



Psychobiotic fermented foods for depression: Current evidence and future directions

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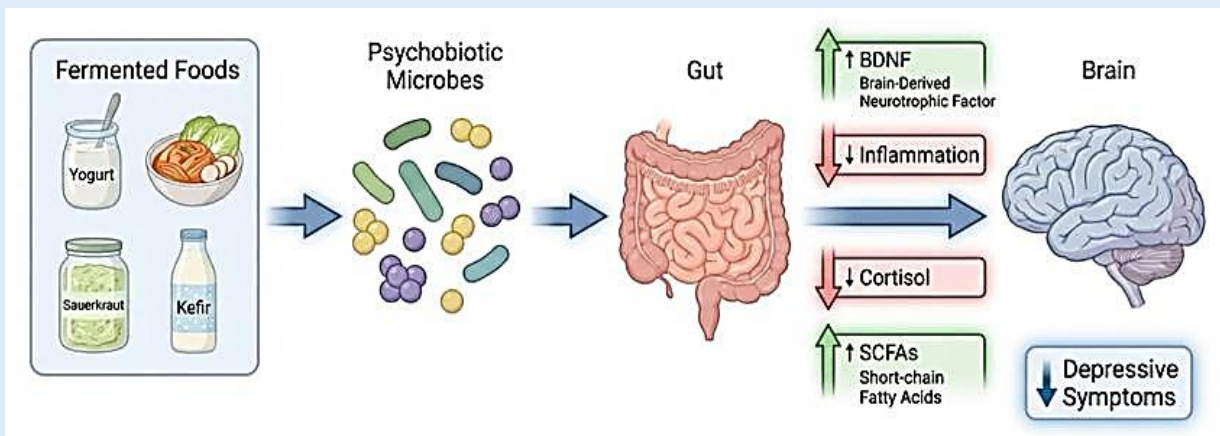
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ABSTRACT

Major depressive disorder (MDD) remains a leading cause of disability worldwide, constrained by incomplete response and side effects in conventional pharmacotherapy. Emerging evidence implicates the microbiota–gut–brain axis in mood regulation, positioning dietary psychobiotics as promising complementary interventions. This mini review synthesizes mechanistic pathways linking psychobiotic activity to neurobiological targets (HPA axis modulation, neurotransmitter synthesis, reduced neuroinflammation, and BDNF enhancement) and evaluates preclinical and clinical data on fermented foods in depressive disorders. Unlike isolated probiotic supplements, fermented foods provide diverse live microbial communities within protective matrices rich in prebiotics and bioactive metabolites, potentially enhancing viability, adherence, and clinical effect sizes.

Novelty: This review prioritizes traditional fermented foods over supplements as psychobiotic delivery systems, integrating nutritional psychiatry with food science frameworks, and aligning with functional food development models, thereby offering a conceptual bridge from ancient dietary practices to evidence-based depression management.

Keywords: Depression, Psychobiotics, Fermented Foods, Microbiota–Gut–Brain Axis, Functional Foods, BDNF.



Graphical Abstract: Proposed gut–brain axis mechanism by which psychobiotic fermented foods may alleviate depressive symptoms.

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INTRODUCTION

Major depressive disorder (MDD) is one of the most common and disabling health conditions worldwide. Beyond the personal toll, it carries major economic costs through healthcare spending and reduced productivity, and it can deeply disrupt daily functioning and quality of life [1-2]. Although antidepressants help many people, they also have clear disadvantages: delayed onset, side effects that result in poor tolerability, and ineffectiveness for about one-third of patients who try the treatment [3-4]. Consequently, there is increasing interest in interventions targeting biological systems involved earlier in the pathway of mood regulation. One system drawing significant attention is the microbiota–gut–brain axis—a two-way communication network connecting the gut and the brain through neural signaling, hormones, immune activity, and microbial metabolites [5–7]. A consistent finding across studies indicates that individuals diagnosed with depression often exhibit differences in gut microbiota composition; crucially, these microbial shifts appear to influence mood and stress regulation, rather than serving as a biomarker of

the disorder alone [8–10].

