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Advances in lactic acid bacteria and its fermented milk mitigate depression in mice via the microbiota–gut–brain axis

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ABSTRACT: Depression is a highly prevalent and complex mental disorder with significant therapeutic limitations. This review comprehensively examines how lactic acid bacteria (LAB) and fermented dairy products alleviate depressive symptoms via the microbiota-gut-brain axis (GBA). It further summarizes recent advances in probiotic delivery technologies and outlines future directions for developing effective LAB-based interventions. Acting as psychobiotics, LAB can mitigate depressive-like behaviors in rodent models. Evidence indicates this effect occurs through multiple pathways, including the modulation of tryptophan metabolism, the suppression of neuroinflammation, and the engagement of vagus-nerve-mediated signaling. Specific strains such as *Lactiplantibacillus plantarum* and *Lacticaseibacillus paracasei* have demonstrated pronounced antidepressant effects. This is reflected by elevated levels of serotonin (5-HT) and brain-derived neurotrophic factor (BDNF). These effects are coupled with reductions in inflammatory markers. The synergistic effects of LAB within fermented-milk matrices further enhance functionality through the generation of bioactive metabolites such as γ -aminobutyric acid (GABA), short-chain fatty acids (SCFAs), and peptides. Translating these findings into practice requires overcoming crucial delivery challenges. Advances in microencapsulation and targeted delivery systems are pivotal for protecting LAB viability and ensuring effective colon release. Future integration of AI for modeling gut-flora homeostasis and personalizing delivery platforms holds great promise. In conclusion, this review consolidates the potential of LAB and fermented dairy products as dietary strategies against depression, synthesizes underlying mechanisms, and highlights delivery technologies. Together, these insights provide a foundation for developing next-generation functional foods and precision-nutrition interventions targeting the GBA.

Keywords: Lactic acid bacteria; Fermented milk; Depression; Gut-brain axis; Microencapsulation; Targeted delivery technology

1. Introduction

Depression is a debilitating mental disorder affecting over 300 million people worldwide, constituting a leading cause of disability and a major public-health challenge ^[1]. Although conventional antidepressants

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such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are available, their therapeutic efficacy is limited. Key reasons for this include delayed onset, adverse effects, and high rates of treatment resistance [2-3]. These limitations highlight the pressing need for novel, multi-targeted therapeutic strategies. In recent years, the gut-brain axis (GBA) concept has provided a new perspective for investigating the pathological mechanisms of depression. This bidirectional communication system, facilitated through the vagus nerve, immune signaling, and metabolic pathways, links gut function to brain health [4-5]. The gut microbiota acts as a key regulator of this system. It produces active metabolites including short-chain fatty acids (SCFAs) [6] and tryptophan derivatives such as serotonin precursors [7]. These metabolites subsequently influence blood-brain barrier permeability and neuroinflammation [5]. The pathophysiology of depression is closely linked to gut-microbiota dysbiosis, typically characterized by a decrease in beneficial bacteria, an increase in pro-inflammatory bacteria, and reduced microbial diversity. Numerous studies have shown altered intestinal flora composition in patients with depression or in animal models of the disorder [8-9]. This dysbiosis is typically characterized by a rise in potentially harmful bacteria (e.g., *Proteobacteria* and *Enterobacteriaceae*) a decline in beneficial taxa (e.g., *Lachnospiraceae*, *Oscillospiraceae*, and *Faecalibacterium prausnitzii*). Consequently, modulating the gut microbiota has emerged as a promising therapeutic avenue [10].

Lactic acid bacteria (LAB) are considered ideal candidates for GBA-targeted interventions due to their probiotic functions (e.g., immunomodulation and neurotransmitter precursor production), high safety profile, and diverse sources. Studies indicate that LAB in fermented foods are not only safe but also uniquely capable of synthesizing neuroactive compounds like 5-HT precursors and γ -aminobutyric acid (GABA), which can positively influence host mood and behavior [11-12]. LAB interventions counteract depression-associated dysbiosis through multiple pathways. They restore populations of SCFA-producers (e.g., *Lachnospiraceae*) [13], inhibit harmful bacteria such as *Proteobacteria* [14], and boost beneficial genera like *Lactobacillus* and *Bifidobacterium* [15-16]. Furthermore, LAB can attenuate neuroinflammatory responses and modulate host immunoregulatory processes. Their multi-targeted, multi-pathway effects characterize LAB as potential “psychobiotics” and a viable adjunctive strategy for depression [17-18]. Earlier reviews have outlined probiotics (including LAB) combat depression via pathogen exclusion, anti-inflammatory action, and neurochemical modulation. This positions them as promising adjuvant therapies [19]. The most effective way to harness the health benefits of LAB is to incorporate them into the daily diet. Consuming fermented yogurt is one practical example of this approach. This dietary integration enhances both the viability and the market potential of LAB as natural therapeutic options for depression [20]. However, the stability and functionality of LAB preparations face significant challenges from both processing and physiological stresses. These include adverse conditions during production and storage, as well as the complex environment of the human gastrointestinal tract. This fundamental challenge applies equally whether they are utilized as a dietary supplement or a food ingredient.

To ensure sufficient live bacteria and their metabolites reach the intestinal target and exert intended effects, targeted delivery technologies offer a crucial solution. Microencapsulation creates a physical barrier that shields bacteria from gastric acid and bile salts, significantly improving their survival probability [21-22]. Current materials and techniques include alginate-chitosan composites, montmorillonite-reinforced pectin-alginate matrices, and whey-protein gels. Utilizing mucoadhesive polymers like carboxymethyl chitosan, these delivery systems enhance LAB survival and function. Specifically, they improve acid resistance and bile-salt tolerance, while also promoting adhesion to the intestinal mucosa. This leads to prolonged retention time and higher colonization efficiency. [23]. Additionally, synbiotic co-encapsulation strategies (e.g., incorporating prebiotics like fructooligosaccharides) provide dedicated nutrient sources that support LAB growth and stimulate metabolic activity after release [24].

This review discusses the theoretical basis of GBA-targeted therapy and the efficacy limitations of traditional antidepressants. It thoroughly examines the synergistic network through which LAB reshape intestinal flora, regulate neurotransmitters, repair the intestinal barrier, and inhibit neuroinflammation. Furthermore, it illustrates the synergistic effects of LAB within fermented-milk matrices and evaluates advanced delivery systems designed to overcome gastrointestinal barriers and enhance probiotic efficacy. By systematically elucidating the multiple mechanisms by which LAB and fermented dairy products alleviate depression via the GBA, this review also synthesizes recent progress in targeted delivery technologies and explores future directions for developing LAB-based interventions for depression.

2. The therapeutic dilemma of depression: from monoamine-based drugs to the microbiota-GBA

Depression is a mental disorder characterized by persistent and pervasive low mood, accompanied by diverse clinical manifestations. Patients commonly experience anhedonia, fatigue, changes in appetite and sleep patterns, diminished self-esteem, difficulty concentrating, and various physical discomforts. These symptoms persist for at least two weeks and significantly impair daily functioning and social interactions [25-26]. Major depressive disorder (MDD) arises from the complex interplay of genetic predisposition, environmental stress, and multiple pathophysiological systems. While genetic factors influence individual vulnerability, chronic environmental stress acts as a primary trigger, disrupting brain function through abnormal corticosteroid levels, neuroinflammation, and hypothalamic-pituitary-adrenal (HPA) axis dysregulation [27]. Current evidence-based treatment employs a comprehensive approach combining pharmacotherapy, psychotherapy (e.g., cognitive behavioral therapy), and lifestyle modifications to alleviate symptoms, improve prognosis, and enhance quality of life [28]. Decades ago, the monoamine hypothesis led to the development of drugs such as SSRIs and SNRIs, which remain the mainstay of conventional pharmacotherapy. These agents exert antidepressant effects primarily by increasing synaptic levels of monoamine neurotransmitters, notably 5-HT and norepinephrine [29-30]. However, the pathophysiology of depression extends far beyond the disruption of a single neurotransmitter system. Genetic studies have identified risk loci linked to neuroinflammation and neuroplasticity, while clinical research consistently

confirms persistent low-grade inflammation and HPA-axis dysfunction in patients. This underscoring the disease's essential nature as a multisystem condition ^[31-32].

Although widely used, conventional antidepressants face several notable limitations that constrain their clinical utility. First, their onset of action is delayed, often requiring 4-6 weeks of continuous dosing to achieve full efficacy. This prolongs patient suffering and may extend the window of heightened suicide risk ^[3]. On the other hand, problematic side effects, including weight gain, sexual dysfunction, and cardiovascular problems, remain common and adversely affect patients' quality of life and treatment adherence. ^[33-34]. Most worryingly, more than 30% of patients present with treatment-resistant depression (TRD), which is unresponsive to existing therapies; even among responders, persistent symptoms and partial remission are common. ^[2,35]. These drawbacks highlight the difficulty of addressing depression's complex etiology with approaches that target only the monoamine system. Given these treatments, there is an urgent need to explore interventions acting on novel targets. Although emerging therapies such as the NMDA-receptor antagonist ketamine and anti-inflammatory agents show promise, they are accompanied by challenges, including the risk of addiction, dissociative effects, and uncertain long-term efficacy ^[36]. Consequently, the GBA has attracted considerable attention as a new frontier for research.

