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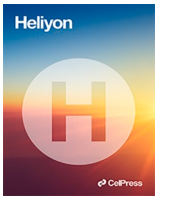

Review article

Ameliorating effect of psychobiotics and para-psychobiotics on stress: A review on *in vivo* and clinical studies and mechanism of action

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ABSTRACT

Chronic stress can negatively affect cognitive ability, behavioral functions, and gut microbiota balance. The gut microbiota communicates with the brain through the gut-brain axis to influence brain responses and behavior. The positive effects of psychobiotics and para-psychobiotics (viable and non-viable probiotics, respectively) on decreasing stress and stress-related disorders have been approved, previously. It has been suggested that the benefits of such probiotics are provided through different probable routes including the hypothalamic-pituitary-adrenal (HPA) axis, the immune system modulation, and the production of neurotransmitters. The recent review aims to explore the different potentials of psychobiotics and para-psychobiotics based on recent literature. The recent literature revealed that psychobiotics and para-psychobiotics could be considered as an alternative to psychotropic drugs which present dependence and side effects compared to chemical drugs.

1. Introduction

Stress is recognized as a state that exists in daily life and is caused by different environmental and individual factors, such as chronic diseases, bereavement, and examinations. Stress occurs as a result of facing an incompatible environment that exceeds individual adaptive capacity [1]. Stress exists in our daily lives and influences us all the time. Positive stress refers to the stress that we can control. Positive stress leads us to successfully adopt to environmental changes through different transient psychological and physiological reactions including anxiety, increased blood pressure, elevated heart rate, and tension [2]. Negative stress refers to uncontrolled, long-term, and high-level stress that imposes an adverse effect on mental and physical health and interrupts our daily life. Excessive and chronic stress leads to different mental and physiological health risks such as cardiovascular diseases, depression, asthma,

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emotional irritability, digestive diseases, and cancers [3]. Overall, stress is unavoidable in our daily lives. Indeed, looking for an effective method to decrease the adverse effects of stress on life has become an attractive aspect of recent research.

Advances in determining the health effect of microbial ecology have allowed scientists to appreciate the therapeutic role of microbial communities inhabiting different organs of the human body, which improves human overall health [4]. The population of bacteria sharing our body space is more than 10 times of human body cells (Wang et al., 2016). According to various scientific literature, symbiosis of human inhabit bacteria is essential for maintaining human normal physiological state. On the other hand, the loss of microbial balance in the human body may lead to diseases [5,6]. Recent literature has determined the role of bacteria inhabiting the gastrointestinal tract on the central nervous system (CNS), which can affect the host behavior and mind through the CNS. This is termed the microbiota-gut-brain axis (MGBA) [6–8]. Indeed, the microbial balance in the gut may lead to the healthy function of the CNS. MGBA can act as an information transmitter that interprets and transmits information from the periphery to the brain and back. In addition, psychological disorders such as stress can alter the gut microbiota, including the stability and diversity of microbial species [8]. Stress enhances the production of some bioactive factors such as cortisol, serotonin, and brain-derived neurotrophic factors, which affect the development of mental diseases [9]. Also, these bioactive factors can modify gastrointestinal flora. Furthermore, scientific literature has confirmed a relationship between gut flora and stress-associated illness. So, the regulation of the gut microbiota can prevent or treat stress-related diseases.

According to the WHO/FAO definition probiotic refers to viable microbes when administrated at an adequate amount can confer beneficial health effects on the host. Moreover, probiotics have been defined as viable, or non-viable microorganism or their metabolites when administered in an adequate amount can confer health effects [10]. In recent years, many types of research have confirmed the regulating effect of probiotics on brain function [11]. Probiotics play a major role in enhancing mental health through regulating and producing neurotransmitters and regulating factors such as tumor necrosis factor-α (TNF-α), serum corticotropin-releasing factor (CRF), cortisol, which is predicted to develop as a novel therapeutic method for relieving stress [12,13]. However, some studies have determined the influence of probiotics on stress resilience, but a few documents are focusing on the positive effect of viable and non-viable probiotics on decreasing stress and stress-related diseases, so we conducted a review for gathering the data from all randomized controlled trials that have been done to date, focusing the positive or adverse effect of viable and non-viable probiotics on stress.

2. Stress physiology

Stress is defined as any biological response to intrinsic or extrinsic stimulators [14]. The study of stress is difficult due to its widespread effect on the body. The physiological stability of organisms is maintained by adapting their internal milieu to unfavorable environmental demands [15]. Stress consists of a series of events that an organism follows to adapt to an unfavorable situation. Internal and external factors influence the internal milieu of an organism. Any event or factor which leads to stress is named as a stressor. The body adapts to a changing environment through elucidating a response. The sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis activate neurophysiological responses in the brain [16]. Every organism responds to stress through 3 consecutive stages alarm, adaptation, and recovery or exhaustion. The alarm stage is the stage that enables the organism to face and deal with abnormal situations. Indeed, prepares the organism to deal with or escape from an adverse situation. At this stage, the hypothalamus performs various consecutive functions: a. activates the autoimmune nervous system, b. releases corticotropin-releasing hormone (CRH) and stimulates the HPA axis, and c. secretes arginine vasopressin. Different reactions occur in