Within this area, “psychobiotics” refers to live microorganisms that, when taken in adequate amounts, can support mental health by influencing gut microbes and interacting with the body’s neurobiology [11-12]. Most research has focused on probiotic capsules, but fermented foods may be a natural alternative and practical option. They can deliver diverse microbial strains along with fermentation-delivered metabolites and prebiotic compounds that support the proliferation and gastrointestinal survival of beneficial microbes [13–15]. Large observational studies also increasingly report that people with higher consumptions of fermented foods tend to report fewer depressive symptoms and less psychological distress across different populations [16–18].

This mini review consolidates the key mechanisms proposed to explain psychobiotic effects in depression, evaluates the strength of evidence from animal studies and human trials, and considers fermented foods as accessible, culturally sustainable ways to deliver psychobiotics within functional food science.

MECHANISTIC EVIDENCE: MICROBIOTA–GUT–BRAIN AXIS IN DEPRESSION

Bidirectional Communication Pathways: The microbiota–gut–brain axis enables continuous communication through interconnected neural, endocrine, immune, and metabolic routes [5-6,19]. Neural signaling primarily involves afferent vagus nerve pathways transmitting microbial-derived signals from the gut to the brain. Endocrine communication centers on modulation of the hypothalamic–pituitary–adrenal (HPA) axis and regulation of cortisol secretion [20-21]. Immune pathways involve cytokine signaling, including interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and interleukin-1 β (IL-1 β), as well as changes in blood–brain barrier permeability [22-23]. Metabolic communication includes microbial production of short-chain fatty acids, neurotransmitter precursors, and indole metabolites that circulate systemically and influence neurophysiology [24–26]. Psychological stress originating in the brain can reciprocally alter gut permeability and microbial composition, creating self-reinforcing feedback loops relevant to depression pathophysiology [27-28].

Gut Dysbiosis in Depression: Clinical studies consistently report reduced alpha diversity, depletion of beneficial genera such as *Lactobacillus* and *Bifidobacterium*, and enrichment of pro-inflammatory taxa, including Enterobacteriaceae, in individuals with depression [8-9, 29-30]. These alterations correlate with reduced short-chain fatty acids (SCFA) production, increased intestinal permeability, lipopolysaccharide (LPS) translocation, and elevated systemic inflammation—processes closely associated with depressive symptom severity [23,27,31].

The causal relationship between gut microbiota dysbiosis and depression is supported by fecal microbiota transplantation experiments in rodents, in which transfer of microbiota from depressed donors induces depression-like behaviors in recipient animals [32-33].

Key Neurobiological Mechanisms: Psychobiotics exert antidepressant-like effects through multiple convergent mechanisms. HPA axis dysregulation, commonly observed in depression, is modulated by specific psychobiotic strains, thereby restoring cortisol homeostasis and stress resilience [20,34]. Preclinical studies highlight the efficacy of *Lactobacillus rhamnosus* JB-1 and *Bifidobacterium longum* in modulating stress responses [35-36].

Psychobiotics also influence neurotransmission by synthesizing or modulating the availability of γ -aminobutyric acid (GABA), serotonin, dopamine, and norepinephrine via tryptophan metabolism [24,37-38]. Additionally, these microorganisms reduce neuroinflammation by strengthening intestinal barrier integrity, decreasing LPS translocation, and lowering oxidative stress markers [22,31,39]. Elevation of brain-derived neurotrophic factor (BDNF), a key mediator of neurogenesis and synaptic plasticity, has been observed following administration of psychobiotic combinations such as *L. helveticus* R0052 and *B. longum* R0175 [36-40]. Metabolically, SCFAs support blood–brain barrier integrity and microglial function, while indole derivatives activate aryl hydrocarbon receptors involved in neuroimmune regulation [24–26]. Table 1 summarizes the primary mechanistic pathways through which psychobiotics influence depression-related neurobiology, indicating the level of supporting evidence for each.