Rodent models of depression, summarized in Table 1, are broadly categorized by induction method. Chronic-stress models such as CUMS, CSDS, CMS, which mimic prolonged environmental adversity. Another is inflammatory models (e.g., LPS-induced) that directly trigger neuroinflammation. There are also genetic models like FSL rat, which reflect an inherent vulnerability to depression. Finally, hormone-based models (e.g., CORT administration) work by disrupting the HPA axis. These models collectively reproduce core depressive phenotypes such as anhedonia, behavioral despair, and social withdrawal, providing critical platforms for mechanistic inquiry. For instance, Liu et al. ^[37] demonstrated that *Lactiplantibacillus plantarum* PS128, after intestinal colonization, elevates striatal dopamine (DA) and 5-HT levels and reduces anxiety-like behavior. Bravo et al. ^[11] found that ingestion of certain LAB strains can regulate central GABA-receptor expression and emotional behavior in mice via the vagus nerve. Notably, neurotransmitter synthesis depends heavily on precursor availability, and LAB can profoundly influence tryptophan metabolism ^[38-39]. Specifically, certain *Lactobacillus* strains promote a dual influence on tryptophan metabolism. They promote its conversion into the 5-HT pathway while inhibiting the neurotoxic kynurenine pathway. This inhibition is achieved by either suppressing indoleamine 2,3-dioxygenase (IDO) activity ^[40] or by providing metabolic cofactors ^[41]. Therefore, probiotic modulation of the gut microbiota, especially using multifunctional LAB, is regarded as a promising adjunctive strategy. By concurrently targeting multiple key pathological processes (neuroinflammation, neuroendocrine imbalance and neurotransmitter disorder), this approach may overcome the limitations of traditional monoamine drug treatment and offer a new paradigm for multi-target, systemic treatment of depression ^[42-43].

Table 1. Different mouse depression models.

Model	How to Induce	Depressive Behavioral Manifestations	References
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Abbreviation			
CUMS	Apply 2 stressors randomly daily for 3--8 weeks (lighting cycle changes, cage tilting, damp bedding, food/water deprivation, restraint), avoiding animal adaptation	Anhedonia (core symptom), behavioral despair, reduced exploratory behavior	[117]
LPS-Induced Model	Single intraperitoneal LPS injection (830 µg/kg)	Increased immobility in tail suspension (24 h) and forced swimming tests (24 h), reduced sucrose preference (24--48 h)	[118-119]
CSDS	Screen aggressive CD-1 mice (attack latency < 60 s for 3 consecutive days). Expose C57BL/6J mice to social defeat for 10 days (5--10 min/day). House defeated mice with aggressors behind a perforated board for 24 h post-defeat (continuous psychological stress)	Susceptible mice (~60%--70%) show sustained social avoidance, anhedonia (decreased sucrose preference), weight loss, attenuated circadian rhythm amplitude. Resilient mice (~30%--40%) show no social avoidance, increased anxiety-like behavior, increased corticosterone stress response	[120-121]
CMS	Expose male Sprague-Dawley rats to 4 weeks of unpredictable mild stressors, including constant lighting, cage tilting (40°), paired housing, damp bedding, acute water deprivation followed by an empty water bottle, flashing lights (300 flashes/min), white noise (90 dB) (stressors ordered randomly, cycled weekly)	Anhedonia (significantly reduced sucrose intake and preference)	[122]
FSL	Selective breeding: Over multiple generations, select rat strains sensitive to cholinergic agonists (initially based on DFP sensitivity) to create a genetic depression model. No external induction needed	Excessive immobility in forced swimming test, no basal anhedonia (normal sucrose preference under non-stress conditions), reduced social interaction (indicative of social withdrawal)	[123]
CORT	Add corticosterone to mice drinking water (35 µg/ml/day, ~5 mg/kg/day) for 4 weeks	Reduced time in center of open field, increased novelty suppressed feeding latency, worsened fur condition, reduced grooming behavior	[124]

3. Mechanisms of LAB in alleviating depression via the GBA

LAB are Gram-positive, fermentative bacteria widely recognized as probiotics. Their ability to colonize the gut, withstand gastrointestinal stress, and confer beneficial effects makes them ideal candidates for GBA intervention [44-45]. Figure 1 shows the relationship between gut microbiota and depression. In the healthy state (left), beneficial bacteria (e.g., probiotics) reinforce intestinal tight junctions, facilitating normal gut-brain communication and supporting the synthesis of neurotransmitters like serotonin (5-HT). Under depressive conditions (right), pathogenic bacteria compromise gut barrier integrity, leading to interstitial leakage and the translocation of endotoxins. This results in neuroinflammation, dysregulation of the HPA axis, neurotransmitter disorders (e.g., monoamine imbalance), and ultimately interrupts of gut-brain signaling, driving the pathological cascade of depression. Figure 2 outlines the multi-level mechanisms through which LAB alleviate depression. At the Gut Level, LAB initiate the process by modulating the gut microbiota and strengthening the intestinal barrier. For example, they increase beneficial bacteria and metabolites (e.g., SCFAs, GABA) while upregulating barrier proteins like Occludin. This dual action ultimately reduces endotoxin translocation. These changes are communicated to the brain via key Signaling Pathways, notably through vagus nerve stimulation and the suppression of pro-inflammatory cytokines (e.g., IL-1 β , IL-6, TNF- α). Ultimately, these signals converge at the Brain & Behavior Level, promoting hippocampal neurogenesis, increasing BDNF expression, and rebalancing key neurotransmitters (5-HT/DA). This leads to the amelioration of core depressive-like behaviors, including reduced immobility time and increased sucrose preference.

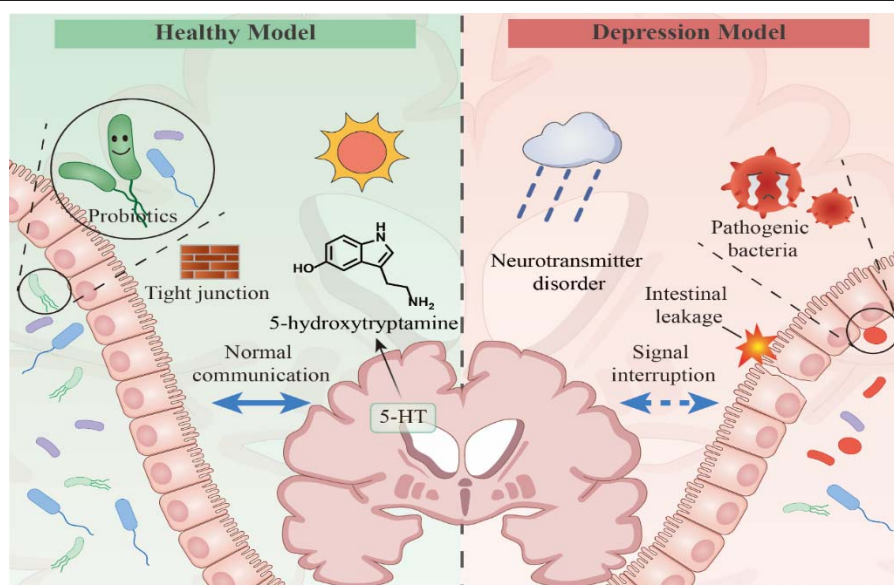


Figure 1 The mechanisms linking gut microbiota and depression. In a healthy model, probiotics maintain tight junctions in the gut, ensuring the normal synthesis of neurotransmitters such as 5-hydroxytryptamine (5-HT) and communication along the gut-brain axis. In the depression model, pathogenic bacteria disrupt the integrity of the gut barrier, causing interstitial leakage and endotoxin entry into the bloodstream, leading to neurotransmitter disorders and gut-brain signal interruption. This ultimately drives the pathological cascade of depression through neuroinflammation, HPA axis dysregulation, and monoamine neurotransmitter imbalance.

