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Probiotics For Depressive Symptoms: Gut–Brain Axis Mechanisms, Evidence, and Functional Food Translation

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ABSTRACT: The prevalence of stress-induced mental health disorders, such as anxiety and major depressive disorder, is increasing globally. Growing evidence suggests that gut microbiota plays a crucial role in cognitive function and emotional regulation via the gut-brain axis. As a result, probiotics have emerged as a promising dietary intervention for mental well-being, supported by their demonstrated ability to alleviate depressive behaviors in both clinical and preclinical settings—primarily through immune modulation, metabolic regulation, and microbial metabolite production. Although numerous studies have confirmed the potential of various probiotic strains to reduce depressive symptoms, only a limited number have been approved for commercial use to date. Key challenges remain, including variable clinical efficacy, instability during production and processing, and safety considerations, which must be addressed to facilitate their integration into functional foods. This comprehensive review discusses the mechanisms by which probiotics exert antidepressant effects, with a focus on host immunity, microbial metabolites, and neuroendocrine pathways. Furthermore, we offer critical insights into the current limitations and strategic directions for the application of probiotics in functional foods aimed at supporting mental health.

Keywords: gut microbiota; probiotic; depression disorder; immunometabolism; microbial metabolites; neuroendocrine;

1. Introduction

Approximately 350 million individuals worldwide suffer from depression, with the incidence of depression escalating, particularly in the aftermath of the global pandemic, rendering it a principal contributor to disability, mortality, and economic disparity ^[1-3]. Nonetheless, the etiology of depression remains enigmatic, underscoring the imperative to unearth novel targets for therapeutic intervention. A promising frontier in this domain has come to light, focusing on the potential impact of intestinal microbiota ^[4]. Accumulating evidence indicates that gut microbes can modulate cognitive and affective processes via the gut-brain axis ^[5]. The microbial-gut-brain axis represents an innovative avenue for developing treatments for cerebral dysfunction, especially via dietary modalities such as probiotic or prebiotic supplementation ^[6]. Probiotics are indeed living non-pathogenic microorganisms commonly utilized to enhance the microbial balance within the gastrointestinal tract. Typically employed as dietary supplements or food additives,

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probiotics serve a crucial role in regulating gut health through multiple mechanisms. These mechanisms encompass tasks such as decreasing intestinal pH levels, inhibiting the colonization and invasion of harmful pathogens, and modulating the host's immune response for overall better well-being ^[7]. Apart from these functions, emerging research suggests that probiotics also have an impact on neurological conditions like depression through what is known as the gut-brain axis ^[8]. This bidirectional communication system between the gut and the brain highlights how gut health can influence mental well-being. These fresh insights proffer a novel avenue for addressing depression therapeutics and prevention.

Intestinal microbiota refers to the community of microorganisms residing in the human intestinal tract ^[9]. It was originally obtained at birth and almost entirely came from the mother. Its composition may be influenced by environmental factors such as age, diet, disease, travel, and drug use. In adulthood, the composition of intestinal microbiota becomes relatively stable ^[10]. Individuals with major depressive disorder (MDD) often exhibit somatic symptoms, with gastrointestinal disturbances being a predominant symptom ^[11]. Recent years have seen widespread documentation of dysbiosis in intestinal microbiota among both patients with depression and animal models of depression ^[1, 12]. Gut microbiota represent a modifiable target with epigenetic modification potential. Probiotics and their metabolites play a crucial role in maintaining human intestinal health by enhancing the balance of microbial flora within the host ^[13]. Consequently, various interventions like probiotics (live bacteria), prebiotics (fiber-rich diet), synbiotics (combination of probiotics and prebiotics), postbiotics (bacterial metabolites or surface proteins), fecal microbiota transplantation (FMT), or antibiotics can be employed to regulate intestinal microbiota, thereby alleviating symptoms of depression ^[14]. Current research also suggests that probiotics serve as a promising new strategy to mitigate depressive behaviors in individuals with depression and animal models ^[4, 15, 16]. Based on these findings, more and more studies have revealed the mechanism of how intestinal microorganisms act on neural activity and behavior regulation circuits. It is worth noting that the composition and metabolites of intestinal microbes can be modulated by host genetic variations, underscoring the need for further exploration into the functional implications of these probiotics in the gut environment and their effects on behavior ^[17].

This review summarizes the molecular mechanisms by which probiotics alleviate depression and outlines their functional roles in ameliorating depressive symptoms. Its primary objective is to provide mechanistic insights to support the exploration, application, and development of probiotics as dietary-based interventions or functional ingredients for mental health, particularly within the context of functional foods for managing depression.

2. The gut microbiota-brain axis and depression

Advances in sequencing technology have allowed for a deeper understanding of the intricate relationship between humans and their microbial communities ^[18]. The diversity of the intestinal microbiota surpasses that of human somatic cells and germ line cells by tenfold. Moreover, the combined genetic

material of these microbial communities, known as the "microbiome," dwarfs the human genome by a factor of 150^[18, 19]. The intestinal microbiota serves as a crucial filter and biological regulator, perceiving, altering, and controlling myriad chemical signals from the environment. These signals are then disseminated throughout the body, exerting profound effects on human brain health^[20]. At present, clinical evidence has firmly established the two-way interaction between brain, intestine and intestinal microbiota^[21]. The communication in the system is bidirectional, with multiple feedback loops, and may involve the interaction between different channels^[22]. Most gut microbial signals produced by microbial flora can regulate these steady-state reflexes by locally acting on intestinal neurons or vagal nerve and sympathetic afferent nerve endings, so as to generate internal receptive signals to the central nervous system, or transmit them to the brain through systemic circulation, or regulate brain signals through brain immune metabolism in brain-gut nerve circuit^[23, 24]. Most of these signal molecules can be divided into food-related metabolites, endogenous molecular metabolites, and microbial cell wall components.

According to the World Health Organization (WTO) forecast, depression is projected to become the leading global disease burden by 2030^[25]. However, the exact cause and pathogenesis of depression remain unclear, making its treatment challenging. Currently, there are four widely accepted etiological hypotheses: (a) The neurotransmitter hypothesis suggests that a reduction in the levels and/or dysfunction of monoamine transmitters such as serotonin (5-HT), dopamine (DA), and norepinephrine (NE) in the brain may lead to depression^[26]; (b) Abnormal elevation of glutamic acid levels can disrupt information transmission in the nervous system and result in depression^[27]; (c) Dysfunction in the hypothalamus-pituitary-adrenal signaling axis can also lead to depression^[28]; (d) Reduced expression and/or abnormal function of brain neurotrophic factors may contribute to depression^[29]. Additionally, various factors such as personality, environment, genes, and other physiological conditions may influence the pathogenesis of depression. Gut brain axis (GBA) coordinates the complex interaction among gastrointestinal tract, nervous system and immune system, playing a vital role in maintaining human nervous system health^[30]. Recent studies have increasingly highlighted the profound impact of the gut microbiota on various neurological disorders, including major depressive disorder (MDD)^[31], Parkinson's disease (PD)^[32], Alzheimer's disease (AD)^[33], Bipolar disorder (BD)^[34], Autism spectrum disorder (ASD)^[35], anxiety^[36], and more.

Probiotics and their metabolites have beneficial effects on maintaining human health. Upon entering the intestine, they can directly interact with nerve endings via intestinal neurons, the vagus nerve, and sympathetic pathways. Additionally, they have the capacity to modulate brain signals through brain immune metabolism, influencing neurotransmitters, brain-derived neurotrophic factors, and the hypothalamic-pituitary-adrenal (HPA) axis, or regulate the brain by modifying gut microbiota composition. For specific related research and mechanisms, refer to Table S1. Gao et al. found that *Lactococcus lactis* could enhance 5-hydroxytryptophan levels by upregulating tryptophan hydroxylase 1 (Tph1) expression in intestinal chromaffin cells. This mechanism helps regulate serum cortisol levels, brain serotonin (5-HT) levels, and brain-derived neurotrophic factor, effectively alleviating depression-like behaviors in mice^[37].

Similarly, Kosuge et al.'s study revealed that the supplementation with heat-inactivated *Bifidobacterium brevis* could prevent social interaction disorder in mice, suppress the increase in IL-1 β levels in the prefrontal cortex and hippocampus, and modulate changes in intestinal microbial composition induced by chronic social defeat stress [12]. Furthermore, fermented foods fermented by microorganisms are considered beneficial to health. During fermentation, food substrates are transformed into nutritionally enriched products with functional properties. These fermented products contain probiotics, prebiotics that support the growth of beneficial intestinal bacteria, and bioactive components [38]. These functional components exert biological effects in the gastrointestinal tract, leading to alterations in gut microbiota, immune activation, improved host health, and relief from symptoms of depression and anxiety. In a study conducted by Chuang et al., oral administration of *Monascus*-fermented food to depressed rats appeared to restore levels of norepinephrine, dopamine (DA), and serotonin (5-HT) in the hippocampus and amygdala. This intervention normalized the turnover rates of 5-HT and DA in these brain regions and potentially reduced the turnover rate of DA in the frontal cortex and striatum, ultimately ameliorating depressive symptoms [39]. Current literature underscores the role of probiotics in ameliorating depression symptoms, with reported mechanisms involving direct and indirect signaling pathways encompassing chemical messengers, neuronal circuits, and the immune system. Given the multifaceted nature of biological systems at play, it is plausible that a convergence of diverse mechanisms and pathways collaborates to influence disease pathogenesis and various aspects of host genetics. Thus, further research endeavors are imperative to unravel the intricacies of these mechanisms comprehensively, as the review will delve into the nuances of these relationships in greater detail.