Table 1. Summary of mechanistic pathways linking psychobiotics to depression

Pathway	Key Mediators	Evidence Level
Neural	Vagus nerve	Preclinical strong
Endocrine	HPA axis, cortisol	Preclinical/human
Immune	Cytokines (IL-6, TNF-α), LPS	Preclinical/human
Neurotransmitter	GABA, serotonin, dopamine	Preclinical/human
Neurotrophic	BDNF, neurogenesis	Preclinical/human
Metabolic	SCFAs, tryptophan/indole metabolites	Preclinical strong

CLINICAL EVIDENCE: Human Studies

Human Clinical Trials: Recent meta-analyses and systematic reviews published after 2020, including updated network and umbrella syntheses through 2025, confirm modest to substantial antidepressant effects of psychobiotics, with standardized mean differences ranging from ~0.3 to 1.76 across depressive symptom scales [9,24,28-29,46-47]. Interventions remain generally

well-tolerated, though the majority continue to evaluate isolated probiotic supplements rather than whole fermented food matrices. Table 2 presents representative human clinical studies of psychobiotics and fermented foods, highlighting study types, populations, interventions, durations, and depression-related outcomes.

Table 2. Human clinical studies (representative regimens) relevant to depression outcomes

Study type	Population	Product	Dose	Duration	Outcomes	Effect
RCTs in clinical depression	Adults with MDD	Psychobiotic strains	Typically 10 ⁹ –10 ¹⁰ CFU/day	4–12 weeks	BDI, HAMD, MADRS	Mixed; some trials show symptom reduction; others show no placebo separation
Stress/healthy cohorts	Healthy adults under stress	Fermented milk / probiotic	Typically 10 ⁸ –10 ¹⁰ CFU/day	6–8 weeks	Mood/stress scales, cortisol	Often improves stress-related outcomes; not always depression-specific
Fermented food-focused trials	Adults (varies)	Whole fermented foods	Serving-based dosing; CFU often not fully standardized	4–9 weeks	Mood scales + GI symptoms	Limited but encouraging; standardization remains a key gap
Systematic reviews/meta-analyses	Multiple populations	Probiotic/psychobiotic	Dose window commonly reported: 10–10 ¹⁰ CFU/day	4–12 weeks	Depression symptom scales	Overall small-to-moderate benefit; heterogeneity by strain and baseline severity

Randomized controlled trials in clinical depression demonstrate reduced symptom severity (e.g., Beck Depression Inventory, Hamilton Depression Rating Scale) and increased BDNF with multi-strain formulations or specific combinations, such as *L. helveticus* R0052 + *B. longum* R0175; typical regimens involve 10⁸–10¹⁰ CFU/day for 4–12 weeks [22,31-32]. Benefits extend to anxiety comorbidity and treatment-resistant cases

[22,32]. In healthy or stressed populations, psychobiotics lower perceived stress and enhance mood/resilience [15-19].

Fermented food-specific evidence, though limited, encourages consumption of fermented milk containing *Lactobacillus paracasei* Shirota, which may alleviate depressive symptoms and constipation in patients [22]; higher fermented food intake associates with reduced

distress in pregnant women and stressed students [8,19]; cohort data link fermented dairy to lower depression risk [2,10].

EPIDEMIOLOGICAL EVIDENCE (FFC STEP 16)

Limitation: Epidemiological studies support the feasibility of Step-16 but cannot establish causality due to confounders, including overall diet quality,

socioeconomic factors, and health behaviors. These findings should be used to prioritize hypotheses for Step-10 trials and Step-17 real-world monitoring. Table 3 outlines key epidemiological and population-level studies associating fermented food intake with depression risk or symptoms, noting the direction of findings and their relevance to functional food development.