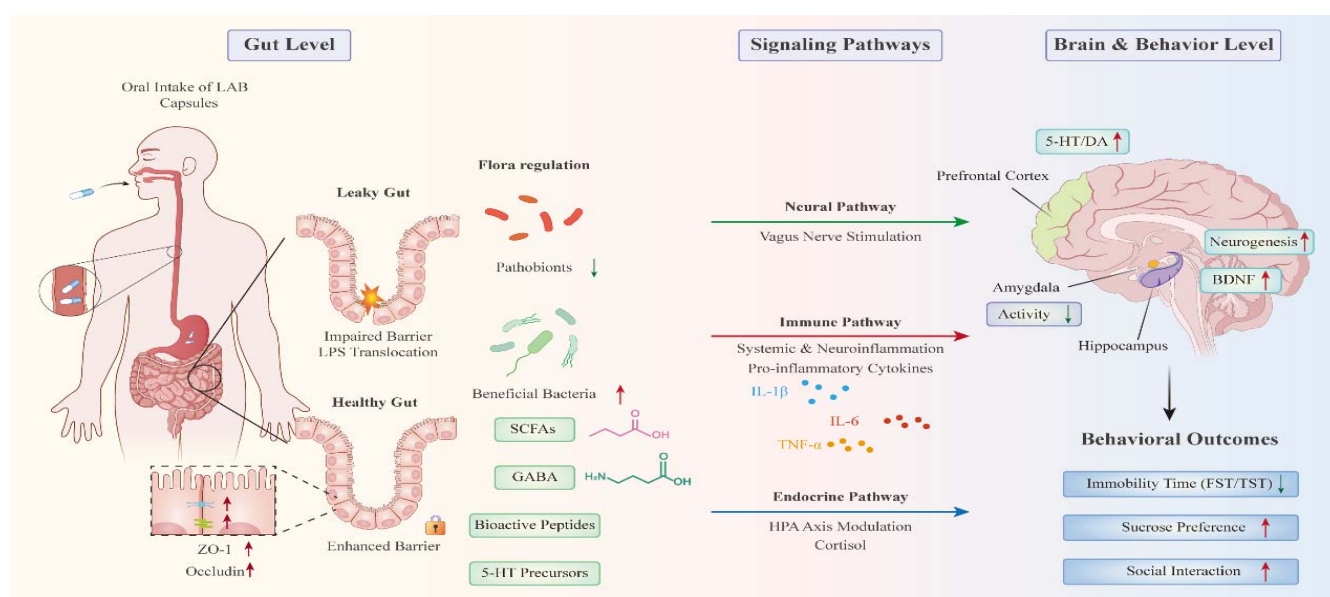


Figure 2 The sequential pathway of LAB-capsules intake alleviating depression via the GBA. This flowchart summarizes key steps starting from oral intake: LAB capsules repair the gut barrier and modulate microbiota balance; the generated signals are transmitted to the brain via neural and immune pathways; ultimately leading to positive outcomes such as improved hippocampal function and restored neurotransmitter balance, manifesting as alleviated depressive behaviors.

3.1 Regulation of gut microbiota composition and function

The antidepressant benefits of LAB, as potent probiotics, are primarily achieved by reshaping the gut microbial environment and restoring eubiosis, a state frequently disrupted in depression [8,46]. Core mechanisms include competitive exclusion and creating an environment that is not conducive to the survival of pathogens. LAB compete with harmful microbes for nutrients and attachment sites of the intestinal epithelium, effectively inhibiting their colonization [47]. Moreover, LAB can lower the pH of the colon by secreting bacteriocins and antibacterial metabolites including lactic acid and acetic acid. This

acidic environment suppresses pathogen growth while favoring beneficial, butyrate-producing bacteria like *Faecalibacterium* and *Bifidobacterium* [48-49]. This modulation of microbial structure also affects the overall metabolic function of the flora. Xu et al. [50] revealed through PICRUST2 functional prediction that the gut microbiota of depressed mice exhibited significant disruptions in key pathways, including purine metabolism and the biosynthesis of tyrosine, tryptophan, D-glutamine, and D-glutamate. Intervention with specific strains like *Lacticaseibacillus paracasei* CCFM1229 and *Lacticaseibacillus rhamnosus* CCFM1228 effectively restored these metabolic processes. For instance, *Lacticaseibacillus rhamnosus* GG regulates the gut flora through specific mechanisms. It secretes metabolites like L-lactic acid and indole lactic acid and promotes co-aggregation with pathogens. Together, these actions create an intestinal environment that is not conducive to the survival of opportunistic pathogens. [51]. This indicates that beyond altering microbial composition, LAB can exert antidepressant effects by regulating the metabolic output of the gut microbiota.

3.2 Modulation of neurotransmitter synthesis and metabolism

In addition to indirect effects from microbiota restructuring SCFAs, certain LAB strains exhibit direct neuroactivity and modulate key neurotransmitters. Bravo et al. [11] demonstrated that ingestion of specific LAB strains could regulate central GABA receptor expression and emotional behavior in mice via the vagus nerve. Similarly, Liu et al. [37] confirmed that intestinal colonization by *Lactiplantibacillus plantarum* PS128 increased DA and 5-HT levels in the striatum and reduced anxiety-like behavior. These monoamine neurotransmitters are essential for regulating mood, motivation, and reward circuits, and their dysfunction constitutes a core pathological feature of depression. The synthesis of neurotransmitter is highly dependent on the supply of precursor substances, and LAB can significantly regulate the tryptophan metabolic pathway [38-39]. Research shows that specific LAB strains can suppress neurotoxic tryptophan pathways. This is achieved either by inhibiting indoleamine 2,3-dioxygenase (IDO) [40] or providing essential metabolic cofactors [41]. A supporting example is *L. plantarum* PS128, which reduces IDO activity [37]. This regulation is critical because kynurenine pathway products such as quinolinic acid are neurotoxic and can induce microglial-mediated neuroinflammation and oxidative stress [53], which are directly involved in the pathological mechanisms of depression [54]. Thus, by optimizing tryptophan metabolic flux, LAB enhance 5-HT bioavailability [55] and reduce neurotoxin accumulation [40], forming a core component of their neuroprotective mechanism.

3.3 Strengthening intestinal barrier and reducing systemic inflammation

The multi-target effects of LAB on the GBA is further demonstrated by their ability to fortify the intestinal barrier and mitigate “leaky gut” phenomena. LAB enhance intestinal barrier integrity and reduce intestinal permeability by stimulating goblet cell mucus secretion and upregulating the expression and function of tight junction proteins (e.g., occludin, claudin, Zonula Occludens-1) [56-57]. This robust barrier function significantly reduces the systemic circulation of pathogen-associated molecular patterns (PAMPs), pro-inflammatory cytokines (e.g., IL-1 β , TNF- α), and microbial metabolites (“danger signals”) [58-60], thereby preventing systemic inflammation and subsequent neuroinflammation. Signals generated by LAB

and their metabolites in the gut can be transmitted directly to the solitary nucleus in the brainstem via vagal afferent fibers, subsequently influencing higher brain regions such as the hypothalamus, amygdala, and prefrontal cortex [61–62]. Studies confirm the critical role of the vagus nerve, as the antidepressant effects of certain LAB disappear after vagus nerve transection [63]. Beyond neural signaling, LAB and their metabolites (especially SCFAs) can stimulate the expression of BDNF both in the gut and the central nervous system [58,61]. Given the common deficits in BDNF and neuronal structure in depression, the LAB-induced enhancement of BDNF serves a critical restorative function. It reverses neural damage and improves plasticity, providing a neurobiological basis for alleviating depressive symptoms [61].

3.4 Multi-target integration and communication via the GBA

The antidepressant potential of LAB stems from integrated signaling connecting the intestinal lumen to the limbic system and cortical networks. Vagal afferents rapidly transmit microbial signals to the hippocampus and amygdala. Experimental vagotomy abolishes the anxiolytic and antidepressant effects of strains like *Lactocaseibacillus rhamnosus* JB-1 [11,64]. LAB-derived SCFAs, particularly butyrate, modulate microglial homeostasis, suppress HPA-axis hyperactivity, and promote a systemic anti-inflammatory state [65]. Butyrate also upregulates hippocampal BDNF expression, thereby promoting neurogenesis and synaptic plasticity. These processes are typically impaired in depression [58,66]. Collectively, these microbial, neural, endocrine, and immune interactions establish LAB as genuine psychobiotics capable of multi-target, systems-level intervention against mood disorders.

This multi-target efficacy arises from a synergistic network of bioactive molecules. SCFAs (particularly butyrate) strengthen the intestinal barrier, exert anti-inflammatory effects, and directly enhance hippocampal BDNF expression and neuroplasticity [65]. Concurrently, certain LAB strains produce GABA, which exerts central inhibitory effects may via vagal signaling [11]. Furthermore, LAB increase 5-HT bioavailability by redirecting host tryptophan metabolism from neurotoxic pathways toward 5-HT production [40]. Elevated 5-HT in turn stimulates BDNF production [57,60], forming a reinforcing circuit that supports neuronal health and mood regulation. Thus, the antidepressant effects of LAB integrate the regulation of SCFAs, GABA, 5-HT, and BDNF into a synergistic mechanism within the GBA framework. Rigorous animal studies have thoroughly validated the multi-target mechanism of LAB. As summarized in Table 2, interventions with various *Lactobacillus* and *Lactococcus* strains consistently ameliorate depressive-like behaviors across different induction models (e.g., chronic stress, LPS). The established mechanisms align with those discussed above and primarily involve several key processes. These include the modulation of gut microbiota composition, the regulation of key neurochemicals (notably elevating brain 5-HT and BDNF while reducing CORT), the strengthening of the intestinal barrier (upregulating tight junction proteins), and the suppression of systemic and neuroinflammation by lowering pro-inflammatory cytokines like IL-1 β and TNF- α and inhibiting TLR4/NF- κ B pathway). This body of evidence solidifies the scientific foundation for LAB as psychobiotics that mitigate depression through multi-faceted communication along the GBA.

