Pharmacological Research 172 (2021) 105840

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

The role of microbiota-gut-brain axis in neuropsychiatric and neurological disorders

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ARTICLE INFO

Keywords:
Microbiota-gut-brain axis
Neuropsychiatric disorders
Neurological diseases
Fecal microbiota transplantation
Probiotics

ABSTRACT

Emerging evidence indicates that the gut microbiota play a crucial role in the bidirectional communication between the gut and the brain suggesting that the gut microbes may shape neural development, modulate neurotransmission and affect behavior, and thereby contribute to the pathogenesis and/or progression of many neurodevelopmental, neuropsychiatric, and neurological conditions. This review summarizes recent data on the role of microbiota-gut-brain axis in the pathophysiology of neuropsychiatric and neurological disorders including depression, anxiety, schizophrenia, autism spectrum disorders, Parkinson's disease, migraine, and epilepsy. Also, the involvement of microbiota in gut disorders co-existing with neuropsychiatric conditions is highlighted. We discuss data from both in vivo preclinical experiments and clinical reports including: (1) studies in germ-free animals, (2) studies exploring the gut microbiota composition in animal models of diseases or in humans, (3) studies evaluating the effects of probiotic, prebiotic or antibiotic treatment as well as (4) the effects of fecal microbiota transplantation.

1. Introduction

The relationship between the gastrointestinal (GI) tract and the brain has been a subject of numerous studies for decades. The specific linkage between the GI tract and the central nervous system (CNS) has been termed the "gut-brain axis" and consists of bidirectional exchange between the two [1,2]. The modulation of the gut-brain axis by gut microbiota has recently gained much attention.

The term "microbiota" refers to consortia of microorganisms living in a defined environment, while the term "commensals" refers to microorganisms that colonize host without causing a disease. The development of omics technologies such as metagenomics, which enables to identify DNA isolated from a specific environment or culturomics, which enables to culture and identify an unknown bacterium, contributed to increasing the knowledge of the diversity of microbiota in humans [3]. The questions that can be answered thanks to advances in the methodology for studying microbiota are the following: which microbes are present in the microbiota? Do different experimental groups show significant differences in alpha- or beta-diversity? Alpha-diversity refers to the richness (the number of taxa) or evenness (the abundance of taxa) within a sample, while beta-diversity refers to the variability between samples. Finally, are there biomarkers of each group [4]? There has been an increasing interest in answering such questions in regard to neuropsychiatric disorders.

The observation that the gut microbiota modulates the gut-brain axis has shed new light on the concept of the pathophysiology of diseases,

Abbreviations: ANS, autonomic nervous system; ASD, autism spectrum disorder; ASDs, antiseizure drugs; BBB, blood-brain barrier; BDNF, brain derived neurotrophic factor; B-GOS®, Bimuno®-galactooligosaccharides; CNS, central nervous system; CUMS, chronic unpredictable mild stress; DHA, docosahexaenoic acid; ECs, endothelial cells; ENS, enteric nervous system; EPA, eicosapentaenoic acid; FDR, false discovery rate; FMT, fecal microbiota transplantation; GF, germ-free; GI, gastrointestinal; HAMA, Hamilton anxiety rating scale; HAMD, Hamilton rating scale for depression; HPA, hypothalamic-pituitary-adrenal; IBS, irritable bowel syndrome; LPS, lipopolysaccharide; MS, maternal separation; NADH, nicotinamide adenine dinucleotide; NTG, nitroglycerin; PF, pathogen-free; PUFAs, polyunsaturated fatty acids; SCFAs, short-chain fatty acids; TJ, tight junction; TLR, Toll-like receptor.

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https://doi.org/10.1016/j.phrs.2021.105840
Received 15 May 2021; Received in revised form 14 August 2021; Accepted 17 August 2021
Available online 24 August 2021

which has been described as a paradigm shift in neuroscience [1,5]. Psychological stress and inflammation are common denominators the pathophysiology of diseases in which microbiota may play a role. Stress plays a role in depression [6], schizophrenia [7], autism spectrum disorder (ASD) [8], epilepsy [9], and migraine [10], whereas inflammation plays a role in depression [11], schizophrenia [7], ASD [12], Parkinson's disease [13], epilepsy [14], and migraine [10]. Furthermore, the above-mentioned diseases often co-exist. For example, depression and ASD are common co-morbidities in epilepsy [14]. Depression also often co-exists with migraine [15]. Moreover, in patients suffering from migraine, there is higher prevalence of gut diseases such as inflammatory bowel disease or irritable bowel syndrome (IBS) [16].