Table 3. Epidemiological and population-level studies relating fermented food intake to depression risk

Study type	Exposure	Outcome	Key finding (direction)	Step-16 relevance
Meta-analysis / pooled cohorts	Fermented dairy intake (e.g., yogurt)	Depression risk/symptoms	Overall association tends to be protective (lower risk with higher intake)	Supports real-world association; not causal
Prospective cohort(s)	Fermented vs non-fermented dairy	Incident depression/symptom scores	Fermented dairy intake tracks with lower depressive symptom burden in some analyses	Long-term exposure-outcome signal
Cross-sectional dietary studies	Fermented foods (varies by region)	Depression/anxiety symptom scales	Associations vary by dietary pattern, baseline health, and confounding	Highlights the need for controlled trials

Preclinical Evidence: In rodent models of chronic stress, forced swim, or learned helplessness, psychobiotic administration reduces depression- and anxiety-like behaviors, while inducing biological changes in depression-relevant pathways [15,20,23,26-27]. Reported effects include normalization of HPA-axis activity and stress hormones, increased hippocampal BDNF and serotonergic signaling, reduced neuroinflammation and oxidative stress, and improvements in gut barrier and neurometabolic markers [15,26-27]. Importantly, these outcomes are strain-dependent, with mechanistic specificity reported for vagus-mediated signaling (e.g., GABA receptor modulation following *Lactobacillus rhamnosus* JB-1) and robust antidepressant-like effects in select *Bifidobacterium* strains (e.g., *B. breve* CCFM1025), supporting that efficacy cannot be generalized across taxa or product types [23,26-27].

Preclinical work justifies dose windows and mechanistic biomarker selection for later Step-10 trials by anchoring behavioral endpoints to measurable pathway readouts (immune, endocrine, and metabolite signaling) [24–26]. While not all supportive animal studies are depression-behavior paradigms, mechanistic dietary models offer strengthened translational plausibility when they demonstrate reliable shifts in gut-protective metabolites implicated in neuroimmune regulation. For example, a steamed broccoli sprouts diet intervention in an ulcerative colitis mouse model increased anti-inflammatory and antioxidant metabolite signatures, including sulforaphane- and microbiome-associated metabolite changes (e.g., SCFAs, tryptophan/indoles), illustrating how a food-based strategy can reshape gut-derived bioactive metabolites relevant to gut–brain axis biology, with potential translational relevance to mood disorders through shared inflammatory and metabolic pathways. Table 4

highlights representative preclinical rodent studies demonstrating antidepressant-like effects of specific psychobiotic strains, along with key behavioral and biological outcomes.

Table 4. Representative preclinical studies demonstrating antidepressant-like effects of psychobiotics in rodent models of depression