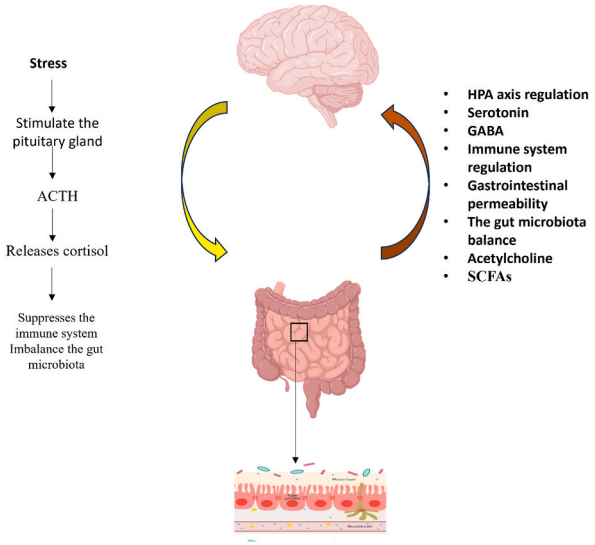

Fig. 1. The gut microbiom and mental health in a stressfull condition.

the brain, including the release of different hormones (noradrenalin, corticosterone, and adrenalin) which causes different changes such as increased heart rate, blood pressure, and blood sugar level [15]. CRH stimulates the anterior pituitary secret Adrenocorticotropin hormone (ACTH). The cortex of the adrenal glands is stimulated by ACTH and secret corticoids, which act as an energizing, urea production enhancer, appetite suppressor, immune system suppressor, depression feeling enhancer, and Blood pressure enhancer. The medulla of the adrenal releases epinephrine and norepinephrine, whose functions are similar to those secreted from the sympathetic nervous system. If the adverse situation continues and isn't removed, the body administers all its capabilities (continuous secretion of stress hormones, providing energy) for adapting to the stressful situation; this stage is the adaptation stage. At the adaptation stage, many physical, mental, and behavioral changes occurred. The recovery stage refers to the state that the body functions have succeeded in overcoming the adverse effect of a stressor (Fig. 1). Whenever the body resources is finished and are unable to recover the normal body function it leads to an exhausting stage. In respect of the long period exhausting stage, the body is at risk of serious health risk factors that may lead to hypertension, depression, and cardiovascular diseases [15].

3. Psychobiotics and para-psychobiotics

A bidirectional interaction exists between the brain and the gut microbiota. Gut microbiota is considered a community of microbes that inhabit the intestinal tract of mammals, and it contributes to different kinds of physiological phenomena. According to the evidence, the gut microbiota imbalance can cause depression and anxiety. In 2013, Dinan et al. introduced the term 'psychobioitic' as a class of viable probiotics. They defined psychobiotic as those living organisms, if adequate amounts of them are consumed by the host it improves his/her psychological health [17]. This new approach can be applied as a novel method for preventing and treating mental disorders. In addition, there is growing evidence that non-viable microbial cells confer beneficial mental health effects on humans and animals. The probable mechanism of these cells is attributed to a direct interaction between the microorganism cell components and host cells. The term para-psychobiotic refers to nonviable microbial cells that exert mental health when consumed in an adequate amount. This capability of nonviable probiotics opens a new window in front of food suppliers and scientists since the application of viable probiotics (psychobiotics) and maintaining their viability during production, storage and transportation are two major problems of producing probiotic food products.

3.1. The current psychobiotic administered in ameliorating stress

In the last few decades, probiotics are known as active microorganisms that can regulate brain function through several activities including regulating responses to stress, lowering the level of systemic inflammatory cytokines, regulating GABA receptors, producing GABA, normalizing the concentration of noradrenaline in the brain, decreasing brain limbic reactivity to negative stressors. In this field, most of *in vivo* trials have been done to investigate the functionality of probiotics in regulating brain functions and decreasing stress and stress-related disorders have been reviewed. As the regulating effect of probiotics is strain-dependent, the administration of the proper strains shall be used to decrease stress. Table 1 represents the probiotic strains administered for lowering stress and the following mechanisms of stress suppression are given in detail. In the present section, we intendto discuss the most effective probiotic strains against stress.

