was only demonstrated in one systematic review, specifically in a meta-analysis for the population with depression, with statistically significant evidence being obtained, except in one meta-analysis for people without depression (Hofmeister et al., 2021). No statistically significant evidence was found in another review for the use of prebiotics (Liu et al., 2019).

Stronger evidence of probiotic efficacy was found in almost all the selected systematic reviews, characterized by statistically significant hypothesis tests in the meta-analyses. However, effect sizes were low: *WMD* = -9.60 (Amirani et al., 2020); *MD* ranging from -3.2 to -1.98 (Desai et al., 2021; El Dib et al., 2021; Lin et al., 2023); and *SMD* ranging from .19 to .78 (Goh et al., 2019; Halemani et al., 2023; Huang et al., 2016; Hofmeister et al., 2021; Le Morvan de Sequeira et al., 2022; Liu et al., 2019; Nikolova et al., 2021; Zagórska et al., 2020; Zhu et al., 2022). These effect sizes may vary depending on factors such as demographic composition (age group, pregnancy), severity of depression (healthy population, those with depressive symptoms, or diagnosed depression), formulation type (single strain or multi-strain), treatment duration, and treatment modality (adjunctive or monotherapy).

Some reviews found greater efficacy of probiotics compared to prebiotics, as evidenced by hypothesis testing and effect sizes (Hofmeister et al., 2021; Liu et al., 2019). For instance, higher effect size for probiotics compared to prebiotics in the population with depression was reported in one review (*SMD* = .31 and .13, respectively) (Hofmeister et al., 2021).

In regard to symbiotics, a review found statistically significant evidence supporting their efficacy, even when implemented in a population without diagnosed depression. This suggests that the combined use of probiotics and prebiotics could yield an additive effect, despite one study conducted in individuals with depression revealing a non-statistically significant difference. However, an analysis of the effect size obtained in the meta-analysis of symbiotics in a healthy population (*SMD* = .68) found that it exceeded those obtained for probiotics or prebiotics (*SMD* = .31 and .13, respectively) (Hofmeister et al., 2021). Moreover, it is worth noting that some meta-analyses conducted for probiotics included studies using symbiotics, as they incorporated prebiotic substances in their formulation.

Significantly, a specific review conducted a subgroup analysis to compare the efficacy of probiotics or symbiotics as monotherapy or as adjunctive therapy to pharmacological treatment. The analysis found a statistically significant effect in the latter group only, with a substantially higher effect size (*SMD* = .83 and -.02, respectively), although the monotherapy subgroup comprised only two studies (Nikolova et al., 2021).

Moreover, the efficacy of probiotics or symbiotics in the treatment of depression appears to be greater when formulations include multiple species, as noted in two systematic reviews (Goh et al., 2019; Le Morvan de Sequeira et al., 2022; Zhu et al., 2022). Additionally, optimal efficacy may be achieved within the initial eight weeks of treatment, although a favorable impact could persist beyond this timeframe (Le Morvan de Sequeira et al., 2022; Lin et al., 2023). Only one review contradicted this pattern, but it included studies involving a healthy population, potentially resulting in less visible effects of adjunctive therapy with probiotics or symbiotics (Zhu et al., 2022).

Moreover, systematic reviews revealed that the efficacy of probiotics or symbiotics in treating depression could be more pronounced in subjects over 40, as demonstrated by subgroup analyses within meta-analyses exclusively involving a population with depressive symptomatology or depression (Amirani et al., 2020; Lin et al., 2023). It is striking that other meta-analyses presenting a contrasting result included a population without depressive symptomatology or diagnosed depression, potentially making the impact of probiotic or symbiotic use less obvious (Huang et al., 2016; Zhu et al., 2022).

It should be noted that none of the selected reviews conducted subgroup analyses for children and adolescents, indicating limited evidence regarding the efficacy of these interventions in these age groups. In addition, subgroup analyses for older adults were only undertaken in two reviews, although depression assessment scales specific to this age group were not used (Huang et al., 2016; Zhu et al., 2022).

Another significant observation is that some reviews conducted special meta-analyses or subgroup analyses for certain specific depression assessment scales, obtaining similar results. Reviews using the Beck Depression Inventory (BDI) scores yield statistically significant evidence (El Dib et al., 2021; Le Morvan de Sequeira et al., 2022; Lin et al., 2023), except for one review that enrolled patients diagnosed with major depressive disorders, although the effect size was large (assessed using *WMD*) (Amirani et al., 2020).Conversely, a review using the Hamilton Depression Scale (HAMD) obtained statistically significant findings involving studies with a population exhibiting moderate to major depression (Amirani et al., 2020), while another review using this scale and comprising a population without a diagnosis of depression failed to yield statistically significant results (Le Morvan de Sequeira et al., 2022). However, as mentioned earlier, this could be because in this group of individuals, it might be more difficult to identify improvements in depressive symptoms.

Other psychometric depression scales, such as the Depression, Anxiety and Stress Scale (DASS), Montgomery-Asberg Depression Rating Scale (MADRS), and Hospital Anxiety and Depression Scale (HADS-D), underwent meta-analyses or specific subgroup analyses, yielding no statistically significant results (El Dib et al., 2021; Le Mor-

van de Sequeira et al., 2022). This underscores the potential variability in the performance of different scales in assessing depressive symptomatology, meaning that it would be important to analyze their documented history of validity and reliability.

Implications for Clinical Practice and Research

In terms of clinical practice, it is worth considering recommending an alternative use of probiotics or symbiotics as adjuvant or complementary approaches to conventional pharmacological treatments to relieve depressive symptomatology. This could have numerous implications for health systems, such as the incorporation of these treatments into formularies and clinical practice guidelines for managing depression. Additionally, proactive interventions for their implementation should be initiated to enhance prescription and utilization.

Research opportunities identified through this review include the following: 1) investigating the efficacy of probiotics, prebiotics, and symbiotics in specific age groups with limited evidence, such as children, adolescents, and older adults, which could require special psychometric instruments to assess depressive symptomatology in these groups; 2) exploring the efficacy of these interventions over a prolonged period of time(beyond six months); 3) conducting meta-analyses of efficacy for particular probiotic species or particular probiotic species combinations; 4) establishing and evaluating treatment protocols to determine optimal doses, types, and durations of probiotic, prebiotic, and symbiotic consumption; 5) assessing the safety profiles and potential adverse reactions associated with short- and long-term consumption; and 6) studying the efficacy of these treatments in preventing depression, especially in populations prone to this disease (with the exception of pregnant women).

Strengths and limitations

Several strengths were identified in the present meta-review: 1) A systematic search was conducted across diverse databases; 2) Numerous systematic reviews on the topic of interest were found in the literature, leading to a meta-review approach; 3) Only systematic reviews with meta-analysis were included, ensuring that conclusions are based on the quantitative synthesis of at least two studies; 4) An evaluation of the quality of the reviews included in the meta-review was undertaken.

However, certain limitations were acknowledged within this meta-review. The research question was limited to Patient Reported Outcomes (PROs) as outcomes. However, other potential results, such as biochemical markers and the frequency of adverse events, could be explored.

Conclusions

In this meta-review, after the synthesis of several published meta-analyses, it was found that probiotic or symbiotic consumption tends to improve depressive symptoms, as borne out by comparing results with depression assessment scales. However, there are certain limitations on available evidence, especially for particular age groups (such as children, adolescents, and older adults), as well as specific efficacy analyses for particular species and combinations, among other research opportunities discussed earlier.

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Conflict of interest

The authors declare they have no conflict of interest.

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