Reference	Strain/Intervention	Model	Key Behavioral Outcomes	Key Mechanistic/Biological Outcomes	Notes
Bravo et al., 2011 [34]	<i>Lactobacillus rhamnosus JB-1</i>	Naive mice (elevated plus maze, forced swim test, stress-induced hyperthermia)	↓ Anxiety- and depression-like behaviors	↓ Corticosterone response; region-specific changes in GABA receptor expression; effects vagus nerve-dependent (abolished by vagotomy)	Strong evidence for vagal signaling pathway
Bercik et al., 2011 [35]	<i>Bifidobacterium longum</i> NCC3001	Naive mice + <i>Trichuris muris</i> infection model	Anxiolytic effect (step-down test)	Normalization of BDNF; effect vagus nerve-dependent	Highlights vagal mediation
Ait-Belgnaoui et al., 2014 / Messaoudi et al., 2011 (multi-strain, cited via [36-40])	<i>L. helveticus</i> R0052 + <i>B. longum</i> R0175	Chronic stress/restraint stress models	↓ Anxiety/depression-like behaviors	↑ Hippocampal BDNF; ↓ HPA axis activity (cortisol/corticosterone)	Frequently studied combination with translational relevance
Tian et al., 2021–2023 (<i>B. breve</i> CCFM1025, cited in text [23,27])	<i>Bifidobacterium breve</i> CCFM1025	Chronic unpredictable mild stress (CUMS) mouse model	Robust ↓ depression-like behaviors (forced swim, tail suspension, sucrose preference)	↑ BDNF, serotonin; ↓ neuroinflammation; improved gut barrier	Strain-specific efficacy highlighted
Kelly et al., 2016 [9] / Zheng et al., 2016 [8]	Fecal microbiota transplantation from depressed humans to microbiota-depleted rats	Germ-free/gut-depleted rodents receiving depressed-patient microbiota	Induced depression-like behaviors (forced swim, anhedonia)	Altered tryptophan metabolism, ↑ inflammation	Demonstrates causality of dysbiosis (reverse direction)
General multi-study synthesis [15,20,23,26-27]	Various <i>Lactobacillus</i> and <i>Bifidobacterium</i> strains	Chronic stress, forced swim, learned helplessness paradigms	Consistent ↓ immobility, ↑ exploration, ↓ anhedonia	HPA axis normalization, ↑ BDNF/serotonergic signaling, ↓ cytokines/oxidative stress, improved gut barrier/SCFA production	Strain-dependent; supports convergent mechanisms
Desbonnet et al., 2010 (cited via [37])	<i>Bifidobacterium infantis</i>	Rat maternal separation model	↓ Depressive-like behavior (forced swim test)	Normalized immune response, noradrenaline, and peripheral IL-6; restored basal norepinephrine	Early-life stress model

Note: ↓, decrease; ↑, increase

Strain Specificity & Individual Variability: Psychobiotic effects remain highly strain-specific; commonly studied candidates include *Lactobacillus rhamnosus*, *L. helveticus*, *L. plantarum*, *L. casei*, and *Bifidobacterium*

longum, *B. breve*, and *B. infantis* [9,18,23,27-28]. Multi-strain formulations may yield additive or synergistic benefits, while response heterogeneity—partly driven by baseline microbiome composition—supports the

rationale for stratified, biomarker-guided approaches during development and clinical translation [9,19].

FERMENTED FOOD APPLICATIONS: NATURAL PSYCHOBOTIC SOURCES

Traditional Fermented Foods and Microbial Profiles:

Dairy-based fermented foods are among the most extensively studied psychobiotic sources. Yogurt and kefir commonly contain *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* species, with kefir particularly containing diverse and stable microbial consortia and metabolite profiles [34,36,40-42]. Fermented milk products developed under controlled conditions, such as probiotic dairy beverages, can deliver standardized doses of well-characterized strains (e.g., *Lactobacillus casei* Shirota), supporting reproducibility and clinical translation [38-40].

Vegetable fermentations, including kimchi and sauerkraut, are dominated by *Lactobacillus plantarum*, *L. brevis*, and *Leuconostoc* species and additionally supply polyphenols, organic acids, and dietary fiber that enhance microbiota–gut–brain signaling [13,44]. Fermented soy products (miso, tempeh, natto) contribute bioactive peptides, isoflavones, and vitamin metabolites generated through microbial biotransformation, expanding their potential neuroimmune relevance [15,44-45]. Kombucha and sourdough further broaden the psychobiotic food repertoire by providing organic acids and fermentation-derived metabolites, including GABA-associated pathways linked to gut–brain communication [24,43-44].

Bioactive Compounds Beyond Live Microbes:

Fermentation enhances the production of GABA, antioxidant peptides, exopolysaccharides, and organic acids with immunomodulatory and neuromodulatory properties [44-45]. In parallel, fermentation improves nutrient bioavailability—including B-vitamins, calcium, iron, and zinc—while microbial biotransformation converts dietary polyphenols into enhanced

bioaccessible and biologically active forms [13,15,45]. These fermentation-derived metabolites act synergistically with live microorganisms to amplify gut–brain signaling and downstream neuroimmune effects [18,41].

