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INNOVATIVE MICROBIAL-BASED THERAPIES FOR POST-TRAUMATIC STRESS DISORDER

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Aim. To investigate and systematize the literature data regarding the potential of novel biopreparations based on microorganisms as an innovative approach to the treatment of post-traumatic stress disorder (PTSD) through their impact on the microbiome and nervous system.

Material and Methods. Structural-logical analysis and bibliosemantic analysis were used in this study. The research materials comprised general scientific works and international health care protocols in Ukraine. The search for articles and other scientific papers published in English and Ukrainian was conducted online using electronic databases such as Web of Science, Scopus, PubMed, and Google Scholar.

Results. The relationship between microorganisms and the central nervous system through the so-called "enteric-cerebral axis" has been analyzed and systematized, revealing new opportunities for treating mental disorders, including PTSD. Studies indicate that the gut microbiome plays a crucial role in regulating the gut-brain axis, influencing the neuroendocrine system, immune response, and behavioral outcomes.

Conclusions. The use of probiotics and prebiotics has demonstrated a positive effect in reducing symptoms of anxiety and depression, which are critical components of PTSD. However, further clinical studies are required to confirm the efficacy and safety of these biological treatments in the management of PTSD.

Key words: biologics, probiotics, prebiotics, microbiome, gut-brain axis, mental disorders, post-traumatic stress disorder.

Post-traumatic stress disorder (PTSD) is becoming an increasingly common problem, especially among war veterans, combatants, and people who have experienced other severe traumatic situations. It is a non-psychotic delayed response to traumatic stress that can lead to a range of mental and behavioral disorders [1, 2].

Scientific research in recent years indicates that the gut microbiome plays a vital role in human health and regulating mood and behavior. The effect of microorganisms on the central nervous system through the so-called «enteric-cerebral axis» opens up new possibilities for the treatment of mental disorders, including PTSD [3–6].

Society is increasingly prioritizing the search for natural, less invasive treatments that have minimal side effects. Microorganisms-based biologics can be part of this approach, offering alternative ways to improve mental health without significant pharmacological interventions [6].

Despite the growing interest, research on the effects of microorganisms on mental health is only gaining momentum. Developing a review article on this topic will allow for systematizing existing data and identifying prospects for further research and clinical application. Moreover, this topic is important not only for scientists but also for practitioners, psychologists, and patients who are looking for innovative approaches to the treatment of mental disorders, including PTSD. As traditional treatments for PTSD, such as psychotherapy and drug therapy,

are not always practical or sufficient, newer biologics based on microorganisms may offer alternative or complementary approaches to treatment due to their ability to influence the gut microbiome and, by extension, the mental state.

Our study aimed to investigate the potential of novel microbial-based biologics as an innovative approach to treating post-traumatic stress disorder through their effects on the microbiome and nervous system.

The research materials were general scientific works, normative documents, and protocols on health care in Ukraine, and international protocols. The search for articles and other scientific papers is conducted online using electronic databases such as Web of Science, Scopus, PubMed, and Google Scholar.

The paper uses the methods of structural-logical analysis and bibliosemantic analysis, which allow the selection of scientific data from selected literary sources according to a certain logic, classify them, establish connections and relationships between them, and find out the state of the study of the problem and ways to solve it.

With the development of science and medicine, new approaches to the treatment of various diseases, including mental disorders such as PTSD, are emerging [3, 7]. Current research opens up new horizons in understanding the interaction between the gut microbiome and the central nervous system, enabling the creation of innovative therapeutic approaches focused on the microbiome [8, 9]. Microorganisms-based biologics, such as probiotics, prebiotics, and postbiotics, are becoming promising agents that can change the approach to the treatment of not only mental disorders but also many other diseases associated with stress and microbiome imbalances [10, 11].

Microbiome-gut-brain (MCM) axis

Recent studies suggest that people diagnosed with PTSD show changes in the composition of the gut microbiota compared to people who have been traumatized but have not developed PTSD [7, 8, 11]. The bidirectional relationship between the gut microbiome, gut, and brain, called the microbiome-gut-brain axis, consists of neuronal, neuroendocrine, and immune processes that respond to and influence the gut microbiome [7] (Figure).

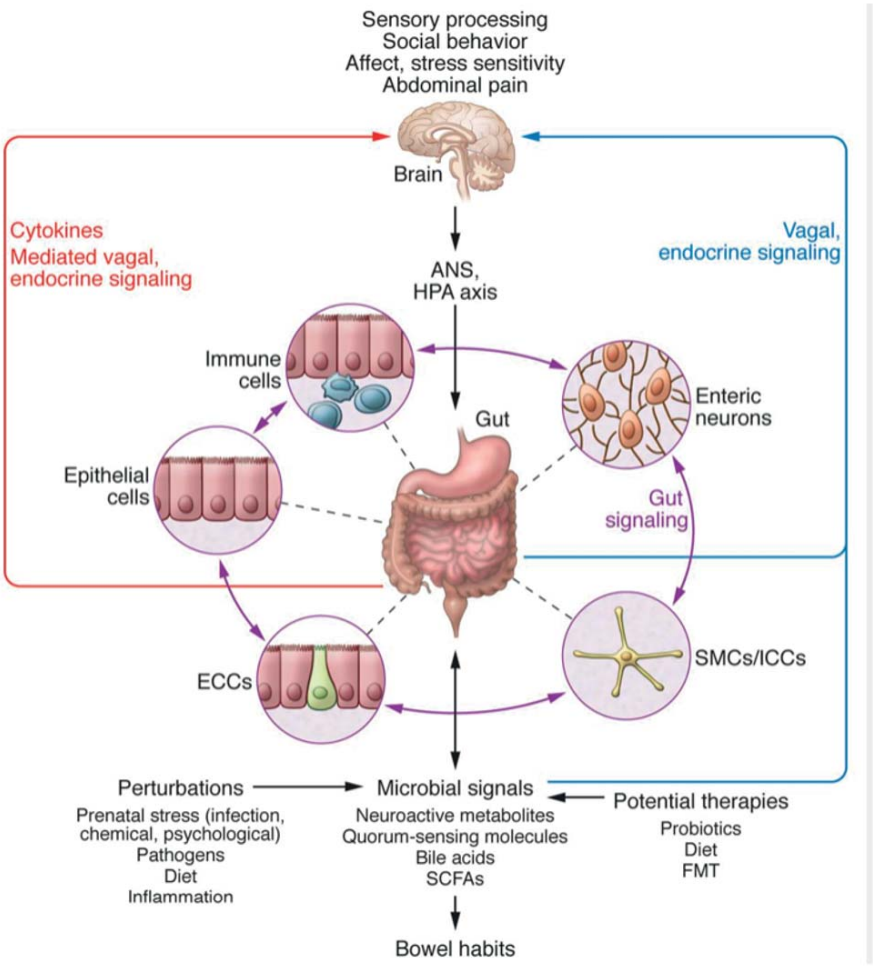
Because the gut microbiome influences the complex interactions of the gut-brain system, it plays a significant role in shaping the two-way communication between the gastrointestinal system and the brain, maintaining a delicate balance. On the one hand, the gut microbiome can influence cognitive function, memory, and complex behavior patterns; on the other hand, stress can disrupt the composition and species composition of the gut microbiota. This results in a complex cascade of interactions that affect reactivity and stress response [8, 9].

CNS-activated MCM axis signaling pathways, including efferent neuronal, neuroendocrine, and CNS-activated immune pathways, work in parallel to mediate homeostatic responses in the gut; similarly, the signaling pathways of the MCM axis, including afferent nervous, metabolite/endocrine, and immune, activated by changes in the gut, may alter CNS function. The results of research by Berkik and colleagues indicate the reliability of this hypothesis. It has been shown that the gut microbiota can alter CNS activity and behavior, contributing to a more anxiogenic or anxiolytic phenotype, depending on the microbiome's composition [12].

Changes in the gut microbiome drive changes in crucial neurotransmitter systems in the central nervous system, including mechanisms related to plasticity, serotonergic excretion pathways, and GABAergic modulation [7, 13, 14].

To date, research on the relationship between the gut microbiome and post-traumatic stress disorder remains relatively limited. However, the results of studies on this "exciting" connection indicate that intestinal dysbiosis is a significant factor in the development of PTSD [15]. Most likely, this dysbiosis indirectly (through long-term effects on the immune system and other physiological processes) makes people more vulnerable to developing PTSD after exposure to traumatic events, which ultimately contributes to the manifestations of the disorder [16]. An imbalance in the composition of the gut microbiota can lead to changes in the types and amounts of active compounds released by the microbiota into the gut, which can affect intestinal permeability, neuronal excitability, and chemical signaling in the host gut [17].

The mechanisms by which the CNS controls the functioning of the gastrointestinal (GI) tract are well understood. At the same time, there is much less data on how the gut environment, including the microbiota, can affect brain function, especially in psychiatric disorders [18]. Changes in the function of some areas of the brain due to microbit imbalances may be significant in determining behavioral



Bidirectional connection of the microbiome-gut-brain axis [73]

responses [19]. Hoban and colleagues investigated that in mice, the gut microbiome alters the expression of genes related to neuronal activity in the amygdala, an area of the brain that is often associated with anxiety disorders and disorders related to trauma and stress, such as PTSD [20]. The species composition of the gut microbiome has been shown to effectively alter the behavior of recall and fear cessation [20, 21].

The most common bacteria that comprise the gut microbiome are representatives of such species as Firmicutes, Bacteriodetes, Proteobacteria, and Actinobacteria [22]. They produce a variety of compounds, including fatty acids, secondary bile acids, and neurotransmitters, which interact with host physiology [23–25]. These metabolites interact with intestinal epithelial cells, stimulate afferent nerve fibers moving in the sympathetic and parasympathetic nerve bundles, enter the bloodstream, are carried to distant locations, and activate immune cells [25].

Research by Hemings and colleagues suggests significant differences in the species composition of the gut microbiome in people diagnosed with PTSD compared to the control group [15]. Three types of bacteria (Actinobacteria, Lentisphaerae, and Verrucomicrobia) were correlated with PTSD progression scores: a decrease in the number of these types of bacteria associated with higher PTSD scores, suggesting an essential role for these bacterial types in distinguishing between traumatic illnesses in individuals diagnosed with and without PTSD [15].

Microbiota dysregulation was characterized by an increase in the relative abundance of gram-negative bacteria from the Proteobacteria phylum and a relatively low number of lactic acid bacteria (*Lactobacillus, Lactococcus, Aerococcus*) and Bifidobacteria.

This model reflects an increased susceptibility to inflammation [26].

In a mouse model of stress, early separation from the mother caused microbial dysbiosis, increased activation of the hypothalamic-pituitary-adrenal axis, and increased anxious, protective behavioral responses in mice in adulthood [27]. These studies provide strong evidence that stress early in life can trigger long-term physiological changes that increase vulnerability to developing PTSD later in life.

A meta-analysis found that human exposure to trauma is associated with chronic low-grade inflammation, as indicated by elevated inflammatory biomarkers such as C-reactive protein, interleukin 1β (IL-1β), IL-6, and tumor necrosis factor (TNF) [28]. Other studies confirm that people diagnosed with stress-related mental disorders, including PTSD, are more likely to develop inflammatory diseases [29, 30]. Stress-induced increases in inflammatory markers associated with changes in the microbiome and behavioral responses similar to anxiety and depression in rodents have also been reported by Wong et al. [31].

Indeed, people diagnosed with post-traumatic stress disorder reliably demonstrate an increase in the pro-inflammatory marker (C-reactive protein) in the circulating plasma [32, 33]. However, it's still unclear whether this inflammation contributes to changes in the microbiome or is a consequence of an altered microbiome, but it's likely a combination of both.

Individuals diagnosed with PTSD exhibit altered plasma metabolite profiles, including changes in fatty acids and bile acids, which are influenced by the gut microbiota [34]. Members of the gut microbiota provide the host with enzymes and metabolites that break down indigestible foods such as fiber and cellulose [17, 35]. They also contribute to digestion and nutrient absorption, antioxidant production, insulin sensitivity regulation, and overall gut "health" [17, 35]. Thus, the microbiota produces a wide variety of metabolites that interact with the physiological processes of the host. Microbial metabolites can also affect the release of chemical signals produced by enteroendocrine cells that line the lumen of the gastrointestinal tract [36]. These cells are crucial in the gut and the brain [37]. For example, the microbiota can influence the amount of glutamate in the gut through glutamate dehydrogenase activity [38, 39]. This direct communication is rapid (within 1 second) compared to stimulation of the nodular ganglia by cholecystokinin, which takes several minutes, involving enteroendocrine cells as an integral component of MGB afferent axis signaling and allowing the CNS to respond almost immediately to the intestinal environment [36].

Dysregulation of serotonin is associated with disorders of intestinal dysbiosis, which, in turn, are related to changes in cognitive and behavioral functions [40, 41].

Hence, the current literature indicates that the species composition of the gut microbiota has a fundamental relationship with health and vulnerability [42, 43]. Thus, there is a growing interest in studying the relevance of dysbiosis or an imbalance in the gut microbiome in the context of the development and persistence of PTSD symptoms.

State-of-the-art microbial-based biologics

In light of findings that identify post-traumatic stress disorder as a significant health problem, understanding the pathophysiological mechanisms underlying post-traumatic stress disorder is critical to developing effective therapeutic interventions [44]. Given that an imbalance in the composition of the intestinal microbiota plays a vital role in the pathophysiological mechanisms that underlie PTSD, modern therapeutic approaches are grouped on the use of biologics based on microorganisms [43]. This concept is supported by clinical studies demonstrating differences in the composition of the gut microbiota in individuals with post-traumatic stress disorder compared to resistant individuals who have experienced trauma [15, 45].

A study of the effects of the use of the probiotic strain of *Lactobacillus farciminis* found that the hypothalamic-pituitary-adrenal (HPA) axis caused by stress was significantly inhibited. This effect was associated with decreased pro-inflammatory cytokine levels in the hippocampus and decreased intestinal permeability [46]. In another study, *Bifidobacterium pseudocatenulatum* CECT 7765 prevented stress-induced HPA axis sensitivity [47]. Using the combined probiotic *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 alleviated chronic stress changes in glucocorticoid receptors in the hypothalamus [46].

Maintaining a properly balanced microbiome is essential for maintaining the

immunoregulatory phenotype [48]. Indeed, probiotics are gaining popularity as one of the therapeutic strategies for the treatment of inflammatory diseases. Many probiotics are effective treatments for inflammatory bowel disease, reducing inflammation and improving ammo awareness [49–51].

Molecular studies are the basis for supporting the use of therapeutic probiotics for the treatment of inflammatory diseases. Using the probiotic *Lactobacillus plantarum*, ZLP001 mitigated *Escherichia coli*-induced cytokine production in intestinal epithelial cells, possibly through the production of CLFAs [52]. Indeed, short-chain fatty acids (CLFAs) increase Treg and, in addition, prevent intestinal, systemic, autoimmune, and even neuroinflammatory reactions [53–56].

Numerous studies have shown that probiotics (primarily those containing microorganisms of the *Lactobacillus* and *Bifidobacterium*) reduce the concentration of C-reactive protein in plasma in sick and healthy people [57].

The cognitive and physiological benefits of probiotics and prebiotics are also often attributed to the immunoregulatory effects of these bacteria. Some members of Actinobacteria increase in response to galacto-oligosaccharide prebiotics, and their presence in the gut is usually associated with positive neuroimmune function [58]. This phenomenon may be partly due to the various antimicrobial effects of Actinobacteria, which can «target» pathogenic species to prevent colonization and dysbiosis [59, 60].

When administered subcutaneously, *Mycobacterium vaccae* NCTC 11659 prevents stress-induced increases in corticotropin-releasing hormone levels in the central nucleus of the amygdala and the nucleus of the terminal strip bed, which are directly related to the manifestation of defenses against behavioral responses, such as anxiety and fear [61]. *Mycobacterium vaccae* also prevents stress-induced colitis and has been shown to promote an anti-inflammatory environment in both the periphery (gut) and brain [62, 63]. *Bifidobacterium bifidum* and *Mycobacterium vaccae* NCTC 11659 induce treg cell proliferation, which may explain their role in attenuating stress-related inflammation [60, 64].

Likewise, probiotics containing some Firmicutes have shown promise in treating neuroimmune dysregulation in different species. Oral administration of *Lactobacillus rhamnosus* JB-1 prevented stress-induced changes in behavior and immune function in mice while promoting an increase in the anti-inflammatory cytokine, interleukin 10 (IL-10), and the production of Tregs [65]. Similarly, *Lactobacillus helveticus* NS8 increased circulating plasma levels of IL-10 and attenuated anxious, protective behavioral responses after chronic stress in rats [66]. In a zebrafish model, *Lactobacillus plantarum* USDA-ARS protected against stress-induced intestinal dysbiosis and stress-response hypersensitivity [67].

Some species of *Clostridium* are immunoregulators, producing CLFAs and stimulating the proliferation of Tregs [68]. Indeed, microorganisms of the phylum Firmicutes produce most of the butyrate, which is believed to be an immunoregulatory metabolite [23].

For people with mild to moderate depression, the probiotics *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 reduced depression scores. They decreased the serum kynurenine/tryptophan ratio, a potential indicator of intestinal insufficiency microbial activity [69]. Another study demonstrated that in individuals with irritable bowel syndrome, the use of *Bifidobacterium longum* NCC3001 reduced rates of depression (using the Hospital Anxiety and Depression Scale) and reduced brain activity in the amygdala, frontal cortex, and temporal cortex in response to stimuli [70].

Clinical trials are currently underway to investigate the potential therapeutic benefit of *Lactobacillus reuteri* DSM 17938 on intestinal permeability, biological symptoms of peripheral inflammation, and measures of stress tolerance in veterans with post-traumatic stress disorder and mild traumatic brain injury [71].

Thus, the use of biological products based on microorganisms makes it possible to influence not only the emotional state and reduce the level of anxiety but also promote recovery after traumatic events, including PTSD. However, there is still a need for large, randomized, double-blind, placebo-controlled clinical trials to understand the benefits of using probiotics and related bioactive substances for the prevention and treatment of trauma and stressors-related mental disorders such as PTSD. A distinctive feature of PTSD is that the diagnosis is mainly established even years later, as this mental illness almost always occurs and persists for a long time after exposure to trauma [72].

Conclusions

The use of probiotics and prebiotics has been shown to have a positive effect on reducing symptoms of anxiety and depression, which are critical aspects of PTSD. The most promising treatments for mental disorders have been proven to be biological products containing microorganisms of the species *Lactobacillus* and *Bifidobacterium*. However, further clinical studies are needed to confirm the efficacy and safety of these biologics in the treatment of PTSD.

Conflict of Interest

The authors state that they have no conflict of interest.

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БІОПРЕПАРАТИ НА ОСНОВІ МІКРООРГАНІЗМІВ ЯК ІННОВАЦІЙНИЙ ПІДХІД ДЛЯ ТЕРАПІЇ ПОСТТРАВМАТИЧНОГО СТРЕСОВОГО РОЗЛАДУ

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Мета. Дослідити потенціал новітніх біопрепаратів на основі мікроорганізмів як інноваційного підходу до лікування посттравматичного стресового розладу через їхній вплив на мікробіом і нервову систему.

Матеріали та методи. У роботі використано методи структурно-логічного аналізу та бібліосемантичний. Матеріалами досліджень були загальні наукові праці та протоколи з охорони здоров'я України, міжнародні протоколи. Пошук статей та інших наукових праць здійснювали в мережі Internet, використовуючи електронні бази даних *Web of Science, Scopus, PubMed* та *Google Scholar*.

Результати. Проаналізовано та систематизовано дані про взаємозв'язок мікроорганізмів з центральною нервовою системою через так звану «кишково-мозкову вісь», що відкриває нові можливості для терапії ментальних розладів, включаючи посттравматичнй стресовий розлад. Дослідження демонструють, що кишковий мікробіом відіграє важливу роль у регуляції вісі «кишківник-мозок», впливаючи на нейроендокринну систему, імунну відповідь та поведінкові реакції.

Висновки. Використання пробіотиків і пребіотиків показало позитивний ефект на зниження симптомів тривожності та депресії, що є ключовими аспектами клінічних досліджень для підтвердження ефективності та безпеки цих біопрепаратів саме у терапії ПТСР.

Ключові слова: біопрепарати, пробіотики, пребіотики, мікробіом, вісь «кишківник-мозок», ментальні розлади, посттравматичний стресовий розлад.