Table 2. General overview of experimental studies of *Lactobacillus* strain interventions in mouse models of depression.

Strain name	Model Type (in Mice)	Dosages	Intervention period	Major outcomes	Mechanism of action	References
<i>Lactobacillus paragasseri</i> OLL2809	CSDS	2×10^9 CFU/day	2 week	Increased DCX-positive neuronal progenitors in the hippocampal dentate gyrus.	Modulating gut microbiota by increasing beneficial bacteria and restoring stress - induced gut dysbiosis, it promotes hippocampal neurogenesis, evidenced by DCX - labeled neural progenitor cells and neurite outgrowth, and improves depression - related neuronal plasticity impairment.	[125]
<i>Lactocaseibacillus paracasei</i> CCFM1229 and <i>Lactocaseibacillus rhamnosus</i> CCFM1228	CSDS	5×10^9 CFU/mL (200uL per mouse)	6 week	Decreased CORT. Increased 5-HT and BDNF.	Reduces depression and anxiety-like behaviors by modulating brain xanthine oxidase activity, improving neurotransmitter metabolism (5-HT, BDNF), and alleviating neuroinflammation and gut dysbiosis.	[50]
<i>Lactocaseibacillus casei</i> HY2782 and <i>Bifidobacterium lactis</i> HY8002	RS and FMd	2×10^8 CFU/mouse /day	10 day	Decreased CORT, IL-1 β , IL-6, and NF- κ B. Increased BDNF and 5-HT.	Modulating gut microbiota composition by boosting bacteria positively linked to BDNF expression and curbing those related to IL-1 β expression, reversing stress-induced dysbiosis. This inhibits the NF- κ B inflammatory pathway, upregulates hippocampal BDNF expression, and alleviates depression/anxiety-like behaviors and neuroinflammation.	[126]
<i>Lactiplantibacillus plantarum</i> WLPL04	CRS	1×10^9 CFU/mL	4 week	Reversed the stress-induced reduction in 5-HT, BDNF, and TrkB.	By modulating gut microbiota composition and diversity (reversing stress - induced dysbiosis), maintaining serum 5 - HT levels, and protecting the prefrontal BDNF/TrkB signaling pathway, it improves chronic stress - induced anxiety/depressive - like behaviors and cognitive dysfunction.	[15]
<i>Lactococcus lactis</i> WHH2078	CUMS	1×10^9 CFU/mL ⁻¹	5 week	Decreased CORT. Increased 5-HTP, 5-HT, and BDNF.	Antidepressant effects through modulation of 5-HT metabolism (increased 5-HTP and Tph1 expression) and amelioration of gut dysbiosis (restoration of alpha diversity and abundance of Firmicutes and Bacteroidetes).	[127]
<i>Lactiplantibacillus plantarum</i> CR12	CUMS	1×10^9 CFU/mL ⁻¹	4 week	Decreased IBA-1/NLRP3. Increased 5-HT, SCFAs and Claudin-1/ZO-1.	Gut microbiota modulation increases butyrate production, reducing hippocampal neuroinflammation, repairing the intestinal barrier to suppress systemic inflammation, and modulating the neurotransmitter (5 - HT) and neurotrophic factor (BDNF).	[16]
<i>Lactiplantibacillus plantarum</i> R6-3	CUMS	5×10^9 CFU/mL	8 day	Decreased CORT and MDA. Increased BDNF, 5-HT/DA/NE and IL-10.	Modulating gut microbiota promotes SCFA secretion, increasing short-chain fatty acids like butyric and valeric acids, and conveying signals via the gut-brain axis. It activates neuro pathways by upregulating hippocampal BDNF/TrkB/ERK/CREB signaling (increasing BDNF and p-ERK), inhibits HPA axis hyperactivity to	[13]

					lower serum CORT, and improves oxidative stress by boosting SOD, GSH-PX activity, and T-AOC levels.	
<i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i>	LPS	A dose of 1.2 mg/kg via intraperitoneal injection for 7 days.	1 week	Decreased IL-1 β , TLR4, NLRP3 and Iba-1. Increased DAT, ZO-1 and E-cadherin.	Inhibiting the TLR4 signaling pathway reduces TLR4/NLRP3 inflammasome activity and IL-1 β release, repairs the intestinal barrier by upregulating tight junction proteins (ZO-1, E-cadherin), and modulates the gut-brain axis to alleviate neuroinflammation and restore dopamine system function.	[128]
<i>Lactococcus lactis</i> subsp. <i>cremoris</i> LL95	LPS	1×10^9 CFU/mouse	1 week	Decreased TNF- α , and IL-1 β .	It has anti-inflammatory effects by inhibiting the release of LPS-induced pro-inflammatory factors (TNF- α /IL-1 β) in the hippocampus, exerts antioxidant properties by reducing hippocampal reactive oxygen species (ROS) levels, and modulates gut microbiota by increasing lactobacilli colonization in the intestine, thereby indirectly regulating the gut-brain axis. Repairing the intestinal barrier reduces colonic inflammatory infiltration and protects goblet cells. To inhibit systemic inflammation, it's effective to reduce LPS translocation and pro-inflammatory cytokines. For neurotransmitter regulation, increasing 5-HT synthesis through the tryptophan metabolic pathway is beneficial. To relieve neuroinflammation, we can reduce the activation of glial cells in the hippocampus and prefrontal cortex, and alleviate IFN- γ while enhancing the TGF- β 1 anti-inflammatory pathway.	[129]
<i>Companilactobacillus zhachilii</i> HBUAS52074 ^T	CSDS	10^9 CFU per 0.1 mL per mouse per day in saline	4 week	Decreased CORT, LBP, TNF- α , IFN- γ , and IL-6. Increased 5-HT and IL-10.	Repairing the intestinal barrier reduces colonic inflammatory infiltration and protects goblet cells. To inhibit systemic inflammation, it's effective to reduce LPS translocation and pro-inflammatory cytokines. For neurotransmitter regulation, increasing 5-HT synthesis through the tryptophan metabolic pathway is beneficial. To relieve neuroinflammation, we can reduce the activation of glial cells in the hippocampus and prefrontal cortex, and alleviate IFN- γ while enhancing the TGF- β 1 anti-inflammatory pathway.	[14]
<i>Pediococcus acidilactici</i> CCFM1344	CUMS	1×10^9 CFU/day/mouse	4 week	Decreased TNF- α , IL-1 β , Iba1, and Serum LPS	Lactic acid production restores intestinal lactic acid levels, improves gut microbiota dysbiosis, and repairs the intestinal barrier. This reduces serum LPS, inhibits the TLR4/NF- κ B pathway, suppresses microglial activation (decreasing Iba1), reduces neuroinflammation, and modulates tryptophan metabolites (decreasing 5-HIAA and increasing Ac-Trp-OH).	[130]
<i>Lactiplantibacillus pentosus</i> LPQ1	CUMS	1.0×10^{10} CFU/(kg·body weight)	5 week	Increased 5-HT, 5-HTP, BDNF, p-TrkB/TrkB ratio, p-CREB/CREB ratio	Restore the 5-HTP-5-HT1A-CREB-BDNF-TrkB signaling pathway, increase the abundance of beneficial bacteria, including Unclassified-f-Lachnospiraceae, Lachnospiraceae-NK4A136-group, Eubacterium_xylanophilum_group upregulate the expression of Tph1 in the colon and Tph2 in the hippocampus, and promote 5-HT synthesis.	[131]

Figure 3 illustrates the proposed pathways through which probiotics (e.g., *Lactobacillus*) counter depressive pathologies. In the gut, probiotics exert their effects by competing with pathogens, promoting the production beneficial metabolites (SCFAs, GABA), reducing levels of pro-inflammatory lipopolysaccharide (LPS), and strengthening the intestinal barrier. These effects are achieved by transmitting signals to the brain via circulatory, neural, and immune pathways, thereby reducing systemic inflammation, regulating HPA-axis function, suppressing microglial activation, enhancing BDNF expression, modulating epigenetic mechanisms in the hippocampus, and restoring neurotransmitter balance (5-HT, DA). Collectively, these changes improve neural plasticity, shifting behavior from a depressive-like immobility state toward an active antidepressant-like response. In conclusion, LAB alleviates depression through multifaceted mechanisms involving restoration of gut microbiota, reinforcement of the intestinal barrier, modulation of neurotransmitter systems, and reduction of inflammation. All these effects are mediated via the GBA.