Attribution notes: Current human evidence rarely supports a sole bioactive compound in fermented foods as being responsible. Benefits likely arise from combined actions of live microorganisms and fermentation-derived metabolites (e.g., GABA, organic acids, bioactive peptides, exopolysaccharides, and biotransformed polyphenols) acting on inflammation, intestinal barrier function, neurotransmission, and stress-axis regulation. Identifying dominant causal bioactives and dose–response relationships should be prioritized in future work.

Food-Based vs Supplement Delivery: Compared with supplements, fermented foods offer matrix-mediated protection during gastric transit, intrinsic prebiotic substrates that support microbial colonization, nutritional synergy, cultural sustainability, affordability, and superior long-term adherence [14-15,18]. However, challenges related to batch-to-batch variability, strain stability, and product standardization persist, underscoring the need to apply controlled functional food development frameworks and validated production criteria to fermented food interventions [13,37].

FUTURE DIRECTIONS AND RESEARCH PRIORITIES

Future research should prioritize personalized psychobiotic strategies informed by baseline microbiome profiling and host biomarkers [45]. Development of standardized, culturally adapted functional fermented foods fortified with validated psychobiotic strains and metabolites represents a promising avenue. Large-scale randomized controlled trials evaluating fermented foods as adjunct or preventive interventions for depression, with integrated mechanistic biomarkers, are urgently

needed [43-44]. Large-scale randomized controlled trials evaluating fermented foods as adjunct or preventive interventions for depression, with integrated mechanistic biomarkers, is imperative—particularly in light of ongoing progress in supplement-focused research [46-47].

POST-MARKET AND AFTER-MARKET EVIDENCE (FFC STEP 17)

Studies on formal post-market (Step 17) effectiveness focused on depressive outcomes for psychobiotic fermented foods are currently limited [14,29]. Most available human evidence consists of short-duration trials and observational dietary associations rather than systematic post-launch outcome monitoring [17,26,29]. Where post-market evidence exists, it is more commonly safety-focused and does not consistently track depression-specific endpoints [14]. Future functional food development should extend beyond Step-10 efficacy trials to include real-world effectiveness monitoring (validated symptom scales, adherence tracking, dietary context, and biomarker panels) and structured adverse-event reporting across diverse populations [14].

NOVELTY AND FUNCTIONAL FOOD PERSPECTIVE

This review uniquely emphasizes whole fermented foods as psychobiotic delivery systems, integrating mechanistic, clinical, and food science evidence within a functional food framework [13-15]. By aligning microbial profiles, bioactive compounds, and validated biomarkers (e.g., BDNF, cytokines, cortisol) with functional food development principles, this work bridges traditional fermentation practices and modern nutritional psychiatry [15,41,45]. The synthesis aligns with key steps of the Functional Food Center's 17-Step Functional Food Product Development Model [14], supporting future development of standardized psychobiotic fermented foods for depression management.

Scientific Innovations and Practical Implications

This review introduces scientific innovation by prioritizing whole fermented foods over isolated probiotic supplements as psychobiotic delivery vehicles, emphasizing their complex microbial consortia, protective food matrices, and fermentation-derived bioactives that may confer superior viability, colonization, and synergistic effects on the microbiota-gut-brain axis. By integrating nutritional psychiatry with functional food science frameworks—particularly the Functional Food Center's 17-step model—this work provides a novel translational pathway from ancient dietary practices to modern, evidence-based depression management.

In practice, fermented foods are accessible, affordable, and culturally sustainable interventions with potential for high long-term adherence, addressing key barriers to conventional pharmacotherapy, such as side effects and non-response. As complementary or preventive strategies, they could broaden mental health support in diverse populations, reduce healthcare burdens, and encourage dietary approaches that align with real-world eating patterns, pending further standardization and large-scale validation.