3.1.1. Bifidobacteria

Bifidobacteria are known as health-improving food supplements in the dairy industry and are capable of inhibiting pathogenic bacteria growth and allergies [18]. Notably, *Bifidobacterium longum* and *Bifidobacterium breve* were shown their capability to regulate the immune system and central nervous system (Table 1). Savignac et al. (2014), administered *Bifidobacterium breve 1205* and *Bifidobacterium longum 1714* in BALB/c mice with the intending to change their behavior. Savignac and coworkers (2014) have administered 1×10^9 CFU/mL of *Bifidobacterium longum (B.longum), Bifidobacterium breve* (*B. breve)*, or antidepressant medicine for a total period of 6 weeks. According to the results, the body temperature was different between groups. Mice fed *by B.longum* induced lower body temperature. Furthermore, *B.longum* treated group could travel more distance than other groups, which indicate less stress in this group. Considering corticosterone concentration, no effect of treatments on decreasing corticosterone levels was observed [18]. According to Canadian Natural and Non-prescription Health Products Directorate recommendations, *Bifidobacterium longum* is a natural inhabitant of the intestinal tract microbiota and is a lactic acid bacterium (LAB) that has been used for many years in fermented food [19]. In a similar study, Tian et al. (2020) evaluated the effect of the administration of *B.breve* on stress-induced symptoms and the gut microbial flora. Forty mice were randomly assigned into four groups (control group, probiotic group, fluoxetine group, and stress-induced group without feeding medicine). After the adaptation period, the probiotic-treated group was daily fed at a volume of 0.1 mL of a probiotic solution (contained 10^9 CFU/mL)/10g body weight for a total time of six weeks. According to the result, the anxiety behaviors of the probiotic-treated group were reversed compared to others. However, the serum corticosterone was raised in stressed mice, but its concentration was reduced significantly between probiotic-treated participants. Probiotic treatment imposed different positive effects on stress-induced mice brain abnormalities including restoring HPA-axis abnormalities, increasing Hippocampal 5-Htrl an mRNA concentration, increase in anti-inflammatory responses, restoring the gut microbiota, normalizing c-Fos expression [20] (Fig. 2). In a randomized placebo-controlled trial, the effect of *B. longum* on neural responses to social stress was evaluated. Forty healthy volunteers received a placebo or probiotic (10^9 CFU/d). Theta bands' power in the frontal cortex was increased in probiotic treated volunteers, while beta-2 bands' in the hippocampus and temporal cortex decreased. A significant positive correlation was observed between theta band power and the quality of life of volunteers. Probiotic-treated participants had better resting quality than the placebo group [21]. Hass and colleagues (2020), have revealed the stress ameliorating effect of

Table 1
Bacterial strains and formulations with psychobiotic potential.

Experimental/ Clinical	Bacteria	Animal or human study/Doses	Viable/ non-viable	Result	Mechanism	Author/ s
Experimental study	*B.adolescentis*	Animal study/1 × 10^9 CFU/kg/ day for 21 days	Viable	Reduced the protein expression of interleukin-1b, tumor necrosis factor a, and nuclear factorkappa. Increased the proportion of Lactobacillus. Reduced the proportion of Bacteroides in feces.	Reducing inflammatory cytokines and rebalancing the gut microbiota.	[46]
	B.breve CCFM1025	Animal study/0.1 × 10^9 CFU/10g weight daily for 5 weeks	Viable	Decreased depression- and anxiety-like behaviors, the hyperactive hypothalamic-pituitary-adrenal response and inflammation Rstored the gut microbial abnormalities.	Regulating the expression of glucocorticoid receptors Mitigation the HPA-axis hyperactivity and inflammation Up-regulation of BDNF coupled with downregulation of c-Fos levels, Enhancing the serotonergic system in both gut and brain, The modification on gut microbial composition and metagenome.	[20]
	B. longum subsp. *longum 35624*	Animal study/1 × 10^9 CFU/ weight daily for 21 days	Viable	Impacted hypothalamic-pituitary-adrenal axis positively Reduced anxiolytic behavior	Enhancing the HPA axis functions	[22]
	L. rhamnosus JB-1	animal study/1 × 10^9 CFU/day for 4 weeks	Viable	Increased anti-depressive-like behavior. Decreased corticosterone concentration.	Not mentioned	[47]
	L. johnsonii BS15	animal study/1 × 10^9 CFU/day for 4 weeks	Viable	Improved memory ability. Modulated the HPA axis. Modulated the memory-related functional proteins. Reduced anti-inflammatory cytokine levels.	Production of neuroactive compounds and reduction of cortisol level	[48]
	L. paracasei PS23	animal study/1 × 10^9 CFU/day for 6 weeks	Non-viable	Reversed corticosterone-reduced protein levels of brain-derived neurotropic factor, mineralocorticoid, and glucocorticoid receptors in the hippocampus. Reversed Abnormal behavioral changes. Reversed corticosterone-reduced dopamine levels in hippocampus and prefrontal cortex.	Not mentioned	[31]
	L. fermentum and L. delbrueckii (ADR-159)	Animal study/3 × 10^9 CFU/day for 3 weeks	Non-viable	Lowered baseline corticosterone levels.	Not mentioned	[30]
Clinical study	*L. casei* sp *Shirota*	Human study/1 × 10^9 CFU/day for 11 weeks	Viable	Positive effect on sleep quality	Unknown	[28]
	L.plantarum DR7	Human study/1 × 10^9 CFU/day for 12 weeks	Viable	Reduced plasma pro-inflammatory cytokines, plasma cortisol level, salivary cortisol level, and alpha-amylase. Increased plasma anti-inflammatory cytokines. Improved cognitive and memory functions. Enhanced the serotonin pathway.	Production of neuroactive compounds	[25–27]
	L. gasseri CP2305	Human and animal study/1 × 10^{10} CFU/ day for 12 weeks	Non-viable	Improved sleep quality. Prevented increases in basal salivary cortisol release and expression of stress-responsive microRNA. Increased the gene expression of neurotrophins in the hippocampus.	activate the afferent vagal nerve from the stomach or the intestine. Bind to a responsible receptor(s) on intestinal epithelial or other cells and promote the dispatch of asignal (s) driving the HPA axis	[32,34, 49]