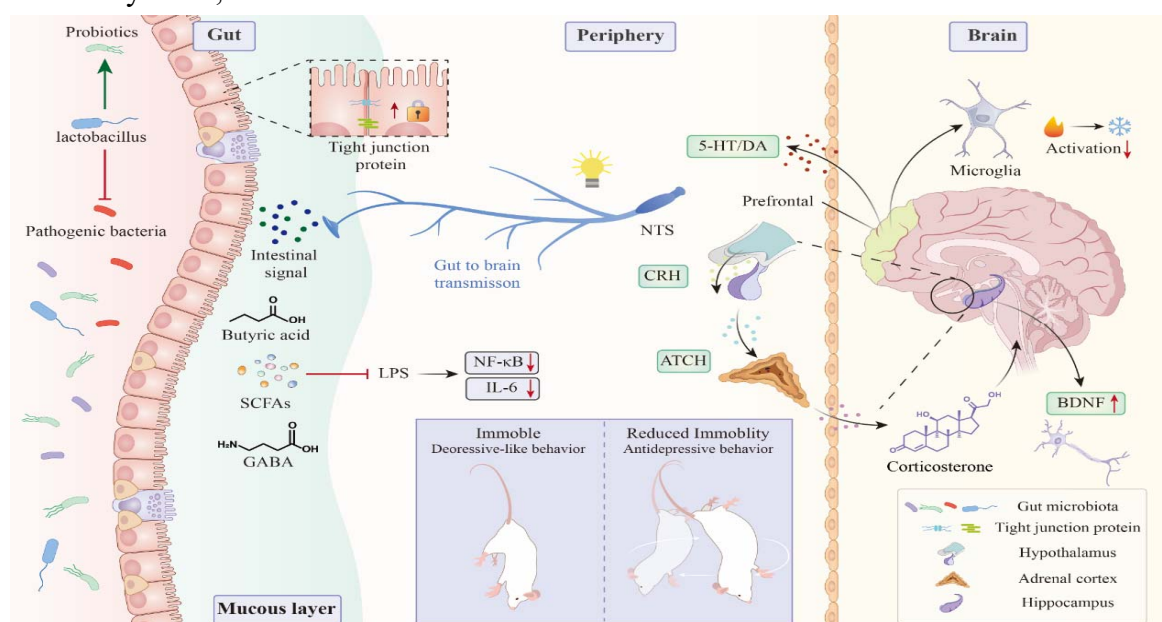


Figure 3 Multifaceted mechanisms of probiotics in alleviating depression via the gut-brain axis. The illustration depicts probiotics suppressing pathogens, producing beneficial metabolites (SCFAs, GABA), and strengthening the gut barrier; these signals are relayed to the brain via immune and neural pathways, regulating the HPA axis, reducing neuroinflammation, promoting neuroplasticity, and ultimately improving depressive behaviors.

4. Synergistic effects of functional fermented dairy products in mitigating depression

While purified LAB supplements show therapeutic promise, their efficacy can be significantly enhanced when delivered within a fermented dairy matrix. In addition to serving as probiotic carriers, functional fermented dairy products also form intricate synergistic systems. That is, live bacteria, fermentation metabolites and milk's inherent bioactive substances work together (usually more effective) to alleviate depressive symptoms by regulating the intestinal flora [18, 67].

4.1 Definition and key components of functional fermented dairy product

Functional fermented dairy products (e.g., specially formulated yogurts and cheeses) are developed from traditional products. They achieve nutritional fortification through the scientific selection and addition of specific probiotic strains with defined health benefits (e.g., *Lactiplantibacillus plantarum* [16]), often

combined with prebiotics and other functional ingredients [68]. These products are designed to exert targeted health effects, including the modulation of emotional health [69]. Figure 4 outlines the fermentation process transforming raw milk into functional foods. Following high-temperature sterilization, LAB ferment the milk substrate. Through metabolic processes such as enzymatic hydrolysis, milk proteins are broken down into bioactive peptides. Concurrently, lactose metabolism produces SCFAs, while the decarboxylation of glutamic acid generates GABA. Consequently, the final product not only contains high concentration of active LAB (e.g., 10^{11} CFU/g) but also integrates these key bioactive compounds, synergistically exerting antidepressant effects via the GBA. These products modulate the GBA through multiple components. The core probiotics and their metabolites, including GABA and SCFAs, contribute to the regulate gut microbiota balance and enhance intestinal barrier integrity [70]. Additionally, bioactive peptides and milk fat globule membrane (MFGM) components produced during fermentation can modulate neuroinflammatory processes [71]. SCFAs, especially butyrate, cross the blood-brain barrier and influence central neurotransmitter metabolism [72]. The milk matrix supports probiotic metabolism and generates products like whey-derived GABA during fermentation, directly contribute to neuromodulation. [73]. Added prebiotics selectively amplify the growth and activity of the co-delivered probiotics [74]. The synergistic interaction among probiotics, metabolites, milk matrix, and prebiotics enables functional fermented dairy products to demonstrate significant potential for alleviating anxiety and depression via the GBA [75-76].

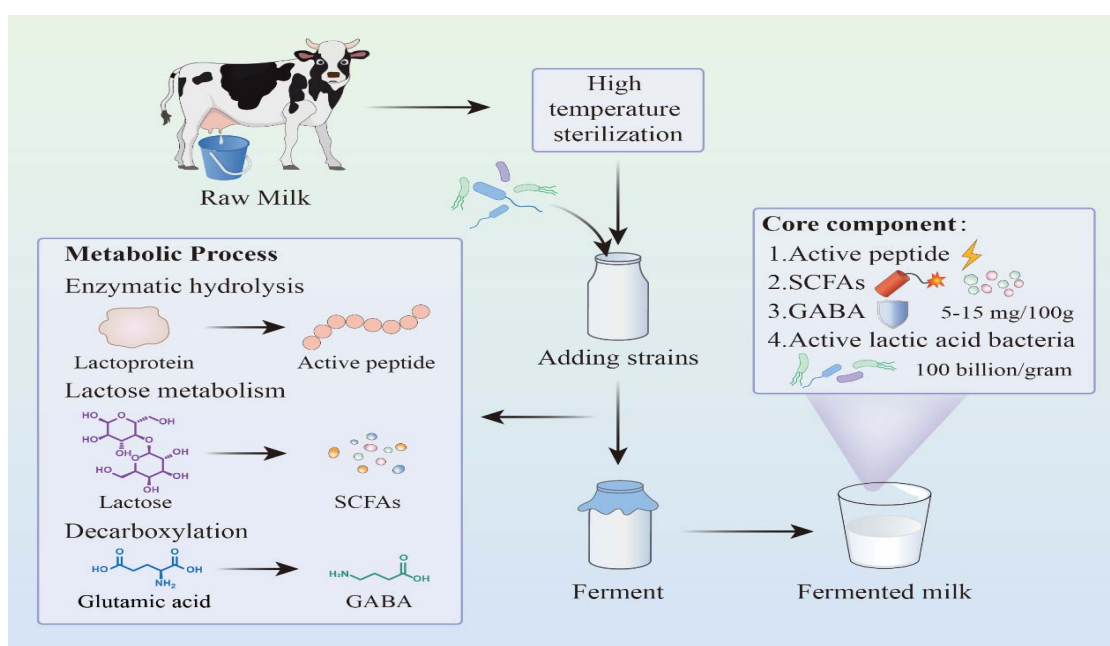


Figure 4 Synthesis of active ingredients in fermented dairy products. The synthesis pathway of active components in fermented dairy products: Raw milk undergoes high-temperature sterilization and then triggers multiple metabolic reactions through the fermentation process-enzymatic hydrolysis generates active peptides, lactose metabolism produces short-chain fatty acids (SCFAs), and decarboxylation converts glutamic acid to γ -aminobutyric acid (GABA). At the same time, active lactic acid bacteria (LAB) (100 billion/g) are enriched. The core components (active peptides, SCFAs, GABA, and probiotics) work together to form the functional basis of fermented milk.

4.2 Mechanisms of action: beyond probiotics to multi-targeted intervention

The antidepressant effects of these products stem from a multi-targeted synergy. By enhancing gut microbiota regulation through the synbiotic effect, the synergistic action of probiotics and prebiotics induces

profound and sustained beneficial shift in microbial composition, thereby increasing the production of SCFAs and other health-promoting metabolites [77]. Beyond ecological changes, fermentation-derived metabolites also act as direct neuroactive signals. GABA interacts with receptors in the gut and central nervous system, while SCFAs like butyrate cross the blood-brain barrier to inhibit histone deacetylase (HDAC), contributing to anti-inflammatory and neuroepigenetic modifications [66, 78]. Furthermore, bioactive peptides and MFGM components strengthen intestinal barrier integrity and reduce systemic inflammation by inhibiting pro-inflammatory pathways such as TLR4/NF- κ B in immune cells [70]. This reduces endotoxin leakage and secondary neuroinflammation. Finally, the synergistic effects of SCFAs, bioactive peptides, and other components effectively regulate neurotransmitter systems and the HPA axis function by increasing BDNF expression and reducing cortisol levels, thereby improving stress responses and maintaining neuronal health [71, 79].