CONCLUSION

The accumulating mechanistic, preclinical, clinical, and epidemiological evidence positions psychobiotic fermented foods as a promising complementary approach within nutritional psychiatry for supporting mental health, particularly in the management of depressive symptoms. Through bidirectional modulation of the microbiota-gut-brain axis, fermented foods deliver diverse live microbial consortia alongside fermentation-derived bioactives—such as GABA, SCFAs, organic acids, antioxidant peptides, exopolysaccharides, and biotransformed polyphenols—that collectively influence key neurobiological pathways, including vagal neural signaling, hypothalamic-pituitary-adrenal (HPA)

axis regulation, cytokine-mediated neuroinflammation, neurotransmitter synthesis (serotonin, dopamine, GABA), and brain-derived neurotrophic factor (BDNF)-supported neurogenesis and synaptic plasticity [5-6,19,24–26,44-45].

Preclinical studies in rodent models of chronic stress and depression-like behaviors provide strong foundational support, demonstrating consistent strain-specific reductions in immobility, anhedonia, and anxiety-like responses, paralleled by normalization of cortisol/corticosterone levels, enhanced hippocampal BDNF and serotonergic signaling, reduced oxidative stress and pro-inflammatory cytokines, and improved intestinal barrier integrity [15,20,23,26-27]. Human data, supported by recent meta-analyses through 2025, indicate modest to substantial improvements in depressive symptom scales, stress resilience, and select biomarkers, with good tolerability and potential adjunctive or standalone roles in major depressive disorder [28,31,46-47]. Observational cohorts further associate higher intake of fermented dairy and other traditional ferments with lower depression risk and psychological distress across diverse populations [16–18].

This review advances the field by uniquely prioritizing whole traditional fermented foods—such as yogurt, kefir, kimchi, sauerkraut, miso, tempeh, natto, kombucha, and sourdough—as superior natural psychobiotic delivery systems compared to isolated probiotic supplements. Unlike capsule-based interventions, fermented foods offer protective food matrices that enhance microbial viability and gastric survival, intrinsic prebiotic fibers for colonization support, synergistic nutritional profiles (e.g., B-vitamins, minerals, bioactive peptides, and polyphenols), and fermentation-generated metabolites that amplify gut–brain signaling [13,15,18,41,45]. This whole-food approach aligns seamlessly with functional food science principles, bridging traditional dietary patterns and

cultural fermentation practices with evidence-based modern strategies for depression management.

From a Functional Food Center perspective, the synthesis presented here integrates microbial profiles, validated biomarkers (BDNF, cortisol, cytokines, SCFAs), and mechanistic pathways within the 17-Step Functional Food Product Development Model [14]. Current evidence establishes reasonable plausibility for early steps (mechanistic rationale, biomarker identification, preclinical anchoring) and supports progression toward standardized product development. However, the field remains supplement-dominated, with fermented food-specific trials limited in scale, standardization, and direct depression endpoints—highlighting persistent gaps in strain-level characterization, viable CFU dosing, metabolite quantification, and matrix-specific synergies.

Scientific innovations of this work include conceptualizing fermented foods as complex, multi-component psychobiotic platforms with potential for superior clinical effect sizes through combined microbial-metabolite actions, while emphasizing strain specificity, individual microbiome variability, and the need for biomarker-guided personalization. In practice, fermented foods offer an accessible, affordable, culturally sustainable intervention with high long-term adherence potential, addressing critical limitations of pharmacotherapy such as delayed onset, side effects, and treatment resistance. As preventive or adjunctive strategies, they could expand mental health support in resource-limited settings, reduce economic burdens from depression-related disability, and promote holistic dietary patterns that integrate seamlessly into real-world eating behaviors.

Nonetheless, rigorous advancement requires addressing methodological challenges through large-scale, well-powered randomized controlled trials focused on characterized fermented food matrices, integrated multi-omics biomarkers, and stratified designs accounting for baseline dysbiosis. Within the Functional

Food Center's framework, priority lies in Step-10 efficacy validation and Step-17 post-market real-world monitoring to confirm sustained effectiveness, safety, adherence, and population-level impacts [14]. Pursuing these structured steps will facilitate the development of evidence-based psychobiotic fermented functional foods, transforming promising gut-brain axis insights into practical, scalable tools for global mental health promotion.

CURRENT LIMITATIONS

Although the body of evidence supporting psychobiotics and fermented foods for depression is growing, several important limitations constrain the strength of conclusions and the translational potential of this research.

First, substantial heterogeneity exists across studies in psychobiotic strains, dosages, intervention durations, outcome measures, and study populations. This variability complicates direct comparisons and limits the robustness of meta-analytic syntheses [41–43, 46–47]. Effect sizes remain modest to moderate in most trials, and results are often inconsistent, particularly when comparing single-strain versus multi-strain formulations or adjunctive versus standalone use.

Second, many clinical trials suffer from small sample sizes, short follow-up periods, and potential publication bias, which reduce generalizability and may overestimate benefits [27–31]. Mechanistic insights in humans are largely indirect, relying on peripheral biomarkers (e.g., cortisol, cytokines, BDNF levels) rather than direct central nervous system measures such as neuroimaging or brain tissue analysis [27–31]. Causality remains difficult to establish definitively in human studies, with much of the mechanistic plausibility derived from preclinical rodent models that may not fully translate to human pathophysiology.

Third, the evidence base remains heavily skewed toward isolated probiotic supplements rather than whole

fermented foods. Despite encouraging observational associations and a small number of fermented milk trials, high-quality randomized controlled trials specifically evaluating traditional fermented foods (e.g., kefir, kimchi, sauerkraut, kombucha) as psychobiotic delivery systems are scarce [13–15, 44–45]. Fermented food research faces unique methodological hurdles, including batch-to-batch microbial variability, challenges in strain-level identification, accurate quantification of viable colony-forming units (CFU) within complex food matrices, and a lack of standardization for serving sizes or metabolite profiles [13,45]. These issues hinder reproducible dosing and reliable comparison across studies.

Fourth, epidemiological data, while supportive of protective associations between fermented food intake and lower depressive symptoms, cannot establish causality due to confounding factors such as overall diet quality, socioeconomic status, lifestyle, and reverse causation [16–18]. Long-term, real-world effectiveness data (post-market monitoring) are virtually absent, limiting understanding of adherence, safety, and sustained benefits in diverse populations [14].

Finally, individual variability in baseline microbiome composition, host genetics, and inflammatory status contributes to heterogeneous treatment responses, underscoring the need for personalized approaches that are not yet feasible in routine clinical or dietary practice [9, 19]. Within the Functional Food Center's 17-step model, current evidence supports the early steps (i.e., mechanistic rationale, biomarkers) but falls short of the rigorous Step-10 efficacy and Step-17 real-world monitoring required for formalized health claims on psychobiotic fermented food products [14].

These limitations highlight the field's preliminary nature and the critical need for larger, longer-term, standardized trials focused on whole fermented foods to bridge the gap between promising mechanisms and evidence-based clinical or dietary recommendations.

Abbreviations: BDI, Beck Depression Inventory; BDNF, brain-derived neurotrophic factor; BBB, blood–brain barrier; CFU, colony-forming units; CNS, central nervous system; FFHD, Functional Foods in Health and Disease; GABA, γ -aminobutyric acid; HDRS, Hamilton Depression Rating Scale; HPA, hypothalamic–pituitary–adrenal; IL, interleukin; LPS, lipopolysaccharide; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; RCT, randomized controlled trial; SCFA, short-chain fatty acid; TNF- α , tumor necrosis factor- α .

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