3. Depression-improving mechanism of the probiotics

3.1 Probiotics improves depression through the immunometabolism

The etiology of depression is complex, with numerous contributing factors, one of which is the neuroimmune hypothesis [40]. In recent years, an increasing number of studies have highlighted the significant role that inflammation plays in the etiology and pathophysiology of depression. Current research reveals similarities in behavior and pathology between human depression and chronic stress in rodents, characterized by mononucleosis, neutropenia, and lymphopenia. Under pressure, there is a down-regulation of pro-inflammatory signaling pathways involving tumor necrosis factor (TNF) and/or nuclear factor- κ B (NF- κ B) in endothelial cells of the NAc [24]. Additionally, the tight junction protein Claudin-5 (Cldn5), which helps maintain barrier integrity, is also down-regulated. Simultaneously, inflammatory monocytes known as Ly6C1 monocytes, along with neutrophils expressing high levels of LY6C, are recruited to the nucleus accumbens. These cells or their secreted factors, such as interleukin-6 (IL-6), can penetrate the damaged blood-brain barrier and enter the brain parenchyma [41]. Once inside, they can directly influence the excitability of neurons. Recent studies have indicated a specific link between the composition of intestinal microflora, inflammatory factors in plasma, markers of inflammation and permeability in the intestinal

mucosa, and the pathophysiology of depression. Liu et al.'s research highlights the substantial differences in the intestinal flora of individuals with inflammatory depression compared to healthy individuals [40]. It is intriguing that supplementing particular bacterial species in animal models can effectively regulate depression-related immune pathways and reduce behavioral despair, including NF- κ B and MAPK [42, 43].

Probiotics stimulate the immune system primarily through their own components or internal metabolites, known as postbiotic. These include extracellular vesicles, surface proteins, antibacterial peptides, teichoic acids, endo- and exopolysaccharides, peptidoglycan, vitamins, plasmalogens, organic acids, and short chain fatty acid [44]. In a study by Morishita et al., they discovered that the production of pro-inflammatory cytokines TNF- α and IL-6 decreased in mouse macrophage-like RAW264.7 cells expressing TLR2 and mouse dendritic DC2.4 cells treated with extracellular vesicles (EV) derived from *Bifidobacterium* and *Lactobacillus* when the TLR2 inhibitory antibody T2.5 was added [45]. It also has been discovered that *Lactobacillus* can stimulate the production of INF γ via antigen presentation, thereby facilitating the behavioral recovery of mice under environmental stress [15]. Furthermore, it was identified that the signaling pathways involving c-Jun-NH2 terminal kinase (JNK)/mitogen-activated protein kinase (MAPK) and nuclear factor-kappa B (NF-kappa B) were also implicated in the production of pro-inflammatory cytokines by EV-treated immune cells. Short-chain fatty acids (SCFAs), which are metabolized by probiotics, also play a crucial role in the differentiation and function of several immune cell types, such as anti-inflammatory regulatory T cells (Treg), CD8 T cells, macrophages, tolerant CD103 dendritic cells, and B lymphocytes [46]. Therefore, these studies provide compelling evidence that probiotics can effectively alleviate depression by regulating immune metabolism, and modulating signaling pathways [47–49]. These specific mechanisms are detailed as follows (Figure 1).

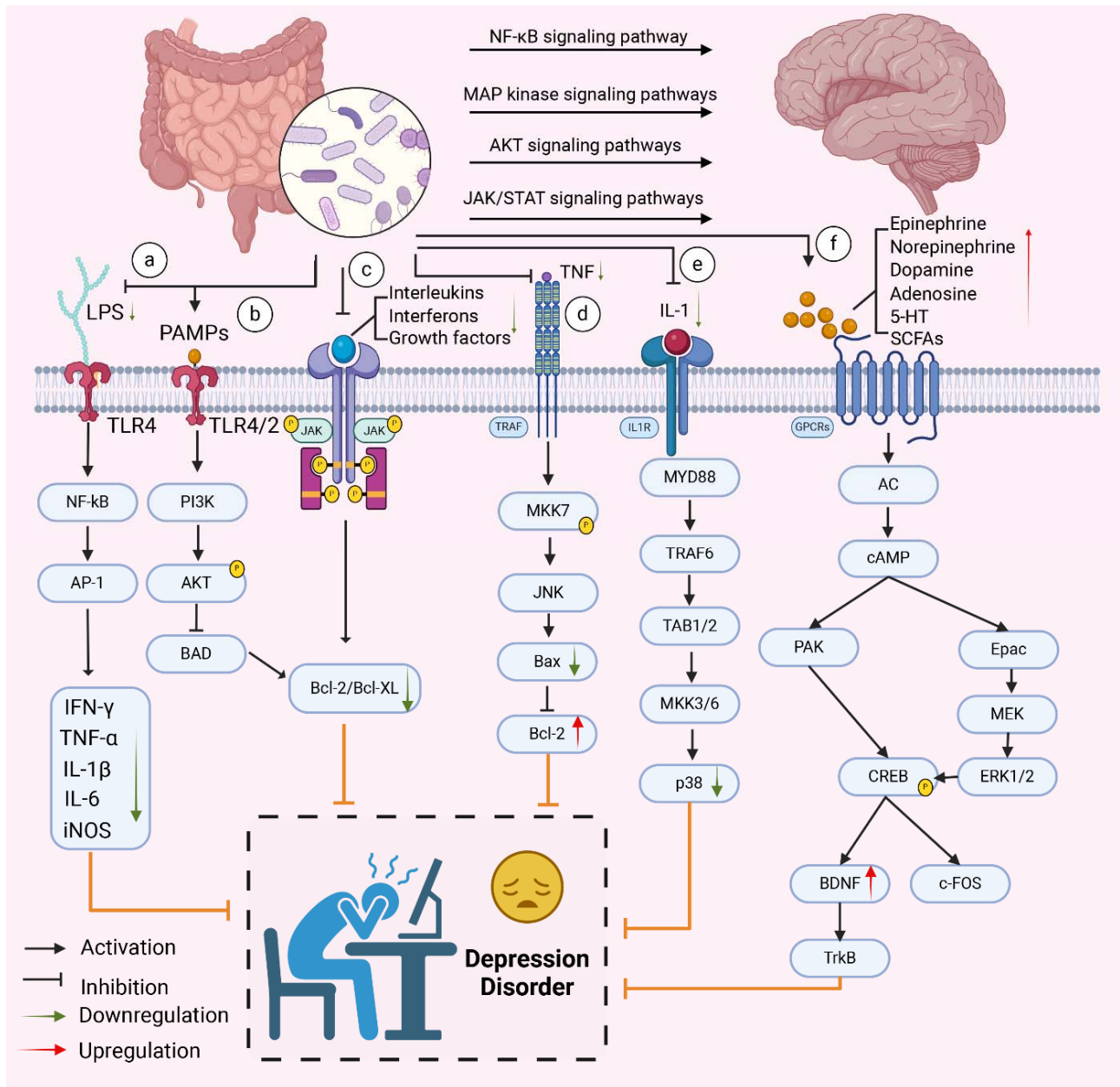


Fig. 1. Probiotics alleviate depression via immune metabolism. (a) Probiotics can alleviate depression by inhibiting the production of lipopolysaccharide (LPS), thereby further suppressing the expression of Toll-like receptor 4 (TLR-4), and subsequently reducing the expression of nuclear factor kappa-B (NF-κB) and activating protein-1 (AP-1), ultimately minimizing the generation of inflammatory factors. (b) Probiotics can trigger the activation of Phosphoinositide 3-kinase (PI3K) by stimulating Toll-like receptor 2 (TLR-2) or 4 (TLR-4), subsequently activating Protein Kinase B (AKT). Via this signaling pathway, (c) Or through modulating the levels of interleukin, interferon, and growth factor in the intestine to activate Janus kinase (JAK), subsequently regulating the levels of signal transducer and activator of transcription (STAT) proteins, they are capable of suppressing B-cell lymphoma-2 (Bcl-2) and B-cell lymphoma-extra large (Bcl-XL), thereby alleviating depression. (d) Probiotics can diminish the levels of serum TNF-α (Tumor Necrosis Factor Alpha), mitogen-activated protein kinase 7 (MKK7), and c-Jun N-terminal kinase 2 (JNK). They also down-regulate the immune content of pro-apoptosis protein Bax (Bcl-2-associated X protein) and up-regulate the immune content of anti-apoptosis protein Bcl-2 (B-cell lymphoma-2), thereby alleviating depression. (e) Probiotics can modulate the levels of interleukin-1 (IL-1), Myeloid differentiation primary response protein 88 (MyD88), mitogen-activated protein kinase 3/6 (MKK3/6), and p38 mitogen-activated protein kinase (p38), while increasing the content of BDNF (brain-derived neurotrophic factor), thereby alleviating depression. (f) Probiotics have the ability to modulate monoamine substances, thereby influencing extracellular regulated protein kinases 1/2 (ERK1/2) and cAMP response element binding protein (CERB). This up-regulation leads to an increase in BDNF (brain-derived neurotrophic factor) and tyrosine kinase receptor B (TrkB), ultimately alleviating depression.

3.1.1 NF- κ B signaling pathway

Probiotics primarily target the NF- κ B signaling pathway to alleviate depression by regulating immunity (Figure 1a). Many studies have demonstrated that depression can induce the production of inflammatory factors in the brain, such as lipopolysaccharide, IL-1 β , and TNF- α [50–53]. This connection also unveils the potential mechanism through which probiotics may alleviate depression. It binds to Toll-like receptors, interleukin-1 receptors, and tumor necrosis factor receptors, subsequently activating myeloid differentiation factor (MyD88) [54]. This activation initiates the production of proinflammatory cytokines and triggers the NF- κ B pathway, ultimately leading to the activation of microglia [55]. Currently, various probiotic strains, including *Bifidobacterium*, *Akkermansia muciniphila*, *Lactocaseibacillus rhamnosus*, and *Komagataella pastoris*, have been shown to alleviate depression by modulating the NF- κ B pathway [42, 49, 53, 56]. Lipoteichoic acids from LGG induces an immune response involving helper T protein 1 through MyD88/NF- κ B signal transduction activated by TLR2/6, while also demonstrating the ability to temper excessive inflammatory responses [57]. Additionally, Lipoteichoic acids aids in augmenting the population of IgA-positive B cells. Unmethylated CpG-rich DNA motifs derived from LGG prompt TLR9-activated MyD88/NF- κ B signal transduction, eliciting a T-helper 1 immune response, fostering B cell proliferation, and inhibiting antigen-specific IgE production [58]. Moreover, probiotics play a crucial role in regulating intestinal microflora, maintaining the integrity of the intestinal barrier, and modulating tight junction proteins and inflammatory factors [52, 59, 60]. A study discovered that secreted proteins present in the cell wall and extracellular vesicles of *Lactobacillus rhamnosus* can activate intracellular signal networks by triggering EGFR activation [61]. This process leads to anti-apoptotic effects and cell protection for epithelial cells, preservation of cell connections, and increased mucus production. Similarly, an animal experiment has demonstrated that *Komagataella pastoris* can modulate the level of IL-1 β in the hippocampus, thereby alleviating depression-like behavior in mice. This adjustment occurs through the regulation of intestinal microflora, maintenance of intestinal barrier integrity, and restoration of ZO-1, ZO-2, and toll-like receptor-4 levels in the small intestine of mice [59]. These studies demonstrate that numerous probiotics have the ability to alleviate depression by modulating inflammatory factors and the NF- κ B pathway.

3.1.2 MAP kinase signaling pathways

The MAP kinase signaling pathways is indeed another pathway involved in probiotic regulation (Figure 1 (d), (e) and (f)). It plays a role in various cellular processes, including responses to stress and inflammation. The MAP kinase signal cascade is a vital intracellular signaling pathway that transduces a diverse array of extracellular signals, regulating cell responses associated with proliferation, differentiation, and apoptosis (cell death)[62]. Three groups of MAP kinases have been identified: extracellular signal-regulated kinase (ERK), P38 MAP kinase, and c-Jun NH2 terminal kinase (JNK). Typically, ERK is activated by mitogenic and differentiation signals, whereas JNK and p38 MAP kinases are activated by stress stimuli [63]. Regarding the extracellular signal-regulated kinase pathway, studies have shown that it can facilitate neurotrophic effects

and synaptic plasticity. Additionally, research indicates that intervention with probiotics can activate the extracellular signal-regulated kinase pathway in the prefrontal cortex and hippocampus, thereby potentially influencing depression-like behavior in mice. The interaction between Brain-Derived Neurotrophic Factor (BDNF) and its receptor TrkB has been found to initiate the MAPK/ERK signal transduction pathway [64]. This interaction leads to an increase in the density of dendritic spines in hippocampal neurons. Moreover, the activated MAPK pathway further promotes the maturation of dendritic spines. For instance, *Lactobacillus plantarum* R6-3 has been shown to modulate the BDNF/TrkB/ERK/CREB signaling pathway in the hippocampus. This activation can lead to increased production of monoamine neurotransmitters, restoration of brain neurotrophic factor levels, and inhibition of the overactivity of the hypothalamic-pituitary-adrenal (HPA) axis [43]. As a result, this intervention may improve both immune responses and oxidative stress levels, thereby safeguarding the hippocampus from damage. Furthermore, it can help maintain a healthy weight and prevent depression triggered by chronic unpredictable stress in mice. In addition, Yang et al.'s research also showed that *Lactobacillus casei* may relieve depression in mice by regulating BDNF-ERK1/2 pathway [65]. The JNK/SAPK (c-Jun N-terminal Kinase/Stress-Activated Protein Kinase) signaling cascades represent another pathway that can be activated by various stimuli such as stress, cytokines, growth factors, and certain G protein-coupled receptors [66]. The research conducted by Zhao et al. demonstrates that DP 189 led to various effects, including the degradation of serum IL-1 β and TNF- α levels, a decrease in hippocampal mitogen-activated protein kinase kinase 7 and c-Jun N-terminal kinase 2 levels, down-regulation of the pro-apoptosis protein Bax immuncontent, up-regulation of the anti-apoptosis protein Bcl-2 immuncontent, improvement in pathological changes of the hippocampus, and a reduction in the number of TUNEL positive cells [67]. The last one is p38 MAPK signaling pathway, which is similar to JNK pathway, and it can also be activated by stress stimulation and proinflammatory factors [68]. In addition, it can be activated by lipopolysaccharide and cell wall components of gram-positive bacteria. The study by Gu et al. revealed that chronic unpredictable stress (CUMS) can lead to depression-like behavior in mice. This stress induces changes in the expression of various proteins including monoamines dopamine, norepinephrine, and 5-hydroxytryptamine, brain-derived neurotrophic factor (BDNF), and its receptors tyrosine kinase receptor B (TrkB) and N-methyl-D-aspartate receptor 1. Additionally, the activation of ERK1/2 and p38 MAPK signaling pathways is seen as a result of CUMS [69]. Interestingly, the intervention of *Lactobacillus casei* was found to reverse this phenomenon. Additionally, exopolysaccharides originating from LGG demonstrates effective inhibition of p38/MAPK and NF- κ B signal transduction, thereby attenuating pro-inflammatory reactions and serving a protective antioxidant function [70]. These data show that probiotics can regulate depression through multiple MAPK pathways. In addition, the mechanism of probiotics regulating depression through MAPK pathways is relatively complex, and there are intersections or correlations among various pathways, so further research and exploration are needed.

3.1.3 AKT signaling pathways

AKT participates in the PI3K/AKT signaling pathway (Figure 1b). When Akt is phosphorylated and fully activated at the serine Ser473 and threonine Thr308 sites, it regulates a variety of cellular functions, including angiogenesis and the recruitment of inflammatory factors ^[71]. When AKT (also known as protein kinase B) undergoes phosphorylation, it activates various downstream factors involved in cell survival and proliferation. One such downstream factor is the anti-apoptotic protein Bcl-2. When AKT is phosphorylated and active, it can phosphorylate and activate Bcl-2, thereby promoting its anti-apoptotic function ^[72]. Conversely, phosphorylated AKT can also inhibit pro-apoptotic factors such as Bax and Bak. These proteins are involved in promoting apoptosis (programmed cell death). When AKT is activated, it phosphorylates Bax/Bak, leading to their inactivation or decreased expression ^[73]. This inhibition of Bax/Bak reduces their ability to induce apoptosis. Furthermore, activated AKT can interfere with the caspase pathway, which is a central pathway for executing apoptosis. Caspases are a family of proteases that are activated during apoptosis and play a key role in cell dismantling ^[74]. Phosphorylated AKT can modulate the activity of caspases directly or indirectly through its downstream targets, ultimately inhibiting their activation or function^[75]. Xu et al.'s research shows that compound probiotics can increase the levels of p-AKT and Bcl-2 in hippocampus of constipation mice by activating Akt signaling pathway, while reducing the concentrations of Bax and caspase -3, thus inhibiting nerve apoptosis and relieving depression-like behavior in mice ^[76]. These findings may also provide a new idea for probiotics to relieve depression.

3.1.4 JAK/STAT signaling pathways

The JAK-STAT signaling pathway plays a pivotal role in cellular communication, involving Janus kinase (JAK) and Signal Transducer and Activator of Transcription (STAT) proteins (Figure 1c). JAK, a non-receptor protein tyrosine kinase, serves as the central element in this pathway, comprising JAK1, JAK2, JAK3, and Tyk2 ^[76]. Within this signaling cascade, JAK acts as the initiator by phosphorylating specific tyrosine residues on STAT proteins, initiating their activation. Post-phosphorylation, STAT proteins undergo conformational changes and form dimers through SH2 domain interactions ^[77]. This dimerization facilitates the translocation of the STAT complex to the nucleus, effectively serving as the key to unlock the process. Activated JAKs act as kinases that trigger the phosphorylation of STAT monomers, setting off the downstream signaling cascade. Ultimately, this series of events leads to the activation of target genes through the transcriptional activity of STAT proteins within the nucleus ^[78]. The clinical trial findings unveiled a noteworthy relationship between depression and the JAK-STAT signaling pathway. Specifically, elevated JAK3 expression and decreased STAT1 expression were observed in the depressed group, suggesting that modulating this pathway could potentially offer therapeutic benefits for individuals with depression ^[79]. Haas et al. discovered through animal experiments that the probiotic *Lactobacillus rhamnosus* JB-1 impacted the anxiety behavior of mice by modulating the NF-KB pathway, which in turn regulated interferon signaling, the JAK/STAT pathway, and TNF- α activity ^[56]. These information indicate that this may be a new strategy for probiotics to regulate depression.

The immunomodulatory mechanisms through which probiotics alleviate depression, as outlined above, represent a significant area of therapeutic potential. However, the comprehensive pathology of depression and its specific intestinal manifestations remain incompletely characterized, underscoring the necessity for more extensive investigation. To optimize the efficacy and precision of probiotic-based interventions, researchers must systematically elucidate the underlying pathological mechanisms of depression and their intricate interactions with intestinal physiology. For example, as recent research has revealed that matrix metalloproteinase-8 (MMP8) originating from peripheral blood immune cells is crucial in stress and depression. MMP8 can penetrate the brain by breaching the blood-brain barrier (BBB) and impact the extracellular space of the Nucleus Accumbens (NAc), which could be linked to alterations in social behavior induced by stress ^[41]. Moreover, the complement system, particularly complement C3, has been established as a pivotal factor in microglia-mediated synaptic pruning, which holds significant importance in neural development and various neurological disorders ^[80]. Recent research by Hao et al. has revealed that an intestinal ecological disorder can induce depression-like behavior through aberrant synaptic pruning by microglia, mediated by complement C3 ^[2]. Researchers should strategically integrate these advancements in depression pathophysiology with mechanistic studies of gut-brain axis regulation, enabling the development of precisely designed psychobiotic formulations and microbiota-focused therapeutic approaches for enhanced neuropsychiatric health.

3.2 Probiotics improves depression through the gut microbial metabolites

3.2.1 Tryptophan metabolic pathway

Tryptophan stands as an essential amino acid vital for human protein synthesis. It emerges as a pivotal player in the intricate microbial community-gut-brain axis, serving as the exclusive precursor of the neurotransmitter serotonin ^[81]. The human body does not naturally produce tryptophan, making it essential for human beings to obtain this amino acid from external sources, primarily through dietary intake from foods like oats, milk, tuna, and cheese ^[82]. Furthermore, the capacity of specific bacteria to synthesize tryptophan has found widespread application in various industrial processes ^[83, 84]. There are three main ways for probiotics to relieve depression through tryptophan (Figure 2a). (1) Direct Conversion: Tryptophan is directly transformed into various molecules, such as aromatic hydrocarbon receptor ligands (e.g., indole IAld, IAA, IPA, IAAlD), by the intestinal microflora ^[17]. (2) Kynurenine Pathway: Within immune and epithelial cells, tryptophan follows the kynurenine pathway catalyzed by indoleamine 2,3-dioxygenase (IDO) ^[85]. (3) Serotonin Production: Enterochromaffin cells synthesize serotonin (5-hydroxytryptamine [5-HT]) from tryptophan with the enzyme tryptophan hydroxylase 1 (TpH1) ^[16].

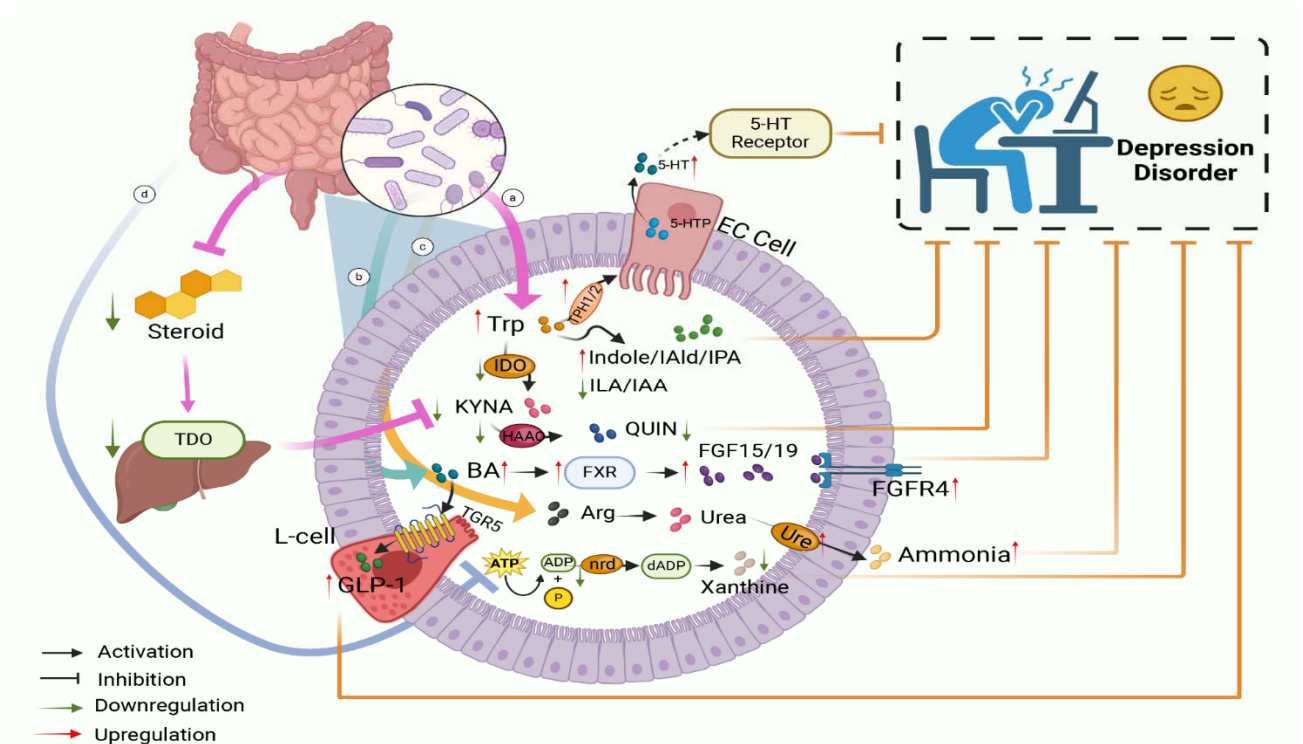


Fig. 2. Probiotics alleviate depression via gut microbial metabolites. (a) Probiotic supplementation can improve tryptophan metabolism. Supplementation of probiotics can enhance tryptophan metabolism, raise the content of 5-hydroxytryptophan, and subsequently elevate the level of serotonin in the brain, thereby alleviating depression. Additionally, it can achieve this by generating indole, indole-3-aldehyde (IAld), and indole-3-propionic acid (IPA), which can reduce the levels of indole-3-acetic acid (IAA) and indole-3-lactic acid (ILA). Secondly, by restricting the metabolic pathway of uric acid in dogs, the level of Quinolinic acid (QUIN) in the brain is decreased. (b) Supplementation of probiotics modulates bile acid metabolism and activates the farnesoid X receptor (FXR), thereby increasing the level of fibroblast growth factor 19 (FGF19), and subsequently indirectly transmits signals to the brain. Secondly, Toll-like receptor 5 is activated by secondary bile acids, which promotes the release of glucagon-like peptide-1 (GLP-1). (c) Supplementation of probiotics could enhance urease expression, facilitate ammonia circulation, and subsequently alleviate depression. (d) Supplementation with probiotics has the potential to regulate purine metabolism, decrease the levels of xanthine and xanthine nucleoside in both serum and the brain via nucleoside diphosphate reductase (nrdB), and thereby alleviate depression.

3.2.1.1 Indole pathway

The breakdown of protein in the diet results in the release of Trp, which is further metabolized by intestinal flora into various compounds such as indole, indole-3-acetic acid (IAA), indole-3-propionic acid (IPA), indole-3-aldehyde (IAld), tryptamine, indole ethanol (IE), and indole-3-acetaldehyde [86]. Indole, the most abundant microbial tryptophan catabolite, is produced by a variety of Gram-positive and Gram-negative bacteria through the enzyme tryptophanase [87]. For instance, *Lactobacillus* and *Bifidobacterium* are known to generate indole-3-acetic acid, while *Lactobacillus* specifically produces indole-3-aldehyde. Additionally, *Clostridium botulinum*, *Clostridium sporogenes*, and *Peptostreptococcus anaerobius* are associated with the production of indole-3-propionic acid. These derivatives serve significant roles in microbial metabolism and intercellular communication within microbial communities. Recent research has highlighted indole and its derivatives as crucial molecular mechanisms in both the pathogenesis and treatment of depression. In a clinical experiment involving 44 subjects with severe or morbid obesity and no clinically relevant neuropsychiatric diseases, the relationship between the levels of plasma Trp and

indole metabolites and depressive symptoms was evaluated [88]. The results indicated that the serum hsCRP level was elevated, whereas the concentrations of Trp and indole were decreased. Specifically, the lower levels of indole-3-formaldehyde (IAld) were associated with more severe depressive symptoms. Numerous studies currently suggest that probiotics can alleviate depression by modulating the mental health of the host through indole and its derivatives. In an animal experiment, Anders et al. used compound probiotics to relieve the depression-like behavior of rats by increasing the level of indole -3- propionic acid [89]. Indole-3-propionic acid serves as an effective neuroprotective agent against a range of oxidative toxins. It effectively alleviates and inhibits central nervous system inflammation, showing promise in combating conditions like Alzheimer's disease [90]. Contrary to this, certain studies have indicated that certain microorganisms can trigger depression by means of indole metabolism. *Gpr35^{-/-}* mice and individuals with depression exhibit elevated levels of *Parabacteroides distasonis*, which induces depression when transplanted into wild-type mice. Mice colonized with *Parabacteroides distasonis* displayed a reduction in indole-3-formaldehyde (IAld) and an elevation in indole-3-lactic acid (ILA), both derived from distinct branches of the tryptophan bacterial catabolic pathway. IAld and ILA exerted opposing effects on the neuroplasticity of the nucleus accumbens [17]. In another study, it was found that psychological stress triggers the sympathetic nerve, resulting in an increase in *Lactobacillus rhamnosus* within the intestine. This surge enhances the production of indole-3-acetate (IAA), which, in turn, disrupts the transferability of intestinal secretory cells [91]. Additionally, it impairs the mitochondrial bioenergy of intestinal stem cells, ultimately leading to damage in intestinal epithelial tissues. These findings indicate that it is feasible for microorganisms to regulate depression through indole metabolism in intestine.

3.2.1.2 Kynurenine Pathway

The Tryptophan-kynurenine metabolic pathway is responsible for degrading over 90% of tryptophan (Trp) in the body. Activation of the key metabolic enzyme, indoleamine 2,3-dioxygenase (IDO), in an inflammatory environment triggers the kynurenine pathway. This activation results in alterations to a series of neuroactive metabolites such as kynurenine, 3-hydroxykynurenine, and quinolinic acid, which are significantly associated with depression and other diseases [92]. Moreover, the "Serotonin Hypothesis" of depression posits that elevated steroid levels in the blood can trigger the activation of liver TRP-pyrrolase (TDO) [93]. This activation, in turn, accelerates the metabolism of the tryptophan-kynurenine pathway, leading to a reduction in serotonin production and subsequently impacting neurological function. Paul et al.'s research discovered that the plasma levels of picolinic acid (PIC), the KYNA/QUIN acid ratio, and PIC/QUIN in MDD patients were low [94]. Conversely, the level of QUIN was high, indicating abnormal pathways in both peripheral and central kynurenine pathways in major depression. One of the current mechanisms through which probiotics may regulate depression involves influencing the canine uric acid pathway. Feng et al.'s research revealed that *Bacillus licheniformis* reversed depression-like behavior in rats subjected to chronic unpredictable stress [95]. The study highlights a significant decrease in kynurenine, norepinephrine, and glutamic acid levels, alongside an increase in tryptophan, dopamine, epinephrine, and

γ -aminobutyric acid (GABA) concentrations in the brain. Notably, KYNA is predominantly synthesized in astrocytes through the downstream metabolism of KYN, while microglia are responsible for the synthesis of 3-HK and QUIN, its subsequent product [96, 97]. It is essential to note that QUIN acts as an agonist of the NMDA receptor, triggering a cascade of neurotoxic effects, which represents a critical mechanism in depression [98]. Probiotics prove effective in relieving depression by inhibiting the downstream metabolism of indoleamine 2,3-dioxygenase (IDO), tryptophan 2,3-dioxygenase (TDO), and kynurenine. An animal experiment demonstrated that administering *Roseburia intestinalis* to mice significantly ameliorated depression induced by chronic restraint stress (CRS) [16]. This improvement was linked to the notable inhibition of key enzymes responsible for Kynurenine production, such as indoleamine 2,3-dioxygenase 1 (IDO1), and Quinolinic acid production, including 3-hydroxy-o-aminobenzoic acid 3,4-dioxygenase (3HAO), thus reducing the levels of kynurenine and quinolinic acid. Additionally, *Roseburia intestinalis* played a crucial role in safeguarding against CRS-induced synaptic loss, microglia activation, and astrocyte maintenance.

3.2.1.3 Serotonin Production

Depression is the result of abnormal serotonin (5- hydroxytryptamine or 5-HT) in the brain, which has been influenced for decades, including selective serotonin reuptake inhibitors, which are also the main prescription drugs for depression [99]. The emerging recognition of the impact of intestinal microflora on behavior highlights a significant trend. The relationship between tryptophan, serotonin, and gut health underscores the potential importance of intestinal alterations in the pathophysiology of human central nervous system diseases [100]. Probiotics play a crucial role in regulating depression primarily through their influence on the serotonin production pathway. Tian et al. discovered that *Bifidobacterium breve* can stimulate intestinal chromaffin cells to increase the secretion of 5-hydroxytryptophan, a precursor of serotonin synthesis that can traverse the blood-brain barrier [4]. This stimulation can potentially lead to a significant impact on serotonin production in the brain. Similarly, Zeng et al.'s research discovered that the secretion of *Lactobacillus pentosus* LPQ1 can notably elevate the level of 5-hydroxytryptophan in intestinal chromaffin cells [101]. This effect primarily occurs because probiotics can markedly enhance tryptophan hydroxylase 1/2 (Tph1/2) levels, consequently leading to an increase in the content of 5-hydroxytryptophan [16, 37, 102]. Moreover, probiotics have the potential to influence serotonin receptors and contribute to their regulation. Current research reveals that among the 14 subtypes of 5-HT receptors, at least 5 are notably involved in various physiological processes [103]. Of these subtypes, the 5-HT1ARs is gi/o-coupled metabotropic receivers. Upon activation, 5-HT1ARs can inhibit cyclic adenosine monophosphate (cAMP) levels, thereby suppressing neuronal activity [104]. The 5-HT1A receptor predominantly acts as a somatic dendritic receptor located on neurons within the raphe nucleus responsible for serotonin production. Furthermore, it serves as a postsynaptic heteroreceptors, facilitating local neuromodulation effects in several brain regions characterized by serotonergic projections [105]. This dual functionality highlights the critical role of the 5-HT1A receptor in mediating essential neurophysiological functions across diverse brain

regions. Animal experiments indicate that the modified outer membrane protein Amuc_1100 from *Akkermansia muciniphila* can elevate serotonin (5-HT) levels and its receptor 5HTR1A in depressed mice [49]. The alteration in 5-HTR1A levels influences CREB1, subsequently impacting downstream Brain-Derived Neurotrophic Factor (BDNF) levels. Therefore, Amuc_1100 may alleviate depression by enhancing the 5-HTR1A-BDNF-CREB signaling pathway in chronic unpredictable mild stress (CUMS) mice. Moreover, studies on *Bifidobacterium longum subsp. infantis* strain CCFM 687 have shown that the Brain-Derived Neurotrophic Factor (BDNF) in the prefrontal cortex also can be enhanced via the 5-HT1A-CREB-BDNF pathway [106]. This mechanism contributes to alleviating depression in mice. The findings underscore the potential of probiotics in alleviating depression.

3.2.2 SCFAs

Short-chain fatty acids (SCFA) play a crucial role in the interaction between diet and intestinal microflora. The discovery that SCFA can act as natural ligand receptors for various cell and tissue types has heightened interest in their role as signaling molecules between gut bacteria and the host [107]. Furthermore, evidence suggests that SCFA also have a regulatory function in local, intermediate, and peripheral metabolism [108-110]. Recent studies have revealed that short-chain fatty acids may play a role in regulating mood and alleviating depression. A recent clinical investigation revealed significant alterations in serum intestinal microbial profiles and short-chain fatty acid levels in patients with Major Depressive Disorder (MDD) [111]. Probiotics have been identified as potentially alleviating depression by modulating short-chain fatty acids, a mechanism that has been discovered in recent years. Short-chain fatty acids (SCFAs) function as endogenous ligands for G protein-coupled receptors (GPCRs) and modulate gene expression by inhibiting histone deacetylase (HDACs). Specifically, SCFA acts as a natural ligand for a subset of GPCRs initially identified as GPR43 and GPR41, now rebranded as Free Fatty Acid Receptor 2 (FFAR2) and FFAR3, respectively [112]. Upon binding to these receptors, SCFAs trigger inhibitory and immunomodulatory responses within the intestinal vagus nerve (Figure 1f). Notably, acetic acid, propionic acid, and butyric acid exhibit the remarkable ability to pass through the blood-brain barrier. This unique feature empowers SCFAs to regulate the neuroendocrine system effectively, mitigating hyperactivity in the hypothalamic-pituitary-adrenal (HPA) axis and thereby alleviating symptoms associated with depressive behavior (Figure 3) [113]. Recent research has unveiled an additional facet of SCFAs functionality by demonstrating their impact on neurotransmitter secretion, particularly affecting serotonin and dopamine levels [114]. The animal experiment demonstrated that *Lactobacillus plantarum* R3-6 increased the secretion of BDNF by modulating short-chain fatty acids [43]. Additionally, it suppressed the excessive activity of the hypothalamus-pituitary-adrenal (HPA) axis, leading to enhancements in immune function and a reduction in oxidative stress. These effects ultimately safeguarded the hippocampus of the mice from harm. Moreover, the data indicates that probiotic therapy has the potential to fully alleviate anxiety and depression-like behaviors triggered by maternal separation in mice [115]. This therapy can restore a balanced neuroinflammatory state through its impact on butyrate levels, leading to the reestablishment of microglial

homeostasis and ultimately promoting neurogenesis. Research on probiotics alleviating depression through short-chain fatty acids has notably focused on butyric acid, propionic acid, and acetic acid. Specifically, adjusting the level of butyric acid has shown to effectively reverse depression-like behavior. Certain studies have shown that supplementing mice with *Clostridium butyricum* can effectively reverse depression-like behavior, highlighting the potential of butyric acid in alleviating depression [40, 116, 117]. The discoveries broaden our understanding of utilizing probiotics to modulate mood states and underscore the significant relationship between gut microbiota and depression.

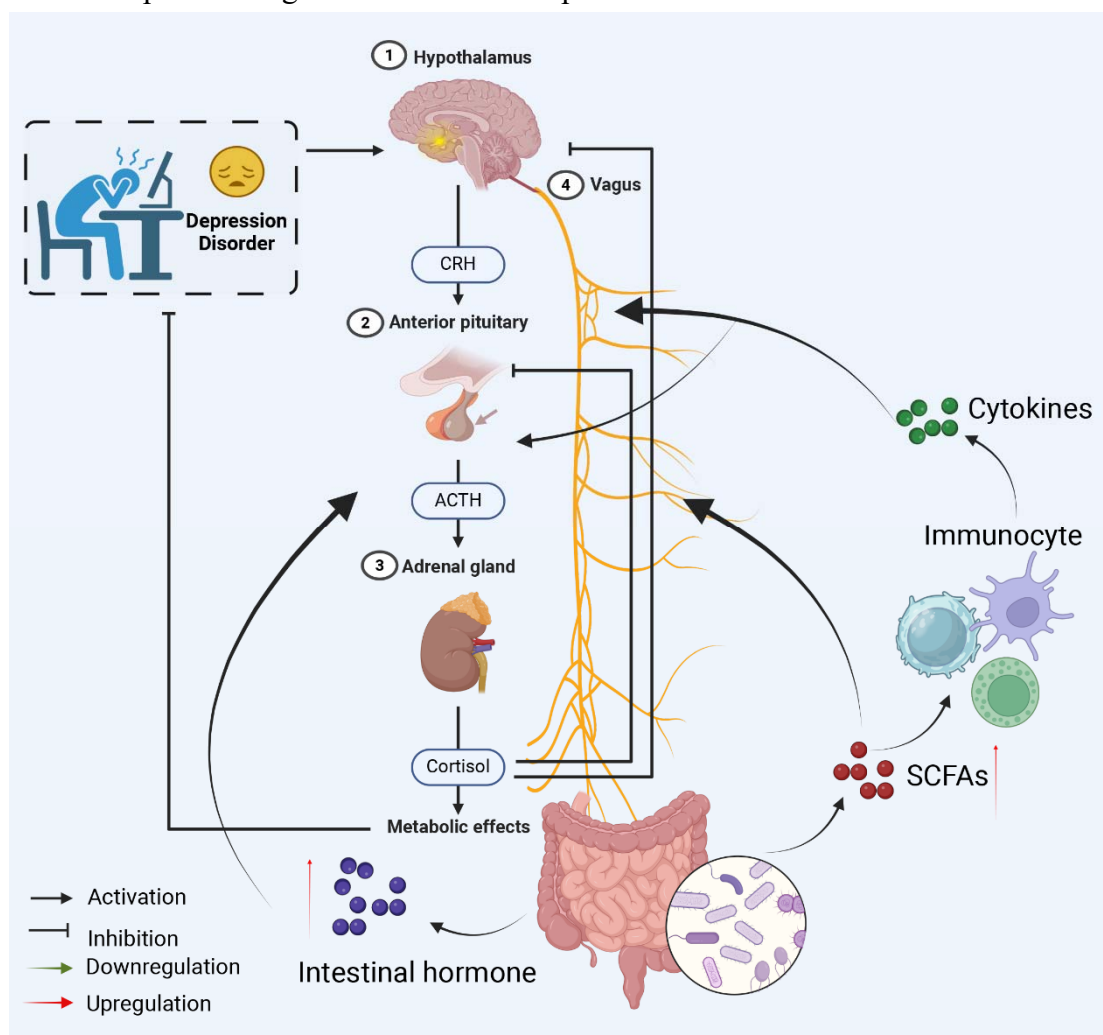


Fig. 3. Probiotics alleviate depression via neuroendocrine system. Probiotics can regulate the HPA axis by metabolizing intestinal hormones and short-chain fatty acids (SCFAs). Among them, short-chain fatty acids can act through the vagus nerve or regulate cytokines.

3.2.3 Bile acids

Hepatocytes synthesize bile acids, with their metabolism controlled by farnesol X receptor (FXR) and G protein-coupled receptor (TGR5). These regulatory mechanisms extend beyond the gastrointestinal tract to impact various tissues and organs, including the brain. Elevated serum bile acid levels can enhance interactions between central FXR and TGR5 across the blood-brain barrier or activate intestinal FXR and TGR5 to release fibroblast growth factor 19 (FGF19) and glucagon-like peptide-1 (GLP-1), respectively (Figure 2b) [118]. Preclinical studies utilizing chronic social defeat stress (CSDS) and chronic restraint stress

(CRS) models have demonstrated that TGR5 exerts bidirectional regulatory control over GABAergic neuronal excitability in the lateral hypothalamic area (LHA). This regulatory mechanism is mediated through extracellular signal-regulated kinase (ERK)-dependent phosphorylation of Kv4.2 channels, which are voltage-gated potassium channels that critically modulate neuronal firing thresholds and action potential repolarization dynamics ^[119]. The interaction between the bile acid signal transduction process and the metabolism of intestinal microflora and the host highlights the potential to regulate bile acid levels using probiotics ^[120]. This modulation can in turn influence mood and behavior through the gut-brain axis. Research by Qian et al. demonstrates that *Bifidobacterium breve* CCFM1025 has the ability to alleviate anxiety-like behavior induced by Chronic Unpredictable Mild Stress (CUMS) ^[121]. This effect could be attributed to the bacterium's capacity to regulate intestinal metabolites effectively. Specifically, the study reveals a notable rise in bile acid and tryptophan metabolites in both the intestinal contents and serum of mice when treated with this strain of *Bifidobacterium*. The findings suggest that through its impact on bile acid metabolism, *Bifidobacterium* may offer a promising avenue for modulating intestinal microflora and achieving emotional regulation. Nevertheless, the mechanistic links between probiotic-mediated modulation of bile acid metabolism and their antidepressant efficacy remain underexplored, particularly regarding the spatiotemporal dynamics of gut-brain axis communication and the precise molecular underpinnings through which microbial-derived bile acid derivatives influence central neurotransmission.

3.2.3 Ammonia

Ammonia is a waste product produced by human metabolism, particularly during the breakdown of proteins. When ammonia levels in the body become elevated, it can have neurotoxic effects on the brain, leading to conditions such as hepatic encephalopathy ^[122]. The liver normally converts ammonia into urea for excretion, but if the liver is damaged or not functioning properly, ammonia levels can rise, causing potential harm to the central nervous system ^[123]. The most recent research by Wang et al. illustrates that endogenous ammonia plays a beneficial role in regulating host stress vulnerability ^[124]. The findings from animal experiments indicate that abnormally low blood ammonia levels restrict the availability of glutamine in the brain. Astrocyte-derived glutamine undergoes enzymatic conversion to glutamate, serving as the primary precursor for γ -aminobutyric acid (GABA) biosynthesis within presynaptic GABAergic terminals. Notably, disruption of this glutamine-glutamate-GABA metabolic axis compromises cortical GABA synthesis efficiency, thereby inducing synaptic neurotransmission deficits that heighten stress susceptibility through impaired inhibitory circuit regulation. It is important to highlight that the depression-like behavior observed in mice due to low ammonia levels can be reversed by supplementing *Streptococcus thermophilus*. This is possible because *Streptococcus thermophilus* is a urease-producing strain, and its supplementation significantly influences ammonia metabolism in the intestines of mice, thereby reversing the depression-like behavior caused by low ammonia in the host (Figure 2c) ^[124, 125]. This discovery offers a fresh outlook on understanding the role of endogenous ammonia in the central nervous system and introduces a novel mechanism for alleviating depression.

3.2.4 Purine metabolism

Purinergic signal transduction involves nucleotides acting as extracellular signal molecules. This signaling pathway comprises four subtypes of P1 receptors (adenosine receptors), seven subtypes of P2X ion channel receptors, and eight subtypes of P2Y G protein-coupled receptors. The preclinical study demonstrated that astrocyte-mediated ATP/P2X7R signaling coordinates with NLRP3 inflammasome activation to drive stress-induced IL-1 β release, which subsequently triggers depressive-like behavioral phenotypes via prefrontal cortical synaptic remodeling ^[126]. The study revealed that the brain's innate immune system detected psychological stress by triggering a cascade reaction involving ATP/P2X7R-NLRP3 inflammatory corpuscles. Similarly, He et al. discovered a connection between abnormal purine metabolism and olfactory bulb dysfunction in chronically unpredictable mild stress (CUMS) depressed rats ^[127]. This pathway sheds light on how the brain responds to stress at a molecular level, influencing both inflammatory responses and behavioral changes associated with depression. Currently, numerous studies have indicated that alterations in the structure of intestinal flora can result in metabolic disorders, impacting the regulation of purine metabolic enzymes and the secretion of inflammatory cytokines ^[128-130]. These findings suggest a potential association between changes in intestinal microflora and purine metabolism. Additionally, the use of probiotics for intervention and regulation shows promise as a strategy in this context. Xu et al.'s research demonstrates that *Lactobacillus paracasei* CCFM1229 and *Lactobacillus rhamnosus* CCFM1228 can alleviate depression-like behavior in mice by decreasing the activity of xanthine oxidase in the brain and enhancing the activity of adenosine deaminase in the liver ^[131]. Additionally, the β chain of nucleoside diphosphate reductase (nrdB), a pivotal gene in purine metabolism, is present in *Bifidobacterium breve* CCFM1025 ^[132]. This bacterium successfully decreased the levels of xanthine and xanthine nucleoside in the serum and brain of stressed mice (Figure 2d). Furthermore, it down-regulated the expression of the adenosine receptor gene (Adora2b), leading to the inhibition of microglia overactivation. The existing evidence highlights the potential for probiotics to modulate purine metabolism as a means to alleviate depression. However, the scarcity of related studies underscores the necessity for more comprehensive research to substantiate these claims.

It is crucial to acknowledge that while the discovery of these molecular mechanisms offers a new avenue for probiotics in regulating depression, much of the supporting evidence stems from animal experiments. Consequently, there are limitations as extrapolating these findings to human research may yield divergent outcomes. Moreover, investigations into how probiotics influence depression via metabolic pathways remain relatively rudimentary, often focusing solely on superficial markers within the intestines and brain without delving deeply into intricate internal mechanisms. Furthermore, current research on the metabolic mechanisms underlying the antidepressant effects of probiotics is primarily limited to functional assessments, with insufficient mechanistic exploration at the molecular level. Comprehensive investigations employing whole-genome sequencing and proteomic approaches to elucidate these mechanisms at the gene and protein levels would establish a more robust and reliable theoretical foundation for clinical applications.

3.3 Probiotics regulate depression through neuroendocrine system

The physiological response to stress heavily relies on the activation of corticotropin-releasing hormone (CRH) neurons by various neurotransmitters. PACAPergic fibers originating from the brainstem parabrachial nucleus demonstrate inverse topographic correlation with hypophysiotropic CRH neuron projection density in the hypothalamic paraventricular nucleus. Mechanistically, PACAP binding to PAC1 receptors activates adenylate cyclase-mediated cAMP/PKA/CREB signaling cascade, which modulates CRH transcriptional dynamics through chromatin remodeling at *Crh* promoter regions. A Single nucleotide polymorphism (SNP) in the pituitary adenylate cyclase activating polypeptide (PACAP) and PAC1 receptor gene has been linked to several mental illnesses, potentially influenced by exposure to stressors and/or an imbalance in the hypothalamus-pituitary-adrenal (HPA) axis ^[133]. Studies with mice have shown that exposure to repeated mutant stress can elevate the expression of PACAP and its homologous PAC1 receptor in the striated peripheral bed nucleus of the stria terminalis (BNST). This region is implicated in anxiety, depression-related behaviors, and HPA axis activity ^[134]. Researchers suggest that alterations in BNST PACAP signal transduction could play a role in the changes in emotional behavior and HPA axis imbalance associated with anxiety and emotional disorders ^[135]. Furthermore, BNST PACAP signal transduction may be linked to plasma corticosterone levels.

Probiotics primarily influence the HPA axis through their own components or metabolites, regulating the immune system and promoting the release of intestinal hormones (Figure 3). Activation of TLR2 by lipoteichoic acid (LTA) on microbial surfaces initiates peripheral immune responses, triggering a neuroinflammatory process in the brain that correlates with the down-regulation of blood-brain barrier (BBB) components and the activation of the HPA axis ^[136]. As a structural component of bacterial cell walls, peptidoglycan (PGN) physically restricts the exposure of underlying pathogen-associated molecular patterns (PAMPs) such as lipoteichoic acid through its cross-linked glycan meshwork ^[137]. Structural modifications to peptidoglycan can impact the innate immune system's ability to detect bacteria, potentially allowing bacterial evasion and alteration of host defense mechanisms, thereby affecting intestinal permeability and activating the HPA axis. Moreover, short-chain fatty acids metabolized by probiotics can stimulate intestinal endocrine cells to release hormones and neuropeptides, including glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) ^[138]. These effects are mediated through the activation of G protein-coupled receptors (GPCRs) such as GPR43, GPR41, and GPR109A. Furthermore, these fatty acids play a crucial role in the maturation and function of microglia ^[139]. Hence, adjusting the intestinal microflora to impact the HPA axis represents a potential mechanism through which probiotics could potentially alleviate symptoms of depression. In an animal experiment, the administration of *Lactobacillus helveticus* NS8 demonstrated the ability to reduce plasma corticosterone (CORT) and adrenocorticotrophic hormone (ACTH) levels in mice subjected to chronic constraint stress ^[140]. Additionally, this treatment restored serotonin (5-HT) and norepinephrine (NE) levels in the plasma and hippocampus. Furthermore, compared to chronically stressed rats, mice receiving *Lactobacillus helveticus* NS8 exhibited increased expression of brain-derived neurotrophic factor

(BDNF) mRNA in the hippocampus, thereby improving depression-like behavior induced by chronic constraint stress. It's interesting how Schell et al. demonstrated that male mice fed with a high-fat diet (HFD) exhibited heightened anxiety and depression-like behavior ^[141]. Remarkably, the administration of *Lactobacillus rhamnosus* not only reversed the reduction of tyrosine hydroxylase caused by HFD but also regulated the expression of the cholecystokinin gene in the dopaminergic brain region, thus normalizing these aspects. The results suggest that potent probiotics can suppress the release of hormones from the HPA axis and alleviate the deficiency of monoamine neurotransmitters associated with depression. In addition, Li et al.'s research revealed that mice experiencing loperamide-induced constipation also exhibited stress behavior ^[142]. Interestingly, *Ruminococcus gnavus* was found to reverse this phenomenon, potentially through its regulation of genes such as intestinal muc2, c-kit, and sert. Moreover, *Ruminococcus gnavus* was associated with the production of somatostatin (SS) and motilin (MTL), which might contribute to alleviating the stress behavior observed in constipated mice. This discovery offers a novel opportunity for probiotics to potentially regulate depression.

In the study on probiotics alleviating depression via the neuroendocrine system, the precise mechanism by which probiotics regulate the neuroendocrine system remains unclear. This phenomenon could potentially be associated with the modulation of the enteric nervous system. The enteric nervous system (ENS) is a vast and intricate network capable of autonomously regulating gastrointestinal functions independently of the central nervous system (CNS). Serving as a pivotal mediator or participant, the ENS is increasingly recognized for its significant role in nervous system disorders ^[143]. Hence, the role of probiotics in modulating the neuroendocrine system and enhancing intestinal hormone production is likely achieved through the regulation of the enteric nervous system. However, current research on this mechanism is limited, underscoring the need for more comprehensive investigations to elucidate the specific pathways involved. Such endeavors are crucial for establishing a robust theoretical framework to potentially alleviate depression.

4. Clinical significance of probiotics in relieving depression

Some strains have been identified as potential candidates for alleviating depression by modulating the levels of intestinal flora, serotonin, brain-derived nutritional factors, and inflammatory factors. The most prevalent probiotics in clinical studies are *Lactobacillus* and *Bifidobacterium* ^[120]. The results of the study on adults with severe depression indicate that consuming freeze-dried powder containing *Bifidobacterium breve* CCFM1025 could potentially be beneficial ^[144]. The mechanism behind these benefits may be connected to alterations in intestinal microflora and tryptophan metabolism. Moreover, a randomized, double-blind controlled study conducted on patients with major depression revealed that the consumption of a mixture of *Lactobacillus helveticus* and *Bifidobacterium longum* significantly reduced both the BDI score and the kynurenine/tryptophan ratio ^[145]. The data from Table S2, summarizing 74 clinical trials on probiotics for alleviating depression and anxiety, revealed positive results. Out of the 67 studies analyzed, it was

consistently observed that supplementing with probiotics, either through supplements or probiotic-rich foods, had a positive impact on the emotional well-being of both patients and healthy individuals. To sum up, these studies show that probiotics are powerful candidates to relieve depression and improve the mental health of hosts. At the same time, there are also many clinical research results showing unsatisfactory results. The observed heterogeneity in probiotic efficacy may be attributable to variations in study design, sample size, placebo controls, and diagnostic criteria for mental health disorders. This inconsistency underscores that the beneficial effects of probiotics on host mental health remain a subject of active investigation. Consequently, it remains highly important to study the effect of probiotics in relieving depression. Researchers should have an in - depth understanding of the complex and variable pathology of depression, its delicate relationship with intestinal health, and strain-specific characteristics, so as to utilize probiotics for precise regulation and effectively achieve the effect of relieving depression.

5. Overview of microorganisms related to depression

5.1 *Bifidobacterium*

Bifidobacterium is indeed one of the earliest microorganisms to colonize the human gastrointestinal tract, offering numerous health benefits to its host. Due to its reputation for promoting health, *Bifidobacterium* has become a key ingredient in many functional foods. Its natural presence in a range of niches directly or indirectly linked to the gastrointestinal tract, such as the human mouth, infant intestine, and breast milk, further emphasizes its importance in maintaining overall health ^[146]. At present, certain animal and clinical studies indicate that *Bifidobacterium* possesses the potential to alleviate depression. *Bifidobacterium*, a well-established probiotic, is recognized for its wide-ranging health benefits. It mitigates host inflammation through the production of short-chain fatty acids—a mechanism also implicated in the alleviation of depression. Research demonstrates that *Bifidobacterium breve*, *Bifidobacterium bifidum* and *Bifidobacterium adolescentis* can ameliorate depressive-like behaviors in LPS-induced mice by lowering the levels of key inflammatory cytokines, including matrix metalloproteinase-2, C-reactive protein, IL-1, IL-6, NF- α , and NF- κ B ^[12, 51, 53, 60]. In addition to immunomodulation, certain *Bifidobacteria* have been found to regulate neurotransmitters via metabolic pathways such as tryptophan, bile acid, and purine metabolism, thereby alleviating depression-like behaviors in hosts ^[106, 121, 132]. However, some cohort analysis results show that *Bifidobacterium* is positively correlated with depression, especially *Bifidobacterium longum* ^[1, 147]. Some indicators show that it is negatively correlated with *Bifidobacterium*. Clearly, this differs from the outcomes of some animal and clinical trials. These findings further demonstrate that different *Bifidobacterium* strains exhibit considerable strain specificity. Not all strains confer beneficial effects; some may even have potential adverse consequences. This observation highlights that researchers should not only identify and screen strains with specific antidepressant properties but also further investigate the increased abundance of *Bifidobacterium longum* observed in patients with depression, in order to clarify the

underlying mechanisms behind this phenomenon. Clarifying these mechanisms is of great significance for understanding the pathology of depression and exploring effective treatments.

5.2 *Lactobacillus*

One of the most crucial sources of probiotics is *Lactobacillus*, which is also the principal component of probiotics with the function of emotional regulation [15]. The main probiotic strains include *Lactobacillus pentosus*, *Lactobacillus plantarum*, *Lactobacillus murinus*, *Lactobacillus helveticus*, *Lactobacillus rhamnosus*, *Lactobacillus kefirianofaciens*, *Lactobacillus paragasseri*, *Lactobacillus gasseri*, and *Lactobacillus reuteri* [91, 101, 148–154]. The antidepressant mechanisms of these strains' viable bacteria or their postbiotics primarily involve immunomodulation and the serotonin (5-HT) metabolic pathway. Immunomodulation acts by reducing the levels of inflammatory cytokines, including IL-1 β , IL-6, IL-18, and TNF- α . This reduction subsequently alleviates the activation of the NF- κ B signaling pathway, ultimately mitigating neuroinflammation and depression-like behaviors. In the serotonin metabolism pathway, enhancing TPH1 expression in intestinal epithelial cells can regulate serotonin levels and modulate the protein expression of BDNF and its receptors (TrkB and the NMDA receptor NR1 subunit). This regulation alleviates stress-induced activation of the ERK1/2 and p38 MAPK signaling pathways, thereby reducing depression-like behavior in the host. Moreover, complex interactions exist among these regulatory pathways. One example is how modulation of serotonin levels by probiotic strains can influence inflammatory factor levels in the host [140]. This integrated action ultimately helps mitigate neuroinflammation and associated depression-like behaviors. Similarly, certain strains within the *Lactobacillus* genus also influence host mental health. Wei et al. found that psychological stress activates sympathetic output, which significantly enriches the intestinal symbiotic bacterium *Lactobacillus murinus* [91]. This increase leads to elevated production of indole-3-acetate (IAA), resulting in a transferable loss of intestinal secretory cells. Hence, specificity of the strains are indeed important issues that need to be addressed. Furthermore, the safety profile of probiotic strains remains a critical concern that must be addressed. Bacteremia, which is the presence of bacteria in the bloodstream, is a potential risk associated with some *Lactobacillus* strains [155]. Additionally, the effectiveness of certain strains in clinical settings and their specificity for certain diseases may vary [156]. Further research and evaluation are necessary to better understand and manage these concerns.