4.3 Supporting evidence from animal and clinical studies

Growing empirical evidence from animal and human studies supports this multi-mechanism framework. Animal research indicates that fermented dairy products containing *Lactiplantibacillus plantarum* PS128 accelerate improvements in depression-like behaviors (e.g., achieving a 42% reduction in immobility time) and promote hippocampal neurogenesis more effectively than probiotic supplements alone [80]. Similarly, studies confirm that kefir peptides exhibit antidepressant-like activity in mice via the BDNF/TrkB pathway [81]. Although animal models provide reliable mechanistic insights, evidence from human depression clinical trials is essential for translation. In a 6-week trial, *Bifidobacterium longum* NCC3001 supplementation significantly lowered depression scores in irritable bowel syndrome patients, an effect correlated with changes in brain activity in emotional regions [82]. Another study found that a multi-strain fermented milk product modulated functional connectivity in emotion-related brain networks of healthy women [76]. These findings imply that specific probiotics and fermented products have the potential to modulate mood. However, clinical outcomes are strain-specific and exhibit considerable inter-individual variability, underscoring the need for larger, personalized trials to translate promising results into reliable dietary interventions [83]. Notably, the effects vary depending on the specific strain and food matrix. Traditional kefir milk drinks often outperform conventional yogurt due to their unique microbial communities and broader spectrum of metabolites [83]. In summary, functional fermented dairy products constitute a potent dietary intervention strategy for depression. Their benefits stem from the synergistic action of probiotics, prebiotics, and bioactive metabolites. This combination achieves more potent and comprehensive regulation of the GBA than supplementation with probiotic alone.

5. Microencapsulation Technology for Enhanced Oral Delivery of Probiotics

The efficacy of LAB as oral psychobiotics in alleviating depression fundamentally depends on a sufficient quantity of viable, functional cells reaching and colonizing the intestinal tract to exert their beneficial effects via the GBA [65]. However, the process of ingestion to colonization is beset with physiological and technological challenges substantially limiting the translation of promising *in vitro* and

animal findings into practical and viable depression therapies. As shown in Figure 5, microencapsulation technology protects probiotics via a specialized wall matrix, enabling targeted intestinal release to ensure sufficient viable bacteria colonize the gut. This system enables site-specific release within the intestinal environment (pH ~ 7), overcoming the gastric barrier (pH ~ 2). Consequently, it successfully achieves microbial colonization, regulates the gut microbiota, and increases production of key metabolites (SCFAs, GABA), which support gut-brain communication. Therefore, advanced delivery technologies, particularly microencapsulation, have evolved from auxiliary process into critical enabler for LAB-based depression management. Microencapsulation provides comprehensive protection and enables controlled release. This ensures that a therapeutic dose of LAB survives transit through the gastrointestinal tract. This delivery of therapeutic doses enables effective GBA modulation. Ultimately, it bridges the gap between the promising mechanisms of LAB and their practical clinical application in depression therapy.

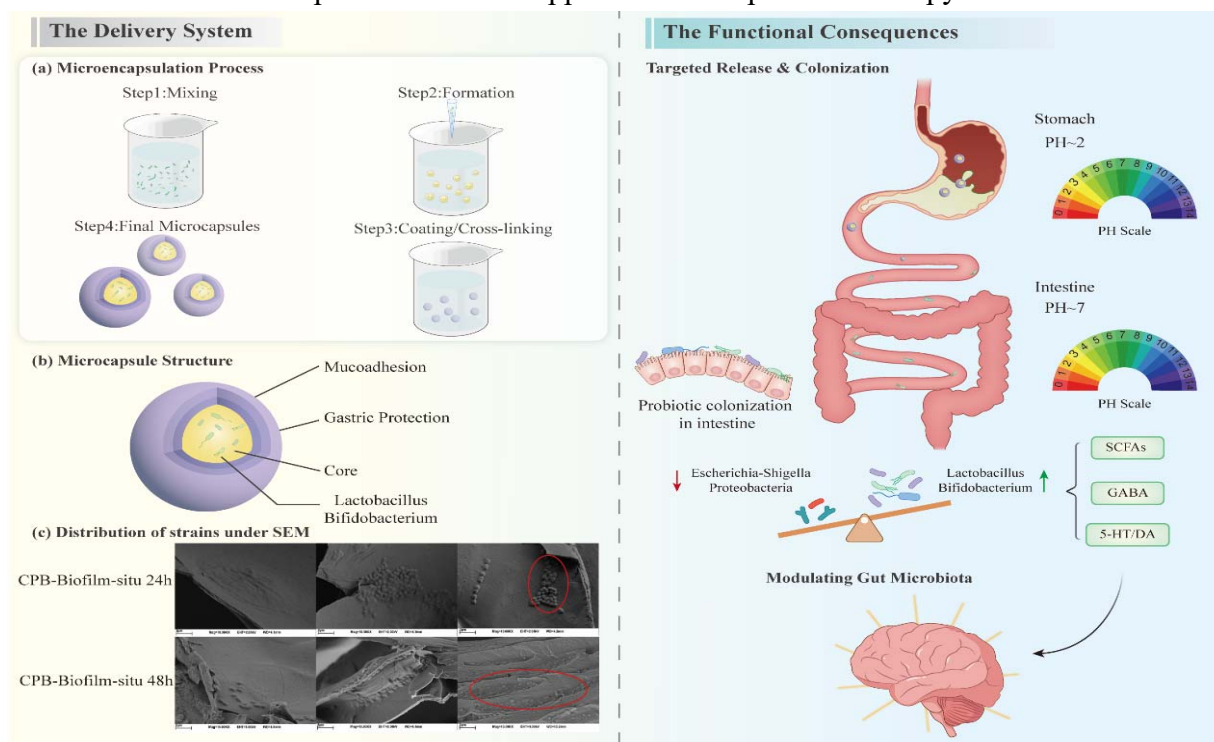


Figure 5 Microencapsulation of probiotics for targeted colon delivery and its functional outcomes. (a) Schematic of the microencapsulation process; (b) Diagram of the microcapsule's protective structure; (c) Scanning electron microscopy (SEM) images showing the distribution of bacterial strains within the microcapsule matrix after 24h and 48h of *in-situ* biofilm culture (Liu et al., 2023) ^[135].

5.1 Formidable Challenges to Oral LAB Delivery in the Context of GBA-Targeted Therapy

Oral LAB must sequentially overcome multiple barriers within the framework of the gastrointestinal barrier to exert their antidepressant effects. The highly acidic gastric environment (pH ~ 2.0) can inactivate over 80% of unprotected bacteria within hours, severely damaging the original strains before they reach the intestinal site of action ^[84-85]. Surviving cells then face bile salts in the small intestine, potent biological detergents that disrupt bacterial membranes ^[86]. Beyond these biochemical barriers, LAB face intense competition from the resident gut microbiota and rapid intestinal transit. These factors typically reduce colonization efficiency to less than 5% of ingested probiotics ^[87-88]. Furthermore, industrial processing

techniques such as spray-drying and prolonged storage contribute to substantial viability loss, with monthly loss rates often approaching 1 log CFU/g [89–90]. These combined barriers significantly diminish the effective dose of LAB reaching target site, directly undermining their core antidepressant functions [91]. Overcoming these challenges is not merely a technical concern but a prerequisite for achieving consistent, dose-dependent psychological probiotic outcomes.

5.2 Microcapsule Wall Material Systems: Functional Design for GBA Modulation

The strategic selection of encapsulating materials is paramount, as their properties directly determine the system's ability to protect LAB and facilitate their targeted release in the gut, ultimately influencing GBA communication [92–93]. Polysaccharides like sodium alginate offer mild, biocompatible gelation but limited acid resistance. This limitation is often overcome by forming polyelectrolyte complexes with chitosan. The resulting coat enhances acid resistance and provides mucoadhesive properties that prolong intestinal residence time, thereby promoting colonization, a prerequisite for sustained GBA modulation [94–96]. Fucoidan can be chemically modified (e.g., carboxymethylation, sulfation) to enhance its solubility and stability, and it readily forms complexes with other biopolymers such as chitosan or proteins, enabling the design of nanoparticles, hydrogels, and emulsions that exhibit tailored release profiles and enhanced protective capabilities for bioactive compounds [97]. The synbiotic encapsulation strategy is perhaps the most relevant for enhancing psychobiotic function, as it co-embeds probiotics with prebiotics (e.g., GOS, FOS) within the same matrix. As illustrated in Figure 6B, the composite material of *Salvia macrosiphon* mucilage (SMM) and sodium alginate significantly improved the outer layer encapsulation efficiency (EE%) and the thickness of the microbeads [98]. This approach protects the probiotic and delivers a nutrient source upon release. This stimulates LAB metabolism, increasing *in situ* production of antidepressant metabolites (e.g., SCFAs, GABA) to amplify the intended signaling along the GBA [23, 98].

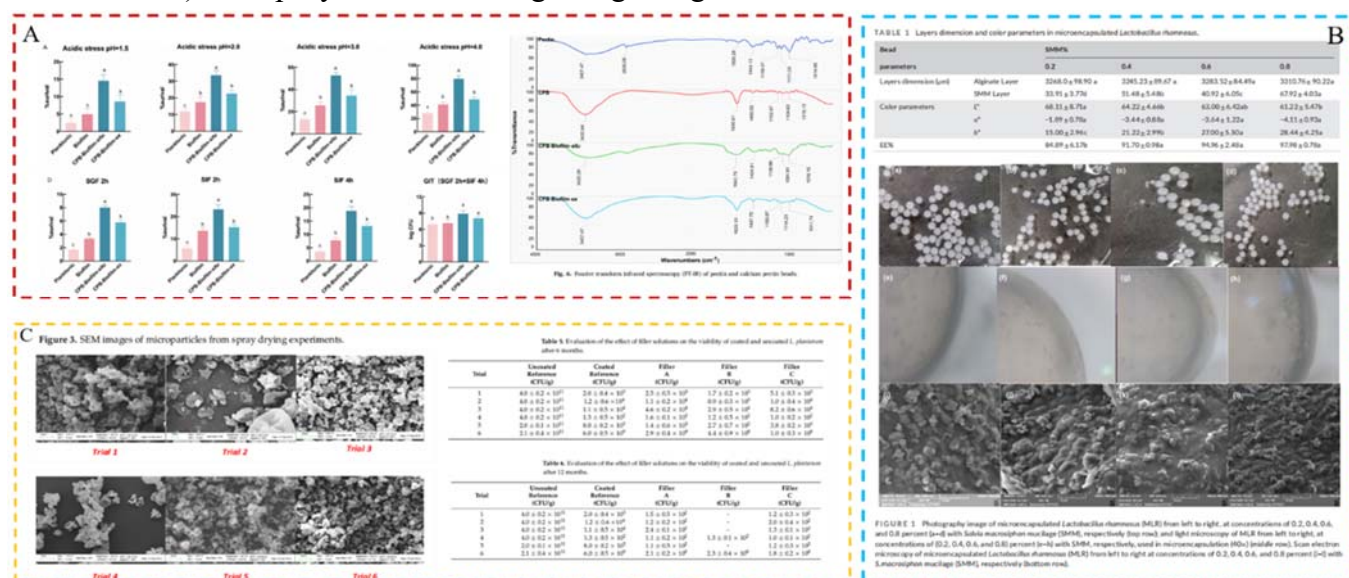


Figure 6 Functional validation of probiotic microencapsulation strategies. (A) Left: Survival of *Lactibacillus paracasei* under acid and simulated GI stress; right: FTIR spectra confirming bacterial encapsulation within pectin beads (Liu et al., 2023) [135]. (B) Top: Encapsulation efficiency (EE%) and layer thickness of beads with varying *Salvia macrosiphon* mucilage (SMM) concentrations; bottom: morphology of extruded beads (Abbasi Saadi et al., 2024) [96]. (C) Top: SEM image of spray-dried probiotic microparticles; bottom: viability of encapsulated *Lactiplantibacillus plantarum* after 12-month storage in fillers at room temperature (Gullifa et al., 2023) [101].

5.3 Preparation Strategies: Balancing Process Scalability with Probiotic Viability for Clinical Translation

The choice of microencapsulation technique critically impacts the viability of the psychobiotic cargo and the functionality of the final product, with implications for its practical use in dietary or clinical settings [99]. Ionic gelation is a common method for producing alginate-based beads, offering simplicity but sometimes yielding large, irregular particles [100]. Extrusion yields microbeads with uniform morphology (Figure 6B), while the surface structure of spray drying particles (visualized by SEM, Figure 6C, top) critically influences their stability and release properties [101]. Spray drying is highly efficient in industrial-scale production, but the accompanying heat and shear stress necessitate the use of stabilizers to maintain viability [102]. Electrospray (ES) technology has recently garnered significant attention as an emerging microencapsulation strategy due to its high efficiency, precise controllability, and broad material compatibility. This technique utilizes a high-voltage electrostatic field to atomize polymer solutions into micro- or nano-scale droplets, which subsequently form microcapsules through solvent evaporation or droplet solidification [103]. Most innovatively, *in-situ* biofilm culture involves cultivating probiotics directly within the encapsulation matrix, allowing them to form protective biofilms [104]. This biomimetic strategy remarkably enhances the encapsulated LAB's resilience to gastrointestinal stress and improves long-term storage stability, which is essential for developing shelf-stable, effective psychobiotic formulations suitable for widespread use in depression management protocols [105].

5.4 Efficacy Assessment: Validating Delivery Success through GBA-Relevant Outcomes

The success of a microencapsulation system is validated through *in vitro* and *in vivo* metrics that reflect its potential to alleviate depression. EE% is the primary indicator, confirming the successful incorporation of a high proportion of viable LAB [96]. Table 3 shows that W/O/W emulsions, polysaccharide-protein complexes and pectin-alginate-montmorillonite matrices all give good protection. Gastrointestinal survival is equally critical. Tests in simulated gastric and intestinal fluids show whether enough cells reach the colon [106]. As shown in Figure 6, microencapsulation markedly improves survival in gastric fluid (Figure 6A) and keeps viable counts high during storage (Figure 6C, bottom table). This preserves dose efficacy. Storage stability is also enhanced. Freeze-dried KGM-SA microcapsules stored at 25°C for 4 weeks decreased by only 0.8 log CFU/g, whereas free cells dropped by 5.9 log CFU/g [107]. Such targeted delivery allows the GBA-mediated antidepressant effect to be fully realized in disease models. In conclusion, targeted delivery technology is a critical enabler for probiotic-based interventions against depression. By providing comprehensive protection and controlled release, it ensures sufficient active LAB reach the gut, effectively modulating the microbiota-GBA. Future research should focus on overcoming remaining challenges such as production costs and individual gut microbiome variations. Breakthroughs may be achieved through AI-driven personalized delivery system design and scalable manufacturing processes like microfluidics [108]. With these advancements, microencapsulated LAB are poised to become a reliable, effective, and mainstream approach in the nutritional management of depression.

Table 3. Key technical parameters and efficacy validation of probiotic delivery systems.

Delivery System	Probiotic Strain	Encapsulation Efficiency (%) / Loading Capacity	Controlled Release Profile	Biocompatibility	Viability Enhancement	References
W/O/W Emulsion	<i>Lactobacillus acidophilus</i> JCM 1132	~93% (of initially included bacteria were enumerated)	Gastric protection (oil phase barrier); Release not explicitly measured but inferred in SIF	Food-grade surfactants and oils used. No additional function stated.	Simulated Gastric Juice (pH 2.0, 2h): 49% relative viability for emulsion. Control (free cells): <1.3% viability at 40 min. Viability increased with larger droplet size and higher inner-phase volume ratio.	[132]
Gum Arabic	<i>Lactocaseibacillus rhamnosus</i> HN001	26% to 110% (Highest for formulations with trehalose, e.g., F2:110%, F4:106%, F6:107%)	Dissolution in SGF for uncross-linked; Sustained release in SIF for cross-linked particles.	Biocompatible food-grade biopolymers. Gum Arabic may act as a prebiotic. Trehalose acts as a cryoprotectant.	Simulated GIT (6h): Free cells: 4.08 log reduction. Best formulation 2.61 log reduction (7.20 log CFU/g survived). Storage (12 weeks): >7 log CFU/g maintained at 4°C and -20°C for most formulations. F6 maintained 7.37 log CFU/g at 20°C for 12 weeks.	[133]
Spray-Dried Alginate-Protein Matrix	<i>Lactobacillus zeae</i> LB1	>80% (Survival rate after spray drying for all encapsulated samples)	Gastric protection (alginate gelation at low pH); Intestinal release (swelling at neutral pH). Best gastric protection with SPI-AG (3:1).	Food-grade polymers. Proteins provide buffering, adhesion, and antioxidant properties.	Simulated Gastric Fluid (pH 2.0, 2h): Free cells: complete inactivation within 1h. Best formulation (SPI-AG 3:1): only 0.61 log reduction. Storage (16 weeks, 25°C): Best stability with NaCas-AG matrices, especially at low a log CFU/g/week. Stability linked to high glass transition temperature.	[137]
Konjac Glucomannan (KGM)-Sodium Alginate (SA) Hydrogel Microcapsules	<i>Lactobacillus acidophilus</i>	62.5% (Embedding rate)	Gastric protection (SA matrix shrinks at low pH); Complete release in Simulated Intestinal Juice within 45 min.	Biocompatible food-grade materials. Konjac Oligosaccharides (KO) acts as a prebiotic and cryoprotectant.	Simulated Gastric Juice (pH 3.0, 2h): Microencapsulation significantly improved acid resistance. Storage (4 weeks): Freeze-dried microcapsules lost only 0.2 log CFU/g at 4°C and 0.8 log CFU/g at 25°C, vs. 4.6 and 5.9 log loss for free cells. Freeze-drying survival: Adding KO (8% w/v) increased survival rate of encapsulated cells from 63.5% to 79.5%.	[107]
Alginate coated with Chitosan + 1.5% GOS	<i>Lactobacillus acidophilus</i> 5	Yield after encapsulation varied (0.3-79.4%); initial cell count 8.3-10.8 log CFU/mL; 1.5% GOS provided best	high release in SIF inferred	GOS acts as prebiotic, providing carbon/nitrogen source; enhances growth in intestine	Simulated GI (pH 1.55 + 0.6% bile): Only 3.1 log reduction (vs 6.7 for control) Yogurt (4°C, 4 weeks): 1.1 log higher than control (no GOS) Orange Juice (4°C, 4 weeks): 0.5 log higher than control; counts maintained >10 ⁷ CFU/g	[98]

		loading			Simulated GI (pH 1.55 + 0.6% bile): Only 2.9 log reduction (vs 6.4 for control) Yogurt (4°C, 4 weeks): 0.4 log higher than control (no GOS) Orange Juice (4°C, 4 weeks): 0.4 log higher than control; counts maintained >10 ⁷ CFU/mL Heat (63°C, 30min): 29.10% (situ) vs 24.13% (ex) Gastric (SGF 2h): Significant protection vs free cells Freeze-drying: 75.50% (situ) vs 67.75% (ex) survival	
Calcium Pectin (CPB)	<i>Lactocaseibacillus casei</i> 01	Bacterial concentration reached >10 lg CFU/g for situ types	High release rate in SIF (~90% after 1h)	Biocompatible; degradable in intestine		
Chitosan-Calcium Pectin (C-CPB)		Bacterial concentration reached >10 lg CFU/g for situ types	High release rate in SIF (~89% after 1h)	Forms polyelectrolyte complex; enhances mechanical strength	Heat (63°C, 30min): 38.26% (situ) vs 31.02% (ex) Osmotic (10% NaCl): 47.68% (situ) vs 44.72% (ex) Freeze-drying: 81.16% (situ) survival	
Sodium Alginate-Pectin-Whey (SPW)	<i>Lactiplantibacillus paraphantarum</i> LR-1	Bacterial concentration reached >10 lg CFU/g for situ types; SPW-situ-LR-1 showed highest density	Sustained release in SIF; 94% release after 2h	Excellent emulsifying properties; provides nutrients; enhances aroma and flavor	Best overall protection: Heat (89°C, 15s): 69.55% (situ) survival Gastric (SGF 2h): Highest survival among all groups Freeze-drying: 85.65% (situ) survival Storage (-20°C, 4 weeks): 93.5% (situ) survival Osmotic (10% NaCl): 61.32% (situ) survival Superior tolerance to all stresses: heat, gastric, intestinal, osmotic, and freeze-drying Prevented colitis in mice: similar efficacy to fresh biofilm cells Modulated gut microbiota: increased <i>Lactobacillus</i> abundance	[134]
SPW (sit biofilm culture)		>10 lg CFU/g	Optimal sustained release in intestine	<i>In-situ</i> biofilm enhances integration with wall material; improves acid resistance and storage stability		
Pectin-Alginate-Montmorillonite (PAMT1, 1% MMT)		97.83 ± 0.52%	Sustained release in SIF; release rate of FDBs at 4 h was 27.67%	Improved structural strength; enhanced swelling ratio (5.34 at 6 h)	Viability decrease in SGF: 0.30 log CFU/g; storage stability: high viability maintained over 2 weeks	
Pectin-Alginate-Montmorillonite (PAMT3, 3% MMT)	<i>Lactobacillus kefirianofaciens</i> JKSP109	95.50 ± 0.28%	Slow and controlled release in SIF; lowest release rate among all groups; rigid structure remained intact after 4 h SIF	Excellent dense structure; strong adhesion to colonic mucus; high swelling ratio (5.41 at 6 h)	Viability decrease in SGF: only 0.07 log CFU/g; best protection in gastric acid; storage: decrease of only 0.46 log CFU/g after 2 weeks (freeze-dried)	[136]
Pectin-Alginate (PA, no filler)		88.33 ± 0.88%	Rapid release in SIF; complete release in FDBs by endpoint; turned into loose gel clusters in SIF	Basic biocompatibility; high water content (96.30%) but weak structure	Viability decrease in SGF: 1.14 log CFU/g (FSBs) and 0.57 log CFU/g (FDBs); poor storage stability compared to PAMT groups	

6. Challenges and Future Perspectives

The compelling preclinical and mechanistic evidence highlights the substantial potential of LAB and fermented dairy products in modulating the GBA for depression treatment. However, several interrelated gaps must be systematically addressed to turn this promise into reliable, mainstream therapies. Multiple obstacles hinder the transition from bench to bedside. Scientifically, strain-specificity of effects ^[109] and incomplete mapping of the biochemical pathways linking microbial metabolites to brain circuits hamper rational design of next-generation interventions ^[110]. Clinically, inter-individual heterogeneity in gut microbiota and host physiology leads to variable treatment responses ^[111-112]. Furthermore, large-scale, long-term randomized controlled trials with stringent psychiatric endpoints are still lacking, so efficacy and safety remain to be definitively established ^[113]. Technologically, scaling up sophisticated delivery systems like microencapsulation poses manufacturing and economic challenges ^[64]. Regulatorily, the pathway for mental-health claim substantiation remains arduous and complex.

To overcome these obstacles, future research must embrace an integrated, interdisciplinary strategy focused on several critical frontiers. We must use multi-omics approaches and advanced experimental models such as gnotobiotic systems and organ-on-a-chip to clarify the gut-brain signaling cascade and identify predictive biomarkers for tailored interventions. Delivery technology should evolve beyond passive protection toward “intelligent” stimuli-responsive systems and even engineered living biological therapies to achieve precise targeting. Clinical trials must evaluate probiotic formulations more comprehensively within an integrated framework, examining synergistic effects with dietary patterns, psychotherapy, and other lifestyle interventions to better reflect real-world complexity ^[114-115]. Ultimately, sustained collaboration among microbiology, neuroscience, food science, clinical psychiatry, and regulatory affairs, supported by shared resources and standardized protocols, will be essential to advance the field. In conclusion, the path forward is challenging, yet the fundamental rationale for targeting the GBA remains compelling. Mechanistic research, rigorous clinical trials, technological innovation, and multi-stakeholder collaboration must be integrated to clear these hurdles. With such efforts, LAB and fermented foods can move from promising research targets to core components of evidence-based, multimodal mental health strategies within nutritional psychiatry ^[116].

7. Conclusion

Given the significant limitations of conventional antidepressants, including delayed onset, debilitating side effects, and suboptimal efficacy, targeting GBA has emerged as a viable therapeutic alternative. This review consolidates evidence that LAB and fermented dairy products can alleviate depressive symptoms through multi-targeted GBA regulation. LAB act as crucial GBA modulators by reshaping the gut microbiota, promoting beneficial SCFA production, and optimizing tryptophan metabolism toward serotonin synthesis. Their effects rely on a synergistic network with SCFAs and GABA serving as direct microbial signals. Meanwhile, the interaction between elevated 5-HT and BDNF supports neuroplasticity and

emotional regulation. Delivering LAB within a fermented milk matrix combines live bacteria, bioactive metabolites (e.g., GABA, peptides), and milk-derived components (e.g., MFGM, oligosaccharides). This combination confers greater efficacy than probiotics monoculture. Preliminary human trials indicate that specific strains and fermented products may alleviate depressive symptoms and modulate associated biological pathways. However, larger, more rigorous and personalized studies are still needed. Advanced microencapsulation technology addresses key challenges in oral drug delivery. Mucoadhesive and pH-responsive materials give gastric protection and colon-targeted release. For instance, pectin-alginate-montmorillonite composite microcapsules exhibit outstanding protective properties, maintaining higher viable counts in simulated gastric acid compared to free cells or single-material systems. Additional strategies can synergistically enhance. These include adding prebiotics, proteins, and using *in-situ* culture technology. The cells then withstand processing, storage, and gastrointestinal transit. These insights are crucial for developing next-generation, high-efficiency probiotic products. In summary, LAB-based therapies demonstrate significant potential as safe and effective GBA-targeted strategies for depression. Fully realizing their potential within nutritional psychiatry requires the continued integration of mechanistic research, delivery innovations, and clinical validation.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of generative AI in scientific writing

Generative AI and AI-assisted technologies should only be used in the writing process to improve the readability and language of the manuscript.

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