(*continued on next page*)

Table 1 (*continued*)

Experimental/ Clinical	Bacteria	Animal or human study/Doses	Viable/ non-viable	Result	Mechanism	Author/ s
	L. gasseri CP 2305	Human study/1 × 10^{10} CFU/ day for 5 weeks	Non-viable	Improved sleep quality. Controlled diarrhea-like symptoms	Unknown	[33]
	L. helveticus R0052 and B.longumR0175 (CEREBIOME®)	Human study/3 × 10^{9} CFU/day for 8 weeks	viable	improvements in subjective sleep, improvement in Beck Depression Inventory score, significant decrease of cortisol, reduction of stress-induced gastrointestinal symptoms	maintain normal neuroplasticity and neurogenesis, occasional neuroinflammation in the limbic system prevention, reduction in the brain apoptosis, reduces apoptosis in the brain, intestinal permeability improvement	[50,51]

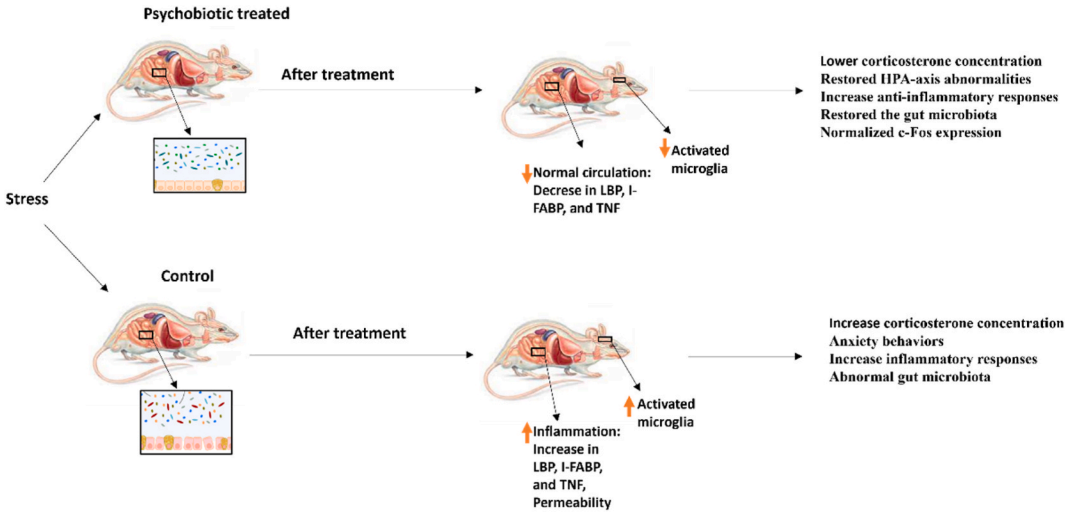

Fig. 2. Effect of dietary psychobiotic on the gut and brain activity of mice in comparison with non-psychobiotic feed after 6 weeks.

B. infantis in male rats. These scientists injected corticosterone (40 mg/kg daily) into the male rats and then treated them with a probiotic capsule (containing 10 ^{9} CFU/mL at the time of manufacturing) for 21 days. According to the obtained results, the administration of probiotics were not able to decrease stress-induced behaviors, while positively affecting the function of the HPA axis and reducing anxiolytic behavior [22]. Boehme et al. [23] have investigated the effect of *Bifidobacterium longum (BL) NCC3001* on stress parameters in healthy adults through a randomized, placebo-controlled, double-blind trial. According to the mentioned result showed 6-week intervention with probiotics (1 × 10^{10} CFU/daily) could reduce stress symptoms and enhance sleep quality, significantly. Salivary cortisol of the placebo group was higher than probiotic treated participants.

3.1.2. *Lactobacillus*

Lactobacillus (L) is one of the most genera habitats in the gut. In addition, probiotic properties of *Lactobacillus* bacteria are reported in different literature. This genus exerts different beneficial health effects ranging from modulation of the gastrointestinal tract to modulation of the immune system. In recent years, the positive effect of Lactobacillus on the gut-brain axis has been approved by scientists. Zhu et al. (2023) indicated the alleviating ability of *Lactobacillus plantarum* JYLP-326 on anxiety, depression and insomnia in college students. They evaluated mentioned effects of psychobiotics on sixty anxious students who were randomly divided into a probiotic group and a placebo group. Both groups consumed their products (maltodextrin for placebo and probiotic product containing 1.5 × 10 ^{10} CFU/product) twice per day for 21 days. The results of Zhu et al. (2023) revealed that anxiety, depression and insomnia symptoms were relieved after consumption. Consumption of probiotic *Lactobacillus plantarum* JYLP-326 could restore the disrobed gut microbiota in the probiotic treated group. The potential mechanism of such beneficial effects has been related to the regulatory effect of probiotics on gut microbiota [24]. The effect of *Lactobacillus plantarum* DR7 on alleviating the stress of 111 stressed adults was evaluated through a randomized, double-blind, and placebo control trial. Participants were divided into two groups (placebo n = 55, and DR7 N = 56). The DR7 group consumed probiotics (10 ^{9} CFU/day) for 12 weeks. The results of this human study indicated that probiotic consumption reduced stress symptoms and anxiety in treated individuals. In addition, the cortisol level in the plasma of probiotic-treated group was reduced compared to the placebo and the memory function of DR7-treated group was better [25]. In a

similar study, the effect of *L. plantarum* 299v consumption on cortisol levels in saliva was evaluated. 41 students (28 females and 14 males) between the ages of 18–30 years (under examination stress) have participated in this randomized trial. Each student consumed a capsule (containing 10^{10} CFU/mL probiotic or placebo product) once a day for 2 weeks. At the end of the trial period, salivary cortisol level was reduced significantly in the probiotic-treated group compared to the first date before probiotic consumption. Although, the salivary cortisol decreased, salivary IgA did not change before and after the trial in the probiotic-treated group [26]. Moreover, the anti-stress effect of *L. plantarum* was approved by Wu et al. (2021). Wu and colleagues evaluated the effect of the administration of *L. plantarum* PS128 on the reduction of stress of 36 IT specialists' participants. Each participant was asked to consume 2 probiotic capsules (equivalent to 2×10^9 CFU) daily for 2 months. The stress level of participants was measured through different standard questionnaires at the beginning and end of the trial time. Also, salivary stress biomarkers were measured at the beginning and at the end of the trial period. After the trial period, probiotics improved the psychological health of participants, including sleep quality, anxiety, and depression. Also, job stress, self-perceived stress, and salivary cortisol levels were reduced significantly after the trial period. The consumption of this probiotic decreased the sensitivity of IT workers in stressful situations and enhanced their capacity to face high-pressure conditions [27]. In addition to *L. plantarum*, the positive psychobiotic and anti-stress effect of *Lactobacillus casei* (*L. casei*) on human and animal models has been approved by Takada et al. (2017). Takada et al. (2017) have evaluated the effect of this probiotic on stress responses in medical students under final examination. 172 students participated in the mentioned three double-blind, placebo-controlled trials. Subjects were asked to take probiotic milk or a placebo for 56 days. The animal study was conducted by feeding rats with or without *L. casei* for 14 days prior to water avoidance stress. The probiotic-treated group had lower salivary cortisol levels and physical symptoms compared to the placebo group. According to animal study results, the plasma cortisol level was suppressed by probiotics [28]. Unlike the reported literature about the positive effect of the Lactobacillus genus, Kelly et al. (2016), did not observe the positive effect of *L. rhamnosus* on healthy volunteers. Kelly et al. (2016) evaluated the antistress impact of *L. rhamnosus* in healthy male subjects. According to the results, the consumption of *L. rhamnosus* had no significant effects on suppressing stress and stress-related behavior compared to the placebo group [29].

4. The current para-psychobiotic administered to ameliorate stress

According to the WHO/FAO definition, the viability of microorganisms is one criterion to consider as a health-benefiting organism, but recently the beneficial health effect of inactivated microbial cells has been approved by literature. Thus, new nomenclatures like para probiotics were created to imply the capability of non-viable bacterial cells to confer health effects if administered at an adequate amount. Different Inactivation methods are applied for producing para-probiotics, including heating, ultrasound, UV irradiation, sonication, ohmic heating, and high pressure. In some cases the application of para probiotics is superior to probiotics due to some advantages including longer shelf life, ease of transportation (no cold chain requirement), no risk of inflammatory responses to vulnerable and allergic individuals, no translocation of pathogenic virulence, or resistance to antibiotics, no loss of activity when used in conjunction with antibiotics or anti-fungal agents [30]. Many health benefits have been reported by animal or human studies in administration of para-probiotics including therapeutic effects on gastrointestinal abnormalities, liver diseases, immune system dysfunctions, and behavioral abnormalities. As paraprobiotcs have been applied with the aim improving brain functions and retrieving psychological abnormalities, the word para-psychobiotic has been proposed as an inactivated bacterial cell that imposes a positive psychological effect. In recent years, a few attempts were made to evaluate the effect of para-psychobiotics on the behavior of animal models or humans. Warda et al. (2019), administered a mixture (ADR-159) of heat-inactivated *L. fermentum* and *L. delbrueckii* in male mice. The animals were fed 3×10^9 inactivated mixed cells per gram of body weight for the time of 3 weeks. After 3 weeks of the trial, all treated animals were subjected to behavioral tests and plasma corticosterone levels (stress hormone). The para-propbiotic-fed fed mice were more sociable, and their plasma corticosterone was lower in treating animals. In addition, the para-probiotic diet led to significant changes in the microbiome of the gut. In 2019, Wei and colleagues evaluated the effect of viable and heat-killed *Lactobacillus paracasei (L. paracasie)* on decreasing stress-related behavior in corticosterone-treated mice, and compared anti-stress and anti-depression effects of probiotic and para-psychobiotic with fluoxetine. Mice were randomly divided into 5 groups ($n = 8$). The probiotic group was fed daily by viable or heat-killed probiotic (10^8 cells/0.2 ml/day) from the first day to 41. The fluoxetine-treated group was orally gavage with saline for the first 16 days of the trial and then received 15 mg/kg/day of fluoxetine until the end of the trial. All groups received 40 mg/kg/day of corticosterone. At the end of treatment, each mouse was forced to swim, and then brain tissue and serum were collected. The behavioral abnormalities were reduced by treating viable and para-probiotics. The corticosterone level in mice was treated by viable probiotics, para-probiotics, and fluoxetine reduced, significantly. The serotonin level of the hippocampus and prefrontal cortex was reversed in probiotic-treated mice, whereas the dopamine level was reversed through the treatment by para-psychobiotic [31]. In addition, the anti-stress effect of heat-inactivated *L. gasseri* was investigated by Toyokda et al. (2020). According to Toyoka and colleagues, 30 male mice were divided into 3 groups: negative control, positive control, and para-probiotic treated (2.25×10^{10} cells/g of feed), the negative and positive groups were orally gavaged AIN-93G powder and para-probioitc group were fed AIN-93G supplemented with heat-inactivated *L. gasseri* from the first day to 47. For inducing stress, the positive group and para-probiotic group were exposed to aggressor mice each day until the end of the experiment. Different tests were performed to evaluate the level of stress in each group, including social interaction tests, sucrose preference tests, nest building tests, tail suspension tests, and forced swim tests. In addition, neurotransmitter levels and corticosterone concentration were determined as stress indicator levels of each mouse brain. Toyokda and coworkers (2020) have reported that receiving para-probiotic reversed suppressed food appetite. In addition, dietary para-probiotic intake enhanced the concentration of neurotrophin in the hippocampus. Moreover, the probiotic group showed slightly suppressed nest building. No significant differences were observed in the results of the tail suspension test, sucrose preference, and forced swim test of three groups of mice [32]. A few clinical studies have been reported

about the positive effect of para-probiotics under stress. However, Nishida and colleagues (2017) have reported the anti-stress effect of para-probiotic *L. gasseri* based on two separate human studies. Nishida and coworkers 92017), administered inactivated *L. gasseri* (10 ^{10} cells/day) to 69 medical students that were under exam stress for 12 weeks. The para-probiotic administration significantly enhanced the sleep quality of a pre-examination time. The salivary corticosterone concentration and stress-related micro-mRNA in paraprobiotic-treated participants were lower than the placebo group. In a similar study, the administration of para-probiotic *L. gasseri* for 5 weeks during the final exam of students caused sleep quality improvement, shortened sleep latency, and improved sleep duration. In addition to the enhancement of nervous functionality, the para-probiotic regulated bowel habits under stressfull conditions [33,34].

5. Mechanisms of action of psychobiotic and para-psychobiotic

The mechanisms of action that psychobiotics and para-psychobiotics exert in their stress ameliorating effect have not been determined completely. However, it has been elucidated that psychobiotic and para-psychbioticbconfer health benefits by regulating CSN, stimulating the immune system, and affecting psychological markers of behavioral abnormalities. The latter potential may happen through different ways including regulation of HPA axis stress response and suppressing systematic inflammation, stimulation of the immune system, and secretion or release of neurotransmitters, short-chain fatty acids, and protein molecules.

5.1. Hypothalamic-pituitary-adrenal axis

The Hypothalamic-Pituitary-Adrenal axis consists of the hypothalamus, adrenal, and pituitary glands which regulate the stress responses. Stimulation of the HPA axis triggers neurons of the hypothalamus that stimulate the pituitary gland to release adreno-corticotropin hormones (ACTH). ACTH stimulates the adrenal cortex to synthesize and release cortisol or corticosterone, aldosterone, and androgens in the blood. In parallel to increasing the cortisol level, further release of ACTH is inhibited and the HPA axis returns to a physiological state followed by acute stress. A high concentration of cortisol in the blood cycle suppresses the activity of the immune system [35]. In addition, a high level of cortisol imposes a negative effect on mood, memory, and other cognitive parts of the brain. Recent evidence found the effect of the HPA axis on the gut microbiota population and balance and affects gastrointestinal permeability.

Microbiome imbalance in the gut can stimulate the HPA axis. Indeed, maintaining the gut microbiota balance imposes a significant effect on regulating the HPA axis. For instance, Mayo-Perez and colleagues have found that the administration of *Bifidobacterium pseudocatenulatum* (*B. pseudocatenulatum*) can modulate the HPA axis response to mice in response to chronic stress. *B. pseudocatenulatum* administration caused a significant decrease in the concentration of basal corticosterone and inhibited the overproduction of corticosterone in response to acute stress. Furthermore, probiotic administration regulated the early and later endocrine responses to the HPA-axis-mediated stress [36]. In a similar study, Tian et al. (2020), evaluated the effect of *B. breve* on the HPA axis responses to chronic stress in mice. They observed that the probiotic supplementation and fluoxetine medicine similarly restored the HPA-axis-related abnormalities. 5-Htr1a mRNA in mice hippocampus was restored by probiotic oral gavage [20]. Takada and coworkers (2017), determined the effect of *L. casei* on HPA-axis regulation of healthy adult students. They found that probiotic supplements suppressed the stress-induced HPA-axis and improved sleep quality, subsequently [28].

5.2. The immune system and inflammatory response

There is a relation between the gut microbiota and aberrant immune responses, which induce the overproduction of cytokines. The gut microbiota can regulate the innate and adaptive immune responses through the secretion of different molecules. However, the epithelial barrier inhibits the microorganism's entrance into the gut, the secreted metabolites can easily pass this barrier and enter the host circulation system and stimulate the immune system. Furthermore, the gut flora can impose a significant influence on the population and function of the immune cells. According to the literature, the gut microbiota can manage the connection between the intestinal immune system and the intestinal epithelium, so regulates overall immunity. Considering CNS, the microglia are the first immune effector cells and resident macrophages in the brain, which play an important role in brain disorders [37]. Recent publications have revealed a direct link between the gut microbiota and the microglia function. The latter capability of microbiota is due to the release of short-chain fatty acids that interact and regulate the microglia's function and development. The gut microbiota can modulate enzymes involved in mitochondrial biogenesis, which is the main resource of reactive oxygen species (ROS), can activate microglia, and release inflammatory cytokines from microglia [37]. In addition, recent literature showed that probiotics can regulate the microglia maturation, and affect its morphology. In addition, to live microorganisms, para-psychobiotics can regulate immune responses and exert anti-inflammatory responses [31]. According to scientific reports, para-probiotics can improve cytokine gene expression (IL-12 and IL-21) that enhances differentiation of native T-cells into precursor cells of follicular helper T (Tfh). IL-21 is a Tfh cell-secreted cytokines that enhance the differentiation of B cells into IgA-positive B cells and also improve the production of antigen-specific IgA in the lung, the small intestine, and serum. The increase in IgA levels in different organs indicates that para-probiotics modulate not only gastrointestinal immunity but also overall immunity. Immunoglobulin A prevents and neutralizes pathogens at the mucosal immune tissue, Indeed imposes a major effect on inhibiting initial infection [38]. Exopolysaccharides of para-probiotics act as Toll-like receptors (TLRs), which exert anti-inflammatory responses by regulating MAPK and NF-kB signaling pathways and reducing the induction of inflammatory cytokines in the intestinal epithelial cells [39].

5.3. Neuroactive compounds

Probiotics can produce different neuromodulators and neurotransmitters including gamma-aminobutyric acid (GABA), serotonin, acetylcholine, short and long-chain fatty acids, dopamine, and noradrenaline which exert different effects on the brain.

5.4. Gamma-aminobutyric acid and glutamate

The primary neurotransmitters of the mammalian CNS are GABA and glutamate. They act as inhibitory transmitters and prevent excitatory factors. The normal function of the brain (synaptic plasticity, cognitive, and neuronal excitability) depends on the coordination of these two neurochemicals. GABA is a non-protein amino acid that is synthetized by inhibitory neurons and mucosal endocrine-like cells. GABA increases the polarization of the neural cell membrane prevents synaptic conductions and decreases activity in the CNS, subsequently. GABA receptors exist in various regions of the brain and the gastrointestinal tract (GIT). GABA modulated GABAergic signaling to GABA receptors localized in human enteric neurons. The dysfunctionality of the GABAergic system causes different mental disorders [40]. GABA acts as the immune modulator in the GIT. Glutamate is the main procure protein for GABA synthesis. Different studies have shown the presence of the coding gene for glutamate decarboxylase among probiotics. *In vivo* experiments determined the ability of lactic acid bacteria to produce GABA. Oral administration of *L.plantarum* and *B.adolescentis* to BALB/mice enhanced the behavioral activity and decreased depressive behavior in mice through the production of GABA and other neurotransmitters. Furthermore, dietary intake of heat-inactivated *L. gasseri* in stress-induced mice has revealed the enhancement of the concentration of GABA in the brains of the animals [32].

5.5. Serotonin

Serotonin is a monoamine neurotransmitter synthesized from tryptophan and involved in regulating mental health. In addition, it plays a role in modulating the psychological processes of the CNS and the gut. Most serotonin is produced by enterochromaffin cells and a few contents of it exist in the enteric nervous system. Due to the existence of most serotonin in the gut, it presumes that serotonin may play a role in regulating the gut functions such as absorption, mobility, and transit. The gut microbiota induces enterochromaffin (EC) cells to synthesize serotonin. In addition, the gut microbiota utilizes luminal tryptophan and synthesize serotonin [41]. The positive effect of psychobiotic *L. paracasei* in the serotonin level of corticosterone-induced mice was observed previously [31]. Furthermore, daily oral administration of non-viable *L. casei* (for 14 days) increases the colonic serotonin level in mice compared to controls. The heat-killed *L. casei* increased the population of 5-hydroxy tryptophan which was located in the epithelium region of the colon. Administration of heat-killed *L. casei* increases the expression level of tryptophan in epithelial cells of the colon; however, the expression of EC cells was not affected [42].

5.6. Acetylcholine

Acetylcholine (ACh) plays the role of the main excitatory neurotransmitter in the hippocampus. It seems to play a role as a neurotransmodulator in the brain: affects the plasticity of the synapse, improves neuronal loops and the dynamics of cortisol during learning, alters the excitability of neurons, and also decreases neuronal adaptation time in response to environmental changes. The release of ACh in the hippocampus is essential for memorizing and learning. Cholinergic mechanism plays an important role in preventing neurological disorders, including Alzheimer's and schizophrenia. Cholinergic functions depend on ACh levels in the CNS [43]. Recent literature has determined the positive effect of probiotic administration on memory. Administration of L. *plantarum* to aging rats improved their learning ability [44]. Additionally, the administration of *L. plantarum* to rats with Alzheimer's disease increased the level of acetylcholine in the cerebral cortex and the hippocampus; however, the concentration of acetylcholine in the cortex and the hippocampus of the control group was decreased over time [43]. Although the beneficial effect of psychobiotics has been approved, so far there has been no report on the effect of para-psychobioitcs on the ACh level.

5.7. Short-chain fatty acids (SCFAs)

SCFAs are saturated fatty acids, which contain less than six carbons including propionate, acetate, and butyrate. The gut microbiome is responsible for producing SCFAs through the fermentation of indigestible or not-absorbed carbohydrates in the small intestine. Fibers are the major source of indigestible carbohydrates in dietary foods, which are consumed by the intestinal microbiota. The amount and the type of consumed fiber significantly influence the intestinal microbiota population and composition and, indeed, the variety and concentration of SCFAs produced. SCFAs influence neural functions through different mechanisms, including improving the integrity of the blood-brain barrier, regulating neuronal transmitters, modulating the level of neurotrophic factors, and improving memory. As SCFAs are probiotic metabolites, we can obtain them from viable or non-viable probiotics [45].

6. Limitations and challenges associated with the application of psychobiotics and para-psychobiotics

A sequence of demanding situations has been pronounced with the aid of researchers investigating the effects of psychobiotics in clinical practice. The high heterogeneity of the microorganisms investigated and products administered for the duration of diverse scientific and preclinical studies, the paucity of properly-designed scientific trials, especially of long duration, in addition to the need to

reach higher-outline goal subpopulations, are but some of the demanding situations confronted by way of the studies of psychobiotics. Additionally, the high heterogeneity of numerous psychiatric nosography categories, e.g., mood problems, anxiety problems, or SSD, makes it tough to detect of psychobiotics. Special interactions between pre-, pro-, or symbiotics and currently administered psychotropics is a hard-to-do away with bias component.

In respect of parapsychobitics, the selection of the best inactivated method for obtaining beneficially inviable cells is a serious challenge. Also, due to the effects of these viable and non-viable cells on the central nervous system, in many cases, the main causes and mechanisms of their effects on humans cannot be accurately identified due to ethical reasons, and only by examining animals and their CNS can some possible mechanisms be identified.

7. Conclusions

Mental stress is the feeling of emotional or physical tension. This complication can be caused by any event or thought that causes your frustration, anger, and nervousness. High levels of stress can lead to unpleasant or negative stress, including decreased performance, internal tension, sadness, anxiety, depression, physical and mental disorders, sleep disorders, forgetfulness and decreased body resistance, recurrent infections, and headaches. There are effective treatments for stress disorder; however, confer some undesirable side effects. Psychobiotics and para-psychobioitcs are novel treatments that confer anti-stressor properties in the host. Recent research reveals some probable mechanisms of action of probiotics, including the HPA axis involvement, the immune system regulation, and the production of some neuroactive compounds. Several current studies have confirmed the potential therapeutic effect of some viable or non-viable bacteria strains against stress in animal models and humans. However, a few studies have focused on the psychobiotic effects of food fortified with viable or non-viable probiotics.

The exact mechanisms by which psychobiotic and para-psychobiotics confer their therapeutic effect are not fully understood yet. There are no studies that define how is the exact mechanism of the relation between microbiota and the CNS. In addition, the production or the existence of neurotransmitters is not determined in most psychobiotics and para-psychobiotics, respectively. One of the major gaps is the lack of systematic studies, which allow scientists to better understand the psychotherapy potential of each probiotic strain and its mechanisms of action.

Due to the complexity of the gut microbiota-brain axis, understanding the exact mechanisms by which probiotic strains confer their mental health effects is difficult. Furthermore, elucidating a systemic method to evaluate the psychobiotic activity of a specific strain or formulation remains a challenge. Overall, we are facing one of the biggest pandemic challenges in the modern world. In addition to respiratory problems, COVID-19 outbreaks can be a challenge and cause problems with mental health such as stress, depression, anxiety, and sleep disorders. Indeed, the consumption of psychobiotics and para-psychobiotics could be considered a valuable method to prevent or treat any mental defects without undesired side effects. Especially because para-psychobiotics are non-viable microorganisms, they may offer a lower risk of allergies.

Based on our investigation, current research has not evaluated the effects of various strains on alleviating stress and the behavior of humans and animals, which can be a unique subject for future works with the aim of achieving the most suitable strain for decreasing stress. The production of inviable probiotic cells (para-probiotics) is achieved by different inactivation methods; however, there are a few published works about the effect of inactivation methods on probiotic cell bioavailability and beneficial characteristics. Indeed, conducting research in this field can open a way for the future.

CRediT authorship contribution statement

Mohammad Mahdi Gholian: Writing – review & editing. **Arash Babaei:** Writing – review & editing. **Fatemeh Zendeboodi:** Writing – review & editing. **Amir M. Mortazavian:** Writing – review & editing. **Vahid Koushki:** Writing – review & editing.

Ethical statement

Not applicable.

Data availability

The raw data supporting the conclusions of this article are available from the authors upon reasonable request.

Code availability

Not applicable.

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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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