In this review, we aimed to summarize data on the role of the microbiota-gut-brain axis in the pathogenesis of neuropsychiatric and neurological diseases, namely depression, schizophrenia, ASD, Parkinson's disease, epilepsy and migraine, in order to provide a current framework in this rapidly evolving research area. We start with background information on the microbiota-gut-brain axis. We then provide information in regard to the above-mentioned diseases based on studies in germ-free (GF) animals, studies exploring the composition of microbiota, relevant microbiome, or genes in animal models or in humans, studies on the effects of administration of probiotics, prebiotics or antibiotics and finally, the effects of fecal microbiota transplantation (FMT; Fig. 1).

Multiple hypothesis testing is an important component of microbiota studies. Adjusting *P* value has become a critical issue when analyzing differences in microbiota composition and the false discovery rate (FDR) approach is one of the most commonly used in such studies. We therefore try to distinguish between studies using adjusted *P* values and studies which used unadjusted *P* values for multiple comparisons so that there would be no doubt about the reliability of the data on changes in the gut microbiota profile. However, in some studies no such information has been provided.

1.1. Gut-brain axis – general information

The communication network between the gut and the CNS is complex and includes the enteric nervous system (ENS), both the sympathetic and parasympathetic autonomic nervous system (ANS) branches, and neuroimmuno- and neuroendocrine signaling pathways [17,18]. Visceral feedback from the intestines to the spinal cord (i.e., thoracic and upper lumbar) and to the nucleus of the solitary tract is carried out through the afferent spinal and vagal sensory nerves. In this way, they engage polysynaptic entrances to higher areas of the brain such as the hypothalamus and limbic forebrain. The cingulate and insular cortex, amygdala, bed nucleus of the stria terminalis, and hypothalamus are regions that modify vagal and spinal autonomic efflux to the viscera. Preautonomous neural projections from all of these structures provide bi-directional control of the gut-brain axis [19]. Not only the mentioned neural pathways, but also hormones and humoral signaling molecules are involved in this communication [17,18].

1.2. Microbiota-gut-brain axis and neurotransmitters

The gut microbiota including *Bacteroides* and *Firmicutes*, the two most prominent phyla of bacteria in healthy individuals [20], affect the host through neural, immune, neuroendocrine, and metabolic pathways [17,21–23]. The key communication routes between the enteric

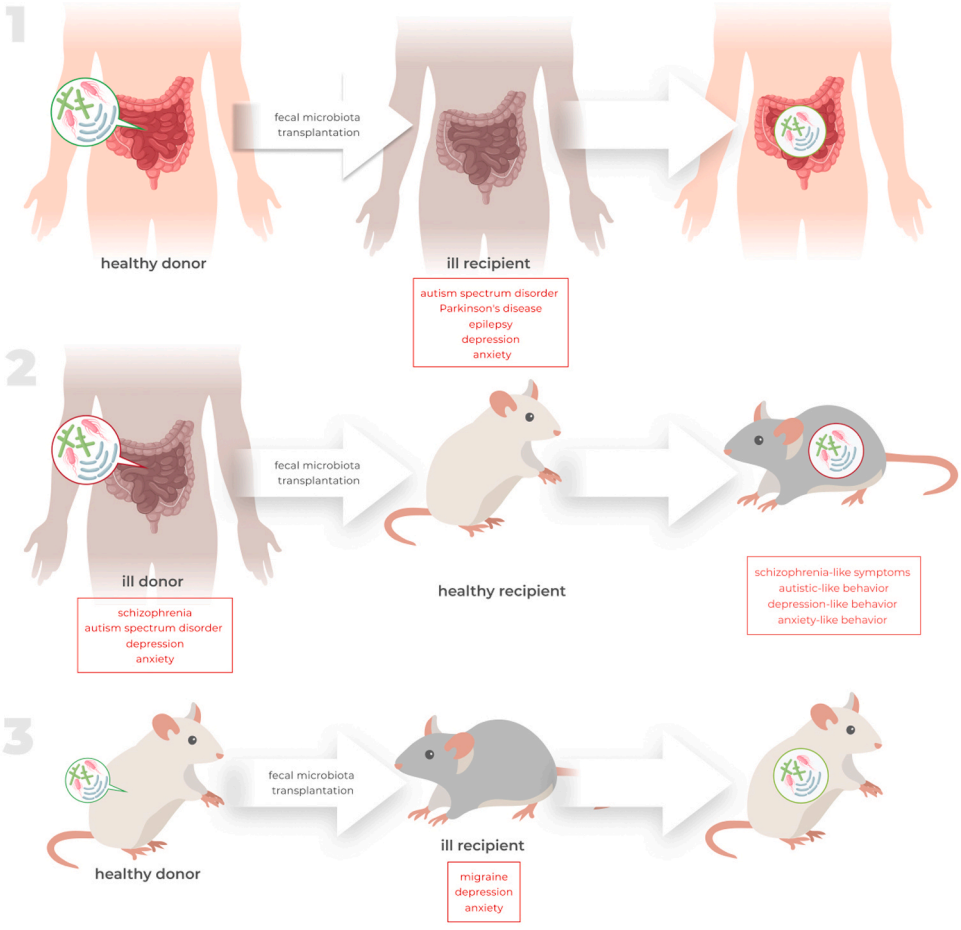

Fig. 1. Summary of the preclinical and clinical studies on the FMT in neuropsychiatric and neurological disorders.

microbiota and the brain are vagal nerve, tryptophan metabolites, and microbial products, such as short-chain fatty acids (SCFAs) or peptidoglycan [1,17,24].

The gut microbiota can affect brain function by modulating serotoninergic, noradrenergic, dopaminergic, glutamatergic, and GABA-ergic neurotransmission [25,26]. Microbiota can either influence synthesis/metabolism of neurotransmitters or produce these neuroactive substances by themselves. For example, *Candida, Escherichia, Enterococcus,* and *Streptococcus* belong to serotonin producers [27], *Bifidobacterium* and *Lactobacillus* generate GABA [1,27,28], *Lactobacillus* – acetylcholine, *Bacillus* and *Serratia* – dopamine, while *Escherichia* and *Saccharomyces* – norepinephrine [29]. Furthermore, in case of increased intestine amount of *Bacillus, Enterococcus, Escherichia, Saccharomyces*, or *Streptococcus* elevated levels of noradrenaline could be detected [1,27]. Because of the presence of the blood-brain barrier (BBB), it is unlikely that neurotransmitters produced in the gut will reach the brain, with the exception of GABA, as GABA transporters are present in the BBB. However, neurotransmitters produced in the gut may influence the brain indirectly, by acting on the ENS [30,31]. Also, the gut microbiota possess enzymes that control tryptophan metabolism pathways, leading to serotonin, kynurenine or indole derivatives. Thus, via influencing the amount of serotonin precursor – tryptophan, microbiota influence the amount of serotonin in the brain [32].

1.3. Blood-brain and epithelial intestinal barriers

The GI tract and the brain develop from closely related parts of the embryo [2,33]. What these two parts have in common are specific, specialized vascular barriers, namely the BBB and the intestinal epithelial barrier.

The BBB consists mainly of capillary endothelial cells (ECs). ECs of the BBB are an essential part of so called "neurovascular unit", built also of neurons, extracellular matrix, pericytes, and astrocytes [24,34–36]. The ECs are sealed by intracellular tight junction proteins, which partly control the BBB's integrity and function [24,34]. Tight junctions (TJs) (occluding junctions, *zonula occludens*) restrict paracellular diffusion of water-soluble substances from blood to the brain parenchyma, therefore providing proper neuronal function [34,35]. They are composed of transmembrane proteins: claudins, occludin and junction associated molecules as well as cytoplasmic accessory proteins [34,37,38].

The BBB development starts during early intrauterine life and continues until the early postnatal stages of life. Proper formation of the BBB provides adequate microenvironment for growth and specification of neurons [34,35]. The BBB, when intact, protects against colonization of microbiota during crucial moment of brain development in neonates. In the postnatal period, it also shields from bacterial metabolites and new molecules exposure during the metabolic switch (when dependence on carbohydrates shifts to fatty acid catabolism) [34,39]. This control over passage and exchange of nutrients and particles between the blood and the brain ensures homeostasis of the CNS [34].

Microbiota can affect the BBB permeability in both fetal and adult mice. Lack of the physiological gut microbiota in GF mice leads to greater BBB permeability, also in the embryos of GF mice, compared to pathogen-free (PF) mice which possess normal gut microbiota [24,34]. This abnormality is due to reduced TJ proteins' (occludin and claudin-5) expression – the ones which are responsible for regulation of the BBB functions in the endothelial tissue and for TJ's disorganization. Adult GF mice, when exposed to microbiota of PF mice, present up-regulation of TJ's proteins and decrease in the BBB permeability [34]. Transfer of SCFAs producing bacteria or fecal transfer from mice with PF gut flora to GF mice help to preserve the integrity of the BBB [33,34].

1.4. The role of stress and "leaky gut"

Results of both preclinical and clinical studies show that alterations in microbiota due to infection, exposure to antibiotics, lack of natural birth or breastfeeding, psycho- and physiological stress, coupled with genetics of the host, can produce long-term modulation of stress response and behavior [17,21,40–43]. Additionally, maternal infection, obesity, underweight, or stress during pregnancy, preterm birth, breastfeeding, mode of delivery (vaginal or cesarean), and antibiotic therapy in early childhood influence the gut microbiota in the offspring.

One of the hypotheses supporting the link between stress and microbiota is the "leaky gut" phenomenon. It is a disruption in the gut barrier, where the epithelium is compromised as a result of stress and it becomes permeable [22]. It causes a translocation of lipopolysaccharide (LPS) of Gram-negative bacteria which results in activation of the immune system (Toll-like receptors – TLRs) and production of pro-inflammatory cytokines (IL-6, IFN-γ, CRP, TNF-α) [1,5,44].

Increased levels of pro-inflammatory cytokines and environmental stress activate the limbic system, which is predominantly involved in memory, emotion and behavior [45]. Activation of the limbic system via the hypothalamic-pituitary-adrenal (HPA) axis leads to cortisol release from the adrenal glands. Cortisol, the core stress hormone, affects multiple human organs, including the brain [46]. There is evidence that GF animals have an increased HPA axis response, which can be reduced by *Bifidobacteria* colonization [5,17]. Stress induces a reduction in the number of *Lactobacillus* and *Bifidobacteria* species [47,48].

GF mice present different morphology and hypertrophied dendrites within the basolateral amygdala, a part of the limbic system, which is responsible for emotions (i.e., anxiety and fear), response to stress, and social behavior [5,17,49]. The behavioral pattern of GF rodents differs widely from that of conventional animals. GF mice display reduced anxiety level, increased stereotyped, repetitive, and locomotor behaviors, as well as cognitive deficits and changes in social behavior [50,51]. This behavioral phenotype is nonspecific and can be important in relation to many psychiatric and neurological conditions, which will be discussed thoroughly in this review.

The behavioral phenotype as well as some neurochemical, molecular, and cellular alterations in GF animals has been provided in Fig. 2.

2. The microbiota-gut-brain axis in neuropsychiatric diseases

2.1. Depression and anxiety

Major depression is one of the most common psychiatric diseases with multifactorial etiology. It is associated with structural and functional brain abnormalities within the hippocampus and the prefrontal cortex. Stress is considered as a precipitant of depression, whereas the HPA axis dysfunction is observed in depressed patients and in animal models of this disease [6]. Animal models of depression are often based on exposure to stress [52]. Furthermore, almost two-thirds of individuals with major depressive disorder have anxiety which can manifest both as comorbidity and as a predominant feature [6,53]. Animal models often manifest anxiety-like behavior in parallel to depression-like behavior [54].

The relationship between stress-induced diseases and the intestinal microbiota is receiving much attention (for review see: [55–57]). Data suggest that the gut microbiota plays an underlying role in several stress-associated neuropsychological conditions, including anxiety and depressive disorders [58–60]. The data on the role of the GI microbiome in modulating stress-induced changes in behavior and brain functioning are mainly provided by preclinical studies. In this part of our article, we review the preclinical (Table 1) as well as clinical (Table 2) reports on the role of the intestine microbiota composition in the pathology and therapy of depressive disorders and anxiety.

2.1.1. Germ free mice as a preclinical model to study gut-brain dysfunction in depression- and anxiety-like behavior

Maternal separation (MS) in rodents is a model of the early-life stress. This procedure may be carried out in various ways. Depending on frequency and duration of MS and postpartum day/days when separation

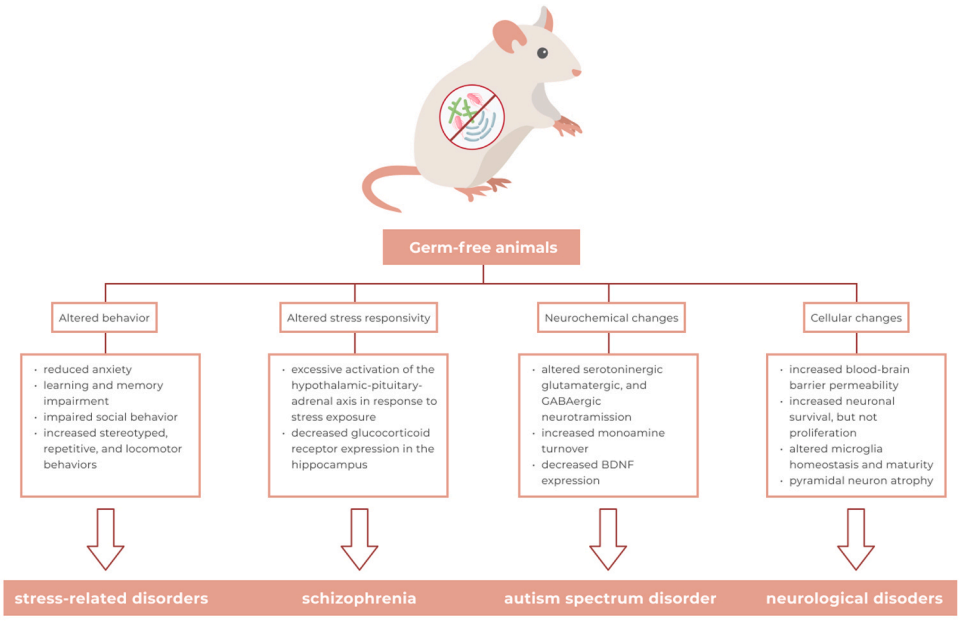

Fig. 2. Examples of the behavioral, neurochemical, molecular, and cellular alterations in GF animals.

starts, different degrees of stress both in mothers and pups were observed. However, in none of the described cases, except during the separation period, the litter was deprived of breast milk (for review see [61]). It was shown that MS elicits the anxiety- and depression-like behavior [61] and gut dysfunction [19]. As presented by De Palma et al. [62], MS induced the anxiety-like behavior in specific PF but not in GF mice. When two groups of adult GF mice – MS and control, were colonized with the microbiota of PF mice, which have not been MS, the microbial composition of the groups differed despite being colonized by the same donor. Moreover, the anxiety- and depression-like behavior were observed only in MS mice, thus suggesting that stress induced by MS leads to dysbiosis, which is a critical determinant of abnormal behavior [62]. GF mice displayed reduced anxiety-like behavior in the elevated plus maze and the light-dark test [62–65]. They also noted that MS caused a significant effect on the corticosterone level in murine serum. In turn, bacterial colonization of GF mice elicited the anxiety-like behavior and behavioral despair in MS mice. GF mice compared to PF animals exhibited also excessive activation of the HPA axis in response to restraint stress, which was reversed by monocolonization with *Bifidobacterium infantis* during the neonate period [66]. Contrary to mice, GF rats were characterized by enhanced anxiety. Absence of the intestinal microbiota was shown to increase the anxiety-like behavior in response to novel challenges in the F344 rats, which correlated with an excessive HPA axis response, as evidenced by a greater increase in the serum corticosterone concentration after acute stress in GF compared to PF rats [67].

The gut colonization of GF BALB/c mice with microbiota from NIH Swiss mice enhanced exploratory behavior and hippocampal levels of the brain derived neurotrophic factor (BDNF), whereas colonization of GF NIH Swiss mice with BALB/c microbiota reduced exploratory behavior [68]. Nishino et al. [69] showed that gut colonization by commensal microflora in GF mice immediately after birth contributed to an increase in the striatal monoaminergic neurotransmission, which resulted in normalization of the anxiety-like behavior. Instead, De Palma et al. [62] noted that colonization of adult GF MS and control mice with the same microbiota produced distinct microbial profiles, which were associated with altered behavior in MS, but not in control animals.

Further, Clarke et al. [63] and De Palma et al. [62] also showed differences in the hippocampal monoamine levels between GF and control animals. The first of the above-mentioned research teams indicated that in GF mice the hippocampal serotonin concentration was markedly higher than in controls [63], whereas the second team demonstrated that the presence of gut microbiota had a significant impact on serotonin as well as on noradrenaline levels in the hippocampus [62]. Additionally, De Palma and co-workers [62] noted no significant changes in serotonin, dopamine and noradrenaline levels in PF MS mice versus the control mice. It was concluded that the CNS neurotransduction can be profoundly disturbed by the absence of a normal gut microbiota and that this aberrant neurochemical, but not behavioral, profile is resistant to restoration of a normal gut flora in later life [63]. Furthermore, it was established that biochemical alterations in GF mice might also depend on sex. Neufeld et al. [65] found decreased 5HT1A receptor gene expression in the dentate gyrus in female, but not in male GF mice. Likewise, changes in BDNF expression were observed only in male GF mice [63]. It was observed that male GF mice presented lower expression of the BDNF gene in the cortex and amygdala [50], while the BDNF levels in their hippocampus were either decreased [50, 63–65] or increased [65]. Notwithstanding, De Palma et al. [62] showed that GF MS mice exhibited higher hippocampal BDNF levels than GF controls, but on the contrary to Clarke et al. [63] and Diaz Heijtz et al. [50], they did not observe any significant gender impact on the BDNF concentration. As demonstrated by Ogbonnaya et al. [70], microbiota was also able to regulate the process of hippocampal neurogenesis. In GF mice, increased neurogenesis was observed in the dorsal part of this brain structure [70].

2.1.2. Possibility of transmitting and alleviating the symptoms of mood disorders by fecal microbiota transplantation

In preclinical studies, behavioral effects of FMT from animals as well as human donors were widely examined. Moreover, both worsening and alleviating properties of the intestinal microbiome transferred from unhealthy and healthy subjects, respectively, were tested. Pearson-Leary et al. [71] observed that rats receiving fecal microbiota from animals exhibiting passive behaviors and short-latencies to defeat displayed depressive-like behaviors. Similarly, Li et al. [72] showed that GF mice transplanted with fecal samples obtained from mice subjected to the chronic unpredictable mild stress (CUMS) presented increased the anxiety- and depression-like behavior. They also found that the intestinal microbiome dysbiosis, mainly *Lactobacillus* depletion and augmented *Akkermansia*, contributed to the exacerbation of

Table 1
Summary of recent preclinical studies on the role of the gut microbiota in depression and anxiety.

Animals	Model and/or treatment	Behavioral test	Key finding (s)	Ref.
Sprague-Dawley rats	**Social defeat model** FMT	Forced swim test Social interaction test	(1) Naïve rats after FMT from SL/vulnerable rats had higher microglial density and IL-1β expression in the ventral hippocampus, and depression-like behaviors relative to rats that received microbiota from LL/resilient rats, non-stressed control rats, or vehicle-treated rats; (2) Anxiety-like behavior was not altered by FMT from SL/vulnerable rats into non-stressed rats	[71]
C57BL/6J mice	**CUMS model** FMT	Sucrose preference test Open-field test Elevated plus maze Forced swim test	(1) FMT from CUMS-donors induced anxiety-like and depression-like behavior in the recipient mice; (2) Microbial dysbiosis, especially *Lactobacillus* depletion and enriched *Akkermansia*, was associated with neuroinflammation	[72]
FSL and FRL rats	FMT	Open-field test Forced swim test	(1) The gut microbiota composition of the depressive-like FSL rats significantly differed from control FRL rats; (2) FSL rats tended to have lower bacterial richness and altered relative abundances of several bacterial phyla, families, and species, including higher *Proteobacteria* and lower *Elusimicrobia* and *Saccharibacteria*; (3) FMT with pooled FSL or FRL feces did not reverse these bacterial differences; (4) FMT altered depressive-like behavior and did not affect the locomotor activity	[78]
C57BL/6N and CD-1 mice	**PTSD model** FMT	Open-field test Novel object test	Transplantation of SHC feces had mild stress-protective effects, indicated by an amelioration of CSC-induced anxiety	[73]
C57BL/6J mice	**CUS model** FMT	Sucrose preference test Forced swim test Open-field test	(1) NLRP3 inflammasome deficiency affected the gut microbiota composition; (2) FMT from NLRP3 KO mice: (a) ameliorated CUS-induced depressive-like behaviors, (b) alleviated astrocyte dysfunction in CUS mice, and (c) inhibited the increased expression of circHIPK2 in CUS mice	[74]
C57BL/6 mice and Sprague-Dawley rats	FMT Antibiotics cocktail (ampicillin, neomycin, metronidazole) in drinking water for 14 consecutive days	Sucrose preference test Tail suspension test Force swim test Locomotor activity test	(1) Abnormal composition of gut microbiota may be associated with individual differences of anhedonia-like phenotype in rats with neuropathic pain; (2) Antibiotics-treated mice (pseudo-GF mice) showed depression-like and anhedonia-like phenotypes; (3) FMT from spared nerve injury rats with or without anhedonia can alter depression-like and anhedonia-like phenotypes in the pseudo-GF mice	[76]
Lewis rats	FMT	Light-dark test Sucrose preference test Elevated plus maze test Open-field test	(1) Incomplete unilateral cervical spinal cord injury induced anxiety-like behavior and alterations in gut microbiota; (2) FMT from healthy rats prevented spinal cord injury-induced dysbiosis and reduced anxiety-like behavior	[77]
Sprague-Dawley rats	FMT from human donors	Sucrose preference test Elevated plus maze test Open field test Forced swim test	(1) FMT from depressed patients to microbiota-depleted rats induced behavioral and physiological features characteristic of depression in the recipient animals; (2) Depression was associated with decreased gut microbiota richness and diversity	[79]
GF and PF Kunming mice	FMT from human donors	Open field test Y-maze test Tail suspension test Forced swim test	(1) Absence of gut microbiota produced depressive-like behaviors mice; (2) FMT from MDD patient induced depression-like behaviors in GF recipient mice; (3) Gut microbiota contributed to depression-like behavior through altering host metabolism	[80]
GF mice	**CUMS and OB model** FMT from human donors	Open field test Tail suspension test Forced swim test Olfaction behavior test	(1) FMT from MDD patient induced depression-like behaviors in recipient mice; (2) Compared with physical and psychological stressors, gut microbes caused distinct molecular changes underlying neurogenesis and canonical pathways	[81]
GF rats	FMT from human donors	Forced swim test Sucrose preference test	FMT from depressed patients: (a) induced depressive-like behaviors in recipient rats as well as (b) reduced the hippocampal neurotransmitter level, (c) promoted HPA axis hyperfunction, (d) increased serum pro-inflammatory cytokine levels, (e) decreased anti-inflammatory cytokine levels, and (f) induced mitochondrial ultrastructural damage in small intestinal epithelial cells	[82]
Mice	**Chronic alcohol exposure model** FMT from human donors	Tail suspension test Open field test	FMT (a) started two-week at the end of alcohol treatment had few effects, (b) started at 8% ethanol exposure alleviated alcohol-induced depression, and (c) started five-week at the end of alcohol treatment significantly decreased anxiety- and depression-like behaviors	[86]
C57BL/6J mice	FMT from human donors	Alcohol preference test Open field test Elevated plus maze test Tail suspension test Social interaction test	FMT from patients with alcoholism: (a) induced spontaneous alcohol dependence in mice, (b) induced anxiety-like and depression-like behaviors changes in mice, (c) declined social interaction behaviors, and (d) decreased mGluR1, protein kinase C ε levels in nucleus accumbens as well as BDNF and α1GABAAR levels in medial prefrontal cortex	[87]
BALB/c mice	Ceftriaxone sodium (250 mg/ml) 0.2 ml/day p.o. once daily for 11 weeks	Open field test Tail suspension test	(1) Ceftriaxone-treated mice exhibited anxiety- and depression-like behaviors; (2) The relative abundance of *Firmicutes* was lower in the antibiotic-treated group than in control group; (3) In the antibiotic-treated group abundance and proportion of gut microbiota composition were changed; (4) Ceftriaxone caused dysregulation of the nerve-endocrine-immunological network	[99]
GF BALB/c mice	FMT from human donors *Bacteroides vulgatus* (5×10^8 CFU/0.5 ml) in skim milk once a week	Open field test Marble-burying test	FMT from patients with anorexia: (a) induced anxiety-like and compulsive behaviors in GF recipient mice, (b) decreased 5-HT levels in the brainstem of recipient mice, and (c) pretreatment with *Bacteroides vulgatus* attenuated compulsive behavior in recipient mice	[88]
GF NIH Swiss mice	FMT from human donors	Light-dark test Step-down test	(1) Microbiota profiles in recipient mice clustered according to the microbiota profiles of the human donors; (2) Mice receiving FMT from IBS patients (a) showed a taxonomically similar microbial composition to that of mice receiving FMT healthy donors and (b) different serum metabolomic profiles	[89]
Sprague-Dawley rats	Antibiotic cocktail (ampicillin,vancomycin, ciprofloxacin, imipenem, metronidazole) in	Open field test Elevated plus maze test Forced swim test	Antibiotic treatment (a) had no impact on anxiety-related behavior, (b) induced depressive-like behaviors, (c) altered brain monoamines and plasma tryptophan levels, and (d) affected gut microbial diversity	[98]

(*continued on next page*)

Table 1 (*continued*)

Animals	Model and/or treatment	Behavioral test	Key finding (s)	Ref.
	drinking water for 6 weeks			
C57BL/6 mice	Ciprofloxacin (10, 20, 30, 40, and 50 mg/kg) p.o. 200 μl for 10 days	Elevated plus maze test	Ciprofloxacin increased anxiety-like behaviors (except dose at 10 mg/kg) and decreased locomotor and exploratory behaviors (at all tested doses)	[102]
C57BL/6 mice	**Chronic social defeat stress**	Open field test Three-chambered sociability test Aggressor interaction test Light-dark test	(1) Chronic social defeat induced behavioral changes that were associated with reduced richness and diversity of the gut microbial community; (2) Defeated mice exhibited: (a) reduced functional diversity and a lower prevalence of pathways involved in the synthesis and metabolism of neurotransmitter precursors and short-chain fatty acids and (b) sustained alterations in dendritic cell activation, and transiently elevated levels of IL-10 + T regulatory cells	[105]
C57/6 mice	**CUMS** Fluoxetine (12 mg/kg) p.o.	Tail suspension test Sucrose preference test Elevated plus maze test Open field test	(1) Stress led to low bacterial diversity, simpler bacterial network, and increased abundance of pathogens, such as *Escherichia/Shigella*, and conditional pathogens, such as *Enterococcus*, *Vagococcus*, and *Aerococcus*; (2) Fluoxetine directly and indirectly attenuated the stress-induced changes in gut microbiota; (3) There were strong correlations between gut microbiota and anxiety- and depression-like behaviors	[107]
GF Zebrafish	**Osmotic stress treatment** *Lactobacillus plantarum* (2×10^7 CFU/ml) injected into the water of the larvae housing flask for 2 day	Locomotor activity test Thigmotaxis test	(1) The absence of a microbiota dramatically altered locomotor and anxiety-related behavior; (2) Characteristic responses to an acute stressor were obliterated in larvae lacking exposure to microbes; (3) Treatment with L. *plantarum* was sufficient to attenuate anxiety-related behavior in conventionally-raised zebrafish larvae	[119]
GF C57BL/6JNarl mice	*Lactobacillus plantarum* PS128 (10^9 CFU/mouse/day) in drinking water for 16 days	Open field test Elevated plus maze test Forced swim test	(1) *Lactobacillus plantarum* PS128 improved the anxiety-like behaviors; (2) The behavioral changes were correlated with the increase in the monoamine neurotransmitters in the striatum	[121]
BALB/c and Swiss Webster mice	**Acute restraint stress** *Lactobacillus rhamnosus* JB-1 (10^9 CFU/day) in drinking water for 28 days	Tail suspension test	*Lactobacillus rhamnosus* JB-1 in BALB/c mice, but not in Swiss Webster mice: (a) reduced depressive-like behavior, (b) attenuated plasma corticosterone, and (c) hastened recovery	[123]
Sprague-Dawley rats	Standard or high-fat diet Probiotic (*Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19, *Lactococcus lactis*W58) 4.5 g (2.5×10^9 CFU/g) of freeze-dried powder dissolved in 30 ml of tap water/cage	Barnes maze test Forced swim test Open field test	(1) Multi-species probiotics clearly lowered depressive-like behavior, and high-fat diet did not affect the effectiveness of the treatