Annals of Agricultural and Environmental Medicine 2022, Vol 29, No 3, 326–335
www.aaem.pl

REVIEW ARTICLE

Influence of pre- pro- and synbiotics on the proper functioning of the Gut-Brain Axis and cognition in exposure to stress – review of the latest scientific reports from *in vivo* studies

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Szala-Rycaj J, Szewczyk A, Zagaja M, Andres-Mach M. Influence of pre- pro- and synbiotics on the proper functioning of the Gut-Brain Axis and cognition in exposure to stress – review of the latest scientific reports from *in vivo* studies. Ann Agric Environ Med. 2022; 29(3): 326–335. doi: 10.26444/aaem/153448

Abstract

Introduction and Objective. Every day, the human body is exposed to various stressors. Constant stress leads to a gradual weakening of the body, the disturbance of homeostasis and the emergence of somatic symptoms that require treatment. Due to chronic stress exposure, it seems important to support the body with natural supplementation, such as pre- pro- or synbiotics. The aim of the study was to review the latest reports from *in vivo* studies on the role of pre- pro- and synbiotics on the microbiota and the gut-brain axis (GBA) in stress exposure.

Review methods. The article is an overview of literature reports from the past 5 years including *in vivo* studies examining the impact of pre- pro- and symbiotics on the gut microbiota and the GBA under stress conditions.

Brief description of the state of knowledge. Data from the World Health Organization (WHO) indicate that continuous exposure to stress contributes to up to 60% of chronic diseases. An important role in responding to stress is played by a properly functioning microbiome. Numerous studies concerning the pathology of the digestive system and disturbed microbiome show their relationship with nervous system disorders, thus confirming the importance of a proper bidirectional communication between these 2 systems.

Conclusions. Daily exposure to stress may disrupt the microbiota and proper functioning of the GBA. The cortisol released in response to stress is an essential physiological response that helps with coping in threatening situations. However, its release triggers a cascade of subsequent biochemical reactions dangerous to health, especially if they are triggered too often, i.e. under chronic stress. The latest scientific reports from *in vivo* studies clearly show that proper supplementation and diet (used with caution) can be a potential add-on therapy in the treatment of neuropsychiatric disorders.

Key words

chronic, microbiome, gut microbiota, gut-brain-axis, prebiotics, probiotics

INTRODUCTION

Chronic stress. Stress, a state of mental or emotional strain, is defined by the relationship between the requirements set for the organism by the adverse or very demanding circumstances and the possibility of their implementation. However, beneficial stress called eustress occurs in the case of positive events and correlates with life satisfaction and well-being, as well as distress, an aversive state manifesting with inappropriate social interaction, such as aggression, passivity, or withdrawal. Data from the WHO indicate that continuous exposure to stress contributes to up to 60% of chronic diseases, hence it is called the 'disease of the century'. Long-term stress which cannot be dealt with decreases immunity, resulting in more frequent infections, and can also affect all organs and systems of the human body, leading to many chronic diseases, addictions, depression, neuroses (including an anxiety neurosis), and serious digestive and eating disorders [1].

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Received: 11.07.2022; accepted: 01.09.2022; first published: 07.09.2022

An important role in responding to stress is played by the proper functioning of the microbiome. Numerous studies on the pathology of the digestive system and disturbed microbiome have shown their relationship with disorders of the nervous system (mainly anxiety, depression), thus confirming the importance of proper bi-directional communication between these two systems [2].

Current scientific knowledge about the correlations between stress and the gut microbiome is based on *in vivo* studies. Therefore, this review is aimed at focusing on and analyzing the latest *in vivo* research on the importance of natural supplementation with pre- pro- and synbiotics in the prevention of the gut-brain signaling disorders.

The autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis are the main pathways activated by stressors, with the hypothalamus secreting corticotropin in response to stress [3]. Chronic stress leads to the constant activation of the sympathetic nervous system, resulting in an increase of norepinephrine and epinephrine levels and a decrease of acetylcholine levels, which in turn leads to a greater release of pro-inflammatory cytokines from the immune cells [4]. As a result, downstream metabolites (ex. quinolinic acid, 3-hydroxyanthranilic acid and

3-hydroxykynurenine) are increased and have a neurotoxic effect on the brain. The neurodegenerative changes caused by the induction of excitotoxicity and apoptosis may contribute to the development of depression. [4].

Recent evidence suggests that long-term exposure to stress may cause irreversible loss of hippocampal neurons and may be of importance for cognitive deficits [5]. Although the effects of stress on the neuroplasticity of the hippocampus are complex, several studies have found impairment of the hippocampal memory processes after stress [6, 7, 8]. The neurotransmitters released during stressful situations, such as cortisol or noradrenaline, can directly affect the functioning of the hippocampus. Memory and learning are based on areas of the hippocampus, stress can therefore interfere with memory processes [9].

Microbiome. The human microbiome evolves with humans and with the development of specific microbes that occupy selected anatomical niches in the human body [10]. The human gut is inhabited by a complex community of microbes (including bacteria, yeast and viruses) called gut microbiota that produces thousands of metabolites [11, 12]. Taxonomically, bacteria are classified into types, classes, orders, families, genera and species. Only a few types are represented, accounting for over 160 species [13].

The main types of intestinal microorganisms are *Fusobacteria, Bacteroidetes, Verrucomicrobia, Proteobacteria, Firmicutes,* and *Actinobacteria*. *Bacteroidetes* and *Firmicutes,* accounting for 90% of the intestinal microflora. The *Firmicutes* cluster consists of over 200 different genera, such as *Bacillus, Ruminicoccus, Enterococcus, Clostridium* and *Lactobacillus*. The *Clostridium* genera make up 95% of the *Firmicutes* cluster. *Bacteroidetes* are composed of the predominant genera, such as *Bacteroides* and *Prevotella*. *Actinobacteria* phyllum is represented by the genus *Bifidobacterium* and is less numerous. [11].

General functions of the gut microbiota. It is currently known that the intestinal microbiota is not only involved in the processes related to digestion and nutrients absorption. The intestinal microbiota perform various functions and their homeostasis (referred to as the eubiosis state) supports the proper functioning of the organism, immunity, metabolism and the synthesis of many neuroendocrine and neurotransmitter mediators [14]. Due to the fact that certain species or types of bacteria living in the gut may be pathogenic, disturbances of the intestinal microflora are associated with many diseases, such as: irritable bowel syndrome and inflammatory bowel disease [15], obesity and diabetes [16], allergic diseases [17] or neurodegenerative diseases. Therefore, it is important that the bacteria positively influencing the processes taking place in the intestines remain in quantitative dominance, which will have a health-promoting effect on the entire body.

Among the multiple functions of the intestinal microbiota, three of the most important can distinguished: metabolic, immune and protective functions:

1) *Metabolic function*: the gut microbiota largely derives its nutrients from dietary carbohydrates. The fermentation of carbohydrate by organisms such as *Bifidobacterium, Enterobacteria, Bacteroides, Fecalibacterium* and *Roseburia*, leads to the synthesis of short chain fatty acids (SCFAs), such as acetate, butyrate and propionate, which are rich energy sources for the host [18]. Butyrate may prevent the build-up of toxic metabolic by-products such as D-lactate [19]. Degradation of oxalate in the gut bacteria reduces the risk of oxalate stone formation in the kidney up to 70% [20]. Moreover, the intestinal microbiota has been shown to play a key role in proteins, lipids and polyphenolic compounds metabolism provided in the diet, vitamins synthesis [21] or linoleic acid synthesis [22].
2) *Immunomodulation.* The intestinal microbiota is largely responsible for the development of the main components of the acquired and innate immune system of the host, while the immune system is responsible for host-microbe symbiosis [26]. Information pointing to the main role of natural bacterial flora in modulating the immune system comes from studies on axenic mice with severely underdeveloped gut-associated lymphoid tissue (GALT). The number of germinal centres is reduced, which translates into a decrease in the number of IgA-producing plasmocytes in the lamina propria [27]. At the same time, the proportion of the lymphocyte population is disturbed in the lamina propria of the large intestine where there is a higher level of Treg CD4 + Foxp3 + cells, with a simultaneous decrease in the number of Th17 cells [28, 29]. Colonization of these mice with even a single commensal, e.g. *Bacteroides fragilis*, restores the normal structure of GALT [30].
3) *Antimicrobial protection.* An important role of the intestinal microflora in maintaining normal homeostasis is the continuous control of the overgrowth of pathogens residing in the intestines. One form of antimicrobial protection is the two-tiered mucus layer that holds the luminal microbes, mainly in the large intestine [23]. In addition, the gut microbiota from the small intestine induces the synthesis of antimicrobial proteins, including cathelicidins, and defensins [24]. Lactic acid that is produced by *Lactobacillus* sp creates an environment that inhibits the growth of pathogens. In addition it potentiates the antimicrobial activity of host lysozyme by disrupting the bacterial outer membrane. [25]. Another way for gut microbiota to control the growth of pathogenic strains is local immunoglobulins induction [26]. This type of antimicrobial protection relies on limiting the translocation of the microflora from the intestinal lumen into the circulation, which results in preventing a systemic immune response.

Factors determining microbiota composition. The process of bacterial colonization in the human intestines begins *in utero* through the microbiota in the amniotic fluid and placenta [31]. One of the first factors determining the development of microflora is the way of childbirth. Vaginally born neonates have primary intestinal microflora dominated by *Lactobacillus* and *Prevotella* [32, 33], while those delivered by caesarean section derive their intestinal microflora from maternal skin and the hospital environment, leading to the dominance of *Streptococcus, Corynebacterium* and *Propionibacterium* [32, 34].

Another key factor in early development is the infant's diet. The difference between microbial communities depending on the feeding method was greatest between infants exclusively breast fed, and those on a mixed diet or formula only. Mixed and formula-fed infants have gut microbial communities similar to those formula-fed only, and relatively different from those who were only breast fed. This is quite important

in promoting exclusive breastfeeding from birth [34]. Breast milk contains oligosaccharides that promote the growth of bifidobacteria, which in turn affects the production of SCFAs and lactate which mediate systemic effects, including immunomodulation [35].

During the first three years of life, extensive changes in the brain architecture occur including extensive synaptogenesis and myelination [36]. At the same time, it is an extremely important developmental period for the intestinal microflora. Exposure of the developing organism to various microorganisms, diets, stressors, antibiotics and other factors has a great influence on the architecture and function of the microbiota, and thus on communication with the developing central nervous system (CNS) [37]. Over time, the composition of the intestinal microbes becomes more stable and relatively resistant to long-term disturbances. Despite the increased stability of the intestinal microflora composition, various factors, such as diet, chronic stress, antibiotics, gender, diseases, environmental and individual factors, can significantly alter the composition of the gut microflora in adulthood (Fig. 1) [38]. In adults, diet is the most important factor influencing the richness and diversity of the gut microflora. Protein, carbohydrates and fat are macronutrients that are essential for maintaining body functions and providing energy. The WHO recommends that dietary fat should not exceed 30%, protein – 10–15%, and carbohydrates should make up the remainder, between 55–75%, of the daily requirement [39].

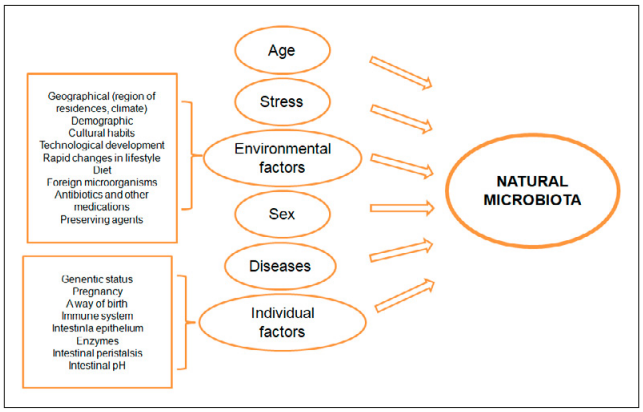

Figure 1. Factors affecting the gut microbiota

Antibiotics are another group of factors with a strong, negative impact on the intestinal microflora. They destroy both pathological and beneficial microorganisms, leading to dysbiosis, which favours the development of undesirable microorganisms, e.g. *Clostridium difficile* [40]. Several studies using such antibiotics as clindamycin [41], clarithromycin, metronidazole [42], and ciproflaxin [43] indicate a long-term detrimental effect on the microbiota.

Finally, stress is another key factor that significantly influences on the composition of the intestinal microflora. The impact of stress factors on the pathogenesis of gastrointestinal diseases has already been proven in a lot of scientific research [44, 45, 46]. Stress can affect the physiological functions of the digestive system, such as motility and intestinal permeability, gastric secretion, blood flow through the mucosa, and visceral sensitivity. Clinical symptoms of stress can manifest as: abdominal pain, diarrhea, dyspepsia, nausea [47]. Stress promotes colonization by pathogenic bacterial species such as *Citrobacter rodentium,* and increases the concentration of cytokines. Gut stress-induced dysbiosis can be caused by alterations in intestinal IgA secretion, leading to dysfunction of the GBA [48]. Stress-induced activation of the HPA axis can affect gut motility and disrupt colon homeostasis. Increasing the permeability of the intestinal barrier leads to the movement of gram-negative bacteria from the intestinal lumen into the blood and induces an inflammatory reaction [49].

Microbiota and GBA. The GBA is a network of neurons connecting the CNS with the gastrointestinal tract [50]. This bi-directional communication system drives sensory signals from the gut to the CNS, allowing the regulation of reflex activity and mood states. In turn, signals from the brain may influence immune, secretory and motor gut functions [51]. The intestine is connected to the brain via the enteric nervous system (ENS), which includes the parallel drainage of the parasympathetic (vagus) and sympathetic (pre-vertebral ganglia) systems and the HPA. The ENS is considered the 'second brain' of the gut and is made up of millions of neurons and is divided into two types of ganglia: spinal and submucosal plexus [52]. The gut microflora can control both the ENS and the CNS through neurotransmitters, neurotrophic factors, bacterial metabolites, intestinal barrier maintenance, and immune regulation [53]. The intestinal nervous system can detect over 30 neurotransmitters, most of which (ex. epinephrine, norepinephrine, acetylcholine, dopamine, and serotonin) are found in the CNS [54]. Over 90% of the serotonin and 50% of the dopamine comes from the gut, which is mainly produced by the intestinal microbiota. Bacterial metabolites, especially SCFAs, are involved in neuro-immunoendocrine regulation, for example, serotonin release in the gut [55]. Emerging data confirm the fact that dysbiosis in the gut microbiota during functional disorders of the gastrointestinal tract disrupts GBA and leads to mood disorders [51]. Experimental evidence also suggests that neurotrophic factors in the hippocampus and cortex regulate cognition. The gut microbiota can modulate the HPA to reduce the release of cortisol from the adrenal glands which, in turn, leads to reduction of anxiety behaviour and reactivity to stress [56].

Disturbed microbiota transmits brain signals through the pathways involved in neurogenesis, cognitive functions, behavioural control, microglial activation and neural transmission in both stable and stressful conditions, which proves the great importance of microbiomes in managing mental health issues [57, 58]. Cognitive impairment is often the first symptom of the development of many serious neurological disorders. Therefore, any disturbances in the microbiota GBA homeostasis can lead to cognitive impairment. It has been proved that 12-week consumption of probiotic (*Lactobacillus fermentum, Bifidobacterium bifidum, Lactobacillus casei, and Lactobacillus acidophilus*) can positively affect some metabolic statuses and cognitive function in patients Alzheimer's Disease (AD) [59]. Frohlich et al. [60] showed that antibiotic-induced microflora dysbiosis in a mouse model is associated with cognitive impairment (decrease in brain-derived neurotrophic factor BDNF, increase in neuropeptide Y and the serotonin transporter). A study by Nimgampalle and Kuna [61] indicated that the treatment of D-galactose-induced animal model of AD with *Lactobacillus plantarum* MTCC1325 improved the cognition deficits and

restored the acetylcholine concentration. Similarly, Athari Nik Azm et al. [62] showed an improvement of spatial memory, orientation, and mood in AD rats treated with *Bifidobacterium lactis, Bifidobacterium longum, Lactobacillus acidophilus* and *Lactobacillus fermentum*.

Taken together, intestinal microbiota is involved in the pathogenesis of neurological disorders via their metabolites, such as neurotransmitters and SCFAs, and that the administration of prebiotics / probiotics may improve cognitive functions by modulating gut microbial metabolism and homeostasis.

Impact of chronic stress on the GBA. There are extensive two-way interactions between the brain and the gut, and it is well known that negative emotions and stress have a strong influence on gastrointestinal (GI) motility, cognition, and immune responsiveness (Fig. 2). Zeng et al. [63] showed that inflammation, which often accompanies stress, causes blooms of pathogenic bacteria that promote dysbiosis and leaky gut. The brain can influence the gut microbiota by regulating endocrine systems (e.g. the HPA axis and hypothalamic-pituitary-gonadal axis), and conversely, the gut microbiome can influence brain function through various mechanisms, including modulation of cytokine, the release by immune cells and the vagus nerve, and through production of neurotransmitters and SCFAs [64, 65]. Taking into account the many negative effects resulting from the disturbance of the microbiota, and thereby the GBA, it is extremely important to properly supplement and support intestinal bacteria

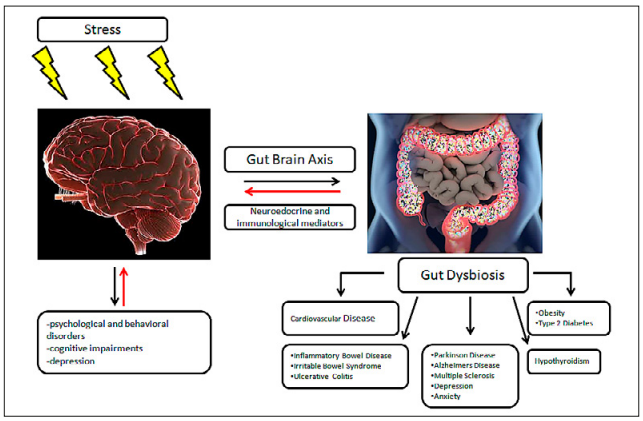

Figure 2. Influence of stress on the functioning of gut microbiota and the GBA

PRO- PRE- AND SYNBIOTIC SUBSTANCES

Much research is currently focused on developing therapies to restore the balance of the gut microbial ecosystem. The great interest in this topic proves how important it is to maintain the intestinal microbiological balance. Moreover, as of today, there is no universal medicine suitable for everyone. One of the most common ways to support microbiota is through prebiotic, probiotic and synbiotics-enriched diets.

PROBIOTICS

The Food and Agriculture Organization of the United Nations (FAO) and the WHO define probiotics as 'live microorganisms that, when consumed in appropriate amounts, confer health benefits to the host' [66]. Probiotic products contain one or more selected strains of microorganisms, such as: *Enterococcus, Streptococcus, Lactococus, Bifidobacterium,* and *Lactobacillus*. In addition, strains of Gram-positive bacteria of the genus *Bacillus* and some strains of yeast of the genus *Saccharomyces* are commonly used [67].

The beneficial effects of probiotics are based on four mechanisms, i.e. competition with pathogens for adhesion to the epithelium and nutrients, host immunomodulation, the production of antimicrobial substances and inhibition of the production of bacterial toxins [68]. It is believed that the administration of probiotics improves the prognosis and treatment of such metabolic diseases as obesity, diabetes and inflammatory bowel disease [69]. Probiotics have also been shown to be effective in improving mood and depression in human studies [70].

PREBIOTICS

The International Association of Probiotics and Prebiotics (ISAPP) has defined 'dietary prebiotics' as 'a selectively fermented ingredient that causes specific changes in the composition and / or activity of the gastrointestinal microbiota, thereby conferring a health benefit on the host.' The prebiotic should meet the following criteria: stimulate the growth / activity of the intestinal microbiota, but cannot be hydrolyzed by mammalian enzymes or absorbed in the gastrointestinal tract, should be resistant to the acidic pH of the stomach, and can be fermented by the intestinal microbiota. [71].

Prebiotics naturally occur in such food products as: Jerusalem artichoke, garlic, asparagus, chicory, sugar beet, onion, banana, honey, barley, wheat, rye, tomato, soybeans, beans and peas, as well as human and cow's milk. Unfortunately, because their percentage in food is low, they are produced on an industrial scale. The main raw material for production is lactose, sucrose and starch [72].

Among the many types of prebiotics the most common are oligosaccharide carbohydrates (OSCs). These include fructooligosaccharides (FOS), galactooligosaccharides (GOS), and oligosaccharides derived from starch and glucose, and pectin derived oligosaccharides (POS) [73]. In addition, there are non-carbohydrate oligosaccharides, such as cocoa derived flavanols [74]. Prebiotics can increase the strength of beneficial microbiota while reducing detrimential gut microflora, improving the host colonic microbiota toward a healthier composition [75].

SYNBIOTICS

ISAPP has defined synbiotics as: 'a mixture of live microorganisms and substrate(s) selectively used by host microorganisms that confer health benefits to the host' [76]. Probiotics are active in the small and large intestines, although the action of the prebiotic occurs mainly in the large intestine. As a result, there is a synergistic effect. Thanks to the use of synbiotics, microorganisms achieve a higher tolerance to environmental conditions, including: oxygenation, pH, and temperature in the intestine of a given organism. Then, more viable microorganisms are formed. Synbiotics reduce the

concentration of undesirable metabolites, as well as inactivate carcinogens and nitrosamines. Their use leads to a significant increase in the levels of carbon disulfides, SCFAs, methyl acetate and ketones, potentially having a positive effect on the health of the host [68, 77].

Influence of pre- pro- and synbiotics on the GBA under chronic stress. Dietary supplements in the form of prebiotics and synbiotics (Tab. 1) and probiotics (Tab. 2) have recently become a very frequent topic in *in vivo* research, mainly in the context of their beneficial properties on GBA microbiota under conditions of exposure to chronic stress.

The most popular prebiotics FOS and GOS have been shown to have a positive impact on GBA and behaviour associated with depression, anxiety, and chronic psychosocial stress response in mice [78]. The obtained results indicate that administration of GOS, FOS or a combination of GOS+FOS for three weeks prevented the harmful effects of stress by lowering plasma corticosterone levels. Animals treated with prebiotics had reduced depression-like behaviour, confirmed by the forced swimming test (FST) and tail suspension test (TST), as well as reduced anxiety levels in the elevated plus a maze test (EPMT), and open field test (OFT). In addition, administration of GOS+FOS prevented the reduction of *Bifidobacterium* and *Lactobacillus* caused by chronic stress.

In a study with GOS/FOS, *L. rhamnosus and B. longum* supplementation in chronic, unpredictable mild stress in rats (CUMS) performed by Li et al. [79], immunofluorescent detection of colonic enterochromaffin cells (ECs) and 5-HT showed a significant tendency to reduce colonic 5-HT, and increase 5-HT in frontal cortex and hippocampus of treated rats, compared to the CUMS control group. FOS and GOS, *L. rhamnosus* and *B. longum* CUMS rats indicated a clear increased sucrose intake in contrast to the control CUMS group. The FST showed that GOS&FOS, *L. rhamnosus* and *B longum* treatment significantly reduced the immovability time in comparison to the CUMS control animals. Compositional examination of the structure of gut microbiota by pyrosequencing revealed that the structure of the colon microflora has changed favourably after treatment with probiotics and prebiotics, especially in the *L. rhamnosus* group.

Mika et al. [80] assessed whether 4-week administration of GOS and polydextrose and lactoferrin glycoprotein alone and in combination in early life in rats, can prevent the effects of inevitable stress. Each diet changed the composition of the gut bacteria, but biochemical studies showed that the diets did not change the effects of stress on corticosterone or glucose levels.

Qiu et al [81] evaluated the effect of inulin-type oligosaccharides obtained from *Morinda officinalis* on behavioural deficits in a rat model of post-traumatic stress disorder. A single prolonged stress (SPS) model was used in this study. Two weeks of treatment with inulin ameliorated the cognitive deficits in the existing model in OFT, EPM and contextual fear paradigm tests. Interestingly, a neurosteroid allopregnanolone level elevated by SPS, turned out to be reversed through the administration of inulin of *Morinda officinalis*. In turn, Chi et al. (2020) [82], evaluated the proper anti-depressive properties of FOS from *Morinda officinalis* in a Sprague-Dawley rat exposed to CUMS. Results obtained from SPT and OPT behavioural tests confirmed the anti-depressant effect of FOS in rats that underwent CUMS; moreover, supplementation with FOS restored corticosterone to its original level. Additionally, FOS supplementation inhibited the occurrence of bacteria associated with depression, such as *Oscillibacter, Anaerostipes, Prevotella, Lachnospiraceae incertae sedis, Streptococcus* and *Proteobacteria,* and promoted the relative abundance of *Cyanobacteria*, *Tenericutes, Firmicutes* and *Actinobacteria* – a group of bacteria known for the secretion of pharmacologically important metabolites exhibiting antidepressant properties.

Neufeld et al. [83] investigated the effect of *Lactobacillus rhamnosus GG* supplementation, alone and in combination with prebiotics: polydextrose and GOS, on the behaviour

Table 1. Impact of selected pre and synbiotics on stress, cognitive functions and microbiome- research from *in vivo* studies

	Supplements	Animal model	Impact on stress / cognitive functions	Impact on microbiome	Ref.
Prebiotics	FOS and GOS	anxiety and chronic psychosocial stress response in mice	reduced depression-like behaviour, reduced anxiety levels,	beneficial effect on the composition of Bifidobacterium and Lactobacillus	[78]
	FOS and GOS	CUMS in rats	reduced depression-like behaviour	beneficial effect on the composition of the colon microflora	[79]
	GOS, polydextrose (PDX) and lactoferrin glycoprotein	inescapable stress in rats	protected against learned helplessness	significant increase in the number of *Lactobacillus species*	[80]
	Inulin-type oligosaccharides	single prolonged stress (SPS) model in rat	reversed the behavioural deficits	--------	[81]
	FOS	CUMS in rats	alleviated depression-like behaviours	inhibition of depression-stimulating bacteria, beneficial effect on intestinal bacteria	[82]
	(PDX) and GOS	maternal separation in rats	amelioration of an anxiety-like behaviour and cognitive deficits	------	[83]
	Inulin	healthy Young rats	promote an anxiety-like effect	------	[84]
Synbiotics	*Lactobacillus rhamnosus GG (LGG)*, PDX and GOS	maternal separation (MS) In rats	alleviating cognitive deficits,	-----	[83]
	Lactobacillus casei 54-2-33, Inulin	healthy Young rats	alleviated depression-like behaviours,	------	[84]

Table 2. Impact of selected probiotics on stress, cognitive functions and microbiome- research from *in vivo* studies

Probiotics	*Bifidobacterium longum* and *Lactobacillus rhamnosus*	CUMS in rats	reduced depression-like behaviour	beneficial effect on the composition of the colon microflora	[79]
	Lactobacillus rhamnosus GG (LGG)	maternal separation in rats	amelioration of early-life stress-induced anxiety-like behaviour and cognitive deficits	------	[83]
	Lactobacillus casei 54-2-33	healthy Young rats	promoted an anxiety-like effect;	------	[84]
	Lactobacillus casei	CUMS In rats	improved depression-like behaviours,	modified the dysbacteriosis and restore the homeostasis of intestinal microflora	[85]
	Lactobacillus helveticus R0052 , Lactobacillus plantarum R1012 i Bifidobacterium longum R0175	mouse model of chronic mild stress (CMS)	ameliorated CMS-induced anxiety- and depressive-like behaviours,	significant increase in the number of Lactobacillus species	[86]
	Clostridium butyricum	CUMS in mice	improved depression-like behaviours	--------	[87]
	Bifidobacterium longum subsp. infantis E41 and *Bifidobacterium breve M2CF22M7*	CUMS in mice	reduced depressive behaviours;	improved the chronic-stress-induced microbial dysbiosis	[88]
	Lactobacillus kefiranofaciens ZW3	CUMS in mice	improved depression-like behaviour and independent exploration ability;	increased the abundance of anti-inflammatory and anti-stress microorganisms	[89]
	Faecalibacterium prausnitzii ATCC 27766	CUMS in rats	Improved depression-like and anxiety-like behaviour,	---------	[90]
	Bifidobacterium adolescentis	chronic restrictive stress (CRS) in mice	anxiolytic and antidepressant effect in CRS mice in behavioural tests, r	increased the sequence proportion of Lactobacillus and reduced the sequence proportion of Bacteroides	[91]
	Bifidobacterium breve CCFM 1025	CUMS In mice	significantly reduced depression- and anxiety-like behaviours;	beneficial effect on the composition of the colon microflora	[92]
	Lactobacillus rhamnosus (LR-JB1 ™)	CUMS In rats	reduction of stress-induced behaviour;	----------	[93, 94]
	Akkermansia muciniphila	CRS in mice	significant reduction of depressive-like behavior	regulated the gut microbial composition	[95]
	Lactococcus lactis WHH2078	CRS In mice	significantly ameliorated depressive and anxiety-like behaviors	modulation of the gut microbiome composition	[96]

and neurochemistry of the brain in rats exposed to early-life stress. Results from the behavioural OFT and Moris Water Maze test showed the beneficial effects of this treatment. The hippocampus was examined to determine any changes in mRNA gene expression for stress-related genes (mineralocorticoid receptor, glucocorticoid receptor, corticotropin-releasing hormone receptor-1), BDNF and gamma-aminobutyric acid (GABA). Obtained data confirmed that probiotic and prebiotic supplementation reversed harmful changes in the expression of the above-mentioned genes.

Another study using pre- and probiotics alone and together was performed by Barrera-Bugueño et al. [84], who assessed the impact of *Lactobacillus. casei* and inulin supplementation (alone and in combination as a synbiotic) for two weeks in healthy juvenile rats, on the selected parameters related to stress. Obtained results showed that *L. casei* and inulin administered alone promoted an anxiety-like effect, but a reverse reaction was observed when inulin was administered in combination with *L. casei*. In turn, Gu et al. [85] evaluated the efficacy of a 3-week administration of *L. casei* in alleviating mental disorders using a rat model with depression-like behaviour induced in a CUMS rat. Results from the behavioural studies (OFT, FST) showed that L. casei supplementation improved CUMS-induced behaviour. Interestingly, CUMS-induced alterations in the expression of BDNF and its receptor tyrosine kinase B (TrkB), 5-hydroxytryptamine and the monoamine proteins dopamine, N-methyl-D-aspartic acid receptor 1, as well as CUMS-induced activation of ERK1/2 and p38 MAPK signalling pathways, were reversed. These findings suggest that *L. casei* may significantly protect against depression in rats, possibly related to changes in the composition of the gut microflora and mediating BDNF-TrkB signalling.

Further investigations by Li et al. [86] involving four weeks multi-strain treatment with *Bifidobacterium longum*, *Lactobacillus plantarum* and *Lactobacillus helveticus* in a mouse model of chronic mild stress (CMS), indicated significant improvement in the structure and community of the gut microbiome and the levels of indoleamine 2,3-dioxygenase-1 (IDO1) protein and pro-inflammatory cytokines in the hippocampus, compared to the control CMS group. This may point to an inextricable relationship between the gut microbiome and the immune and nervous systems. Moreover, the obtained data suggested that probiotics could modulate stress-related behaviour in rodents by lowering the

levels of pro-inflammatory cytokines in the hippocampus (TNF-α and IFN-γ), and by inhibiting IDO1 activity either directly or by inflammation.

Another study evaluating the anti-depressant effect of *Clostridium butyricum* in CUMS mice was undertaken by Sun et al. [87]. The results confirmed that *C. butyricum* played an anti-depressant role by stimulating the intestinal secretion of glucagon-like peptide (GLP1) by the GLP-1R receptor in the brain in CUMS mice. In addition, *C. butyricum* supplementation increased the levels of BDNF protein and 5-hydroxytryptamine (5-HT) in the brain of CUMS mice. Low levels of BDNF and 5-HT occur in people with depression. Moreover, results from behavioural studies (FST and TST) clearly showed that *C. butyricum* supplementation improved the depressive behaviour of CUMS mice.

Tian et al. [88] examined the effect of five weeks lactic acid bacteria treatment on depression induced by CUMS in mice. The results indicated reduction in the behavioural and neurological disturbances induced by chronic stress, mainly by the intervention of specific *Bifidobacterium (B. longum subsp. and B. breve),* and possibly through a 5-HT precursor 5-hydroxytryptophan (5-HTP) dependent mechanism.

Sun et al. [89] assessed the effect of long-term *Lactobacillus. kefiranofaciens* ZW3 supplementation on the depressive-like behaviour in a mouse model of CUMS. Obtained results indicated that *L. kefiranofaciens* administration contributed to the regulation of CUMS-disturbed tryptophan metabolism and plasma corticosterone levels in the mice. Furthermore, supplementation inhibited the inflammatory process and regulated the levels of IFN-γ and IL-6. Analysis of the intestinal microflora showed that the ratio of *Actinobacteria* to *Proteobacteria* was reduced in the CUMS group, compared to the control group, and *L. kefiranofaciens* treatment restored it. Finally, *L. kefiranofaciens* increased the abundance of anti-stress and anti-inflammatory microorganisms, such as *Akkermansia, Actinobacteria, Lachnospiraceae, Bacteroidetes, Bifidobacteriaceae* and *Coriobacteriaceae*, and lowered the levels of microorganisms that are associated with stress, i.e. *Praleobacteria.*

Another very interesting research on one of the largest anaerobic bacteria in the human intestinal microflora, *Faecalibacterium prausnitzii,* using a rat model of CUMS, indicated a significant preventive and therapeutic effects on CUMS-induced depression-like and anxiety-like behaviour. In addition, there was an increase in the levels of SCFAs in the caecum and in cytokine interleukin-10 (IL-10) in the plasma, with a simultaneous decrease in the level of corticosterone, inflammatory response protein (CRP) and interleukin-6 (IL-6). Moreover, *F. prausnitzii* supplementation significantly prevented the decrease in bone density of the entire body [90].

Guo et al. investigated [91] the effects of *Bifidobacterium adolescentis* supplementation on the intestinal microflora, inflammation and behaviur by using mice with chronic restrictive stress (CRS). Research indicated that *B. adolescentis* has an anxiolytic and anti-depressant effect in CRS mice in behavioural tests (OFT, FST). Moreover, the intestinal microflora analysis showed that administration of *B. adolescentis* to CRS mice restored the bacterial balance. *Lactobacillus* levels increased and the percentage of *Bacteroides* responsible for depression decreased. It follows that *Lactobacillus* is effective in improving behaviural deficits. Additionally, a reduction in the levels of TNF-α, IL-1β and NF-κB after the initial *B. adolescentis* treatment was observed, confirming that the reduced level of *Bacteroides* may be an important element of the anti-inflammatory effect of *B. adolescentis*.

Studies by Tian et al. [92] which included five weeks supplementation with *Bifidobacterium breve* in chronically-stressed mice indicated a significant reduction in depression- and anxiety-like behaviours. In addition, an amelioration of the hyperactive hypothalamic-pituitary-adrenal response, as well as inflammation, was observed. Moreover, *B. breve* supplementation also lowered the pCREB-c-Fos pathway and increased BDNF expression. Additionally, chronic stress-induced gut microbial abnormalities were restored.

Kochalska et al. [93], using *in vivo* magnetic resonance spectroscopy analysis, assessed the effect of four weeks supplementation with *Lcatobcillus rhamnosus* (LR-JB1™) in a CUMS rat model. Obtained results indicated that LR-JB1™ supplementation restored the levels of selected metabolites affected by stress (total creatine, GABA, glutamine, glutathione, glutamine/glutamate, N-acetylaspartate) to levels measured in healthy control animals, even in the presence of continued CUMS. Moreover, CUMS animals treated with LR-JB1™ had significantly more favourable behavioural EPM test results than the placebo CUMS group. Obtained results clearly indicate that the microbiotic diet with LR-JB1™ resulted in an improvement in the neurochemical balance and a reduction of stress-induced behaviour in the course of depressive disorders. Furthermore, their subsequent research indicated that a continuous ingestion of LR-JB1™ during chronic stress has a significant beneficial impact on levels of stress-related neurometabolites, such as glutamate, glutathione and taurine in the rat hippocampus, preventing the development of anxiety/depressive-like behaviour [94].

A study by Ding et al. [95] evaluating the anti-depressant effect of *Akkermansia muciniphila*, a gram-negative anaerobic bacterium widely distributed in the layer of human intestinal mucus, confirmed a significant amelioration of chronic stress-induced depressive-like behaviour in a mouse model of CRS. Biochemical analysis showed that *A. muciniphila* did not significantly affect the selected biochemical parameters. *A. muciniphila* inhibited the increase in serum corticosterone levels induced by CRS, which in turn caused significant regeneration in dopamine and BDNF levels, compared to the stressed group. Assessment of the intestinal microflora composition by sequencing the 16SrRNA genes after AKK supplementation indicated an upregulation of *Verrucomicrobia* and downregulation of *Epsilonbacteraeota, Acidobacteria, Chloroflexi* and *Patescibacteria,* compared to the CRS group.

Significantly reduced depressive and anxiety symptoms were observed by Gao et al. [96] in CUMS mice after five weeks oral administration of *Lactococcus lactis* WHH2078. Additionally, they proved that the *L. lactis* clearly increased the expression of tryptophan 1 (Tph1) hydroxylase, which converts tryptophan to 5-HTP in RIN14B cells and the level of 5-HTP precursor. Interestingly, *L. lactis* significantly decreased serum corticosterone levels and restored central levels of 5-HT, BDNF and 5-HTP in CUMS-induced mice. Analysis of the results from high-throughput 16S rRNA fecal sequencing, showed that *L. lactis* administration improved CUMS-induced intestinal microbial dysbiosis by restoring the alpha diversity and abundance of *Bacteroidetes* and *Firmicutes.*

CONCLUSIONS

Currently, many scientific studies have proved that gut microflora plays an important role in the two-way interactions between the gut and the nervous system. This communication takes place in several ways, and recent discoveries indicate that the vagus nerve, the neuroendocrine system and central neurotransmitters, the nervous system and inflammatory factors, are responsible for this connection. Undoubtedly, a key role in the proper maintenance of this communication is played by lifestyle.

Exposing the body to chronic stress can lead to disturbances of the bacterial flora and the gut-brain axis of GBA. Cortisol released in response to a stress stimulus is a necessary physiological response that helps in coping with difficult, threatening situations, but it is worth remembering that its release from the adrenal cortex triggers a whole cascade of subsequent biochemical reactions. This cascade can be dangerous to health if it is triggered too often, for example, in chronic stress. All the animal studies analyzed in this study have highlighted the potential role of pro-, pre- and synbiotics in altering the composition of gut microbiota. Future research in this area may help elucidate the relationship between the microbiota and the CNS and progress in improving brain disorders. Current research indicates that diet is a modulator of microbiota, as well as a potential therapy for the treatment of neuropsychiatric disorders. The positive effects of pro- and prebiotics in animals have also been confirmed in human studies, showing a positive relationship between pre- and probiotic intake, improvement in intestinal dysbiosis and mood. For healthy people, there is no need to take probiotic or prebiotic supplements. A diet consisting of a variety of vegetables, fruits, fermented foods and whole grains, enables people to consume enough probiotics and prebiotics without relying on supplements. However, when using these supplements, one should remember that, like any other, it should be taken with caution and after consulting a specialist.

Acknowledgements
This research was funded by the National Science Center, Poland, grant UMO-2019/35/N/NZ7/00982.

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