5.3 Other

Moreover, the present study further discovered that certain next-generation probiotics possess an efficacious impact on alleviating depression, such as *Akkermansia muciniphila*, *Clostridium butyricum*, and others. However, the safety issues confronted by the next generation of probiotics are more salient. Presently, numerous reports indicate their potential risks [157]. The potential acute and long-term risks, along with the risk of its application among vulnerable groups, are all issues confronted by the next generation of probiotics. Additionally, the difficulty in cultivation is also a crucial factor restricting their application [158]. Furthermore, currently, the functional assessment of it mainly relies on animal experiments, and there is no

corresponding clinical trial to verify its efficacy in the human body. Therefore, more in-depth clinical trials are needed to evaluate its effectiveness and safety in the human body.

6. Probiotic related products for relieving depression currently on the market

Up to now, some probiotics with high safety and good effect in animals and clinic have been commercialized. The emergence of "Happy Probiotics" in the market, featuring beneficial strains such as *Lactobacillus plantarum* PS128, *Bifidobacterium bifidum* B11, *Lactobacillus paracasei* PS23, *Lactobacillus rhamnosus* HN001, *Bifidobacterium breve* M-16V, and *Lactobacillus helveticus* R0052, is a noteworthy development. Products incorporating these strains, available in the form of dietary supplements and solid drinks, signify a significant stride in leveraging probiotics for mental health benefits (Figure 4). However, there are still some issues that need to be addressed urgently. Firstly, the core of probiotics lies in the efficacy of strain functions, and many studies focus on animal research, lacking clinical trial results to ensure their functionality in the human body. Thus, many candidate psychobiotic strains require further research. Secondly, safety is a challenge faced by many probiotics currently. Current safety assessments relying solely on traditional toxicological approaches remain insufficient. A comprehensive strategy should integrate whole-genome sequencing to scrutinize potential virulence factors, toxin production, and antibiotic resistance genes, while also clarifying their taxonomic distribution across species and strains. Furthermore, evaluations must address potential risks to host intestinal barrier integrity, gut microbiota ecology, and metabolic homeostasis. Additionally, it is necessary to further clarify the functional mechanism of the strain itself or its metabolites, and develop postbiotic products with higher safety and stability. Thirdly, many probiotics have strict requirements for culture conditions, which restricts their development potential. Therefore, strain domestication and optimization of culture conditions should be considered as potential strategies for enhancement. Adaptive laboratory evolution could be employed to improve functional properties, while refined fermentation parameters may increase yield and stability. Fourthly, it is difficult for a single probiotic to treat depression as an independent treatment method. Combining multiple strains, drugs, or with some traditional Chinese medicines with the same origin of medicine and food may be a more effective approach. Hence, further studies are needed on the combination of suitable drugs and strains in the future. Finally, probiotics, or as an effective additive in functional foods, should also consider their extreme environmental tolerance and fermentation performance. To maximize the therapeutic potential of probiotics, it is crucial to conduct further research to address these problems. This will enable us to better understand the functionality of probiotics in the human body, enhance their safety and stability, optimize their culture conditions, and explore more effective combinations for the treatment of depression. Additionally, integrating probiotics into a diverse range of foods can offer innovative solutions for managing psychological challenges on a larger scale.

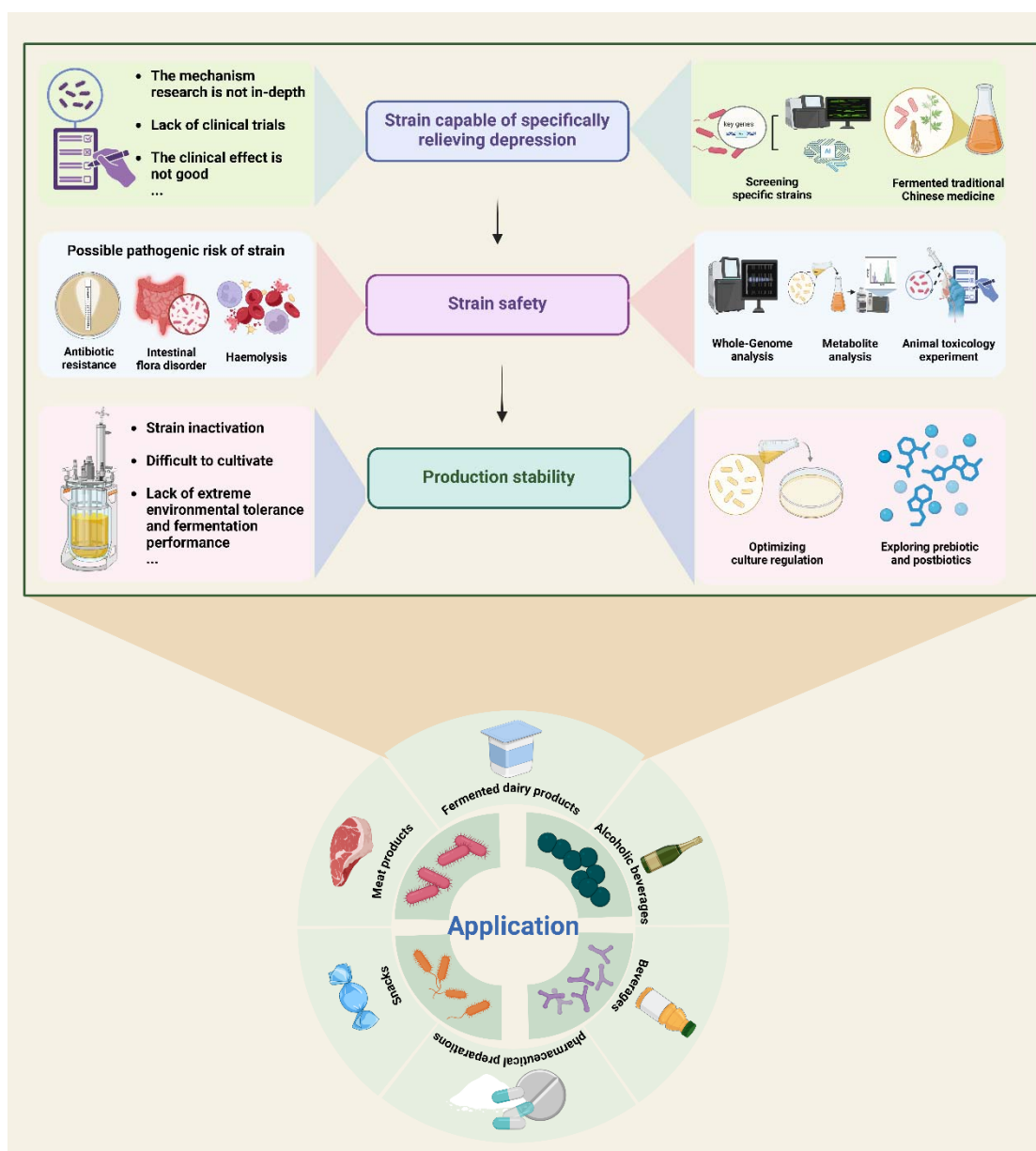


Fig. 4. Problems and Strategies in the Application of Probiotics for Alleviating Depression.

7. Conclusions and perspectives

In a word, depression remains a complex disease that perplexes people worldwide. Current research demonstrates that probiotic supplementation can positively modulate emotional states, mitigate stress, and reduce anxiety, with several clinical studies confirming their therapeutic relevance. The rapid development of bioinformatics and omics technology offers detailed understandings of how to regulate the immune system, microbial metabolites, and the neuroendocrine system. This knowledge is conducive to exploring new microorganisms and related metabolites with beneficial properties. However, given the complex nature of the etiology of depression and the lack of conclusive findings, there are still certain limitations in understanding the application of probiotics in relieving depression. Practical applications may be restricted by several challenges, such as the strains capable of specifically relieving depression under complex

pathological conditions, the stability during the production and application processes, and the safety risks arising from gastrointestinal micro-ecological interactions.

In view of these limitations, in future research, researchers should consider screening more highly - efficient probiotics for relieving depression. At the same time, they should conduct in - depth studies on the pathology of depression and the mechanisms of probiotics in order to identify the key genes, proteins, or substances of probiotics. Thus, they can specifically screen probiotics with relevant functions by using genome - mining strategies like metagenomics. Additionally, the significant progress in the field of artificial intelligence makes it possible to rapidly screen strains with specific proteins or genes, thereby minimizing the time - consuming and labor - intensive trial - and - error process. Consequently, in the future, developing an accurate calculation model to effectively screen specific strains is a promising strategy. Moreover, due to the limited number of participants in some clinical studies, it is necessary to further expand the research scope to clarify the full clinical benefits of probiotics. Furthermore, the safety risks associated with metabolism and the interaction with gastrointestinal microecology are also an inescapable challenge. It is crucial to systematically assess the safety risks related to probiotics and their metabolites for their application in the food and other industries, including considerations of the effects on the intestinal microflora, toxicology, and immunogenicity. Therefore, it is essential to combine whole - genome sequencing with other technologies for determining the virulence, toxins, and impacts on different physiological indexes of the strain and its metabolites. Generally, probiotics have broad potential in relieving depression. To solve these problems, researchers need to adapt to the changes of the times and combine multi - angle technologies to continuously strengthen and develop related research, paving the way for the safe and effective application of probiotics.

Declaration of Competing Interest

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.

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Appendix A. Supplementary data

Supplementary Table S1. Overview of the mechanism of probiotics in relieving anxiety and depression-like behavior in animal models.

Supplementary Table S2. Summary of clinical research on probiotics alleviating anxiety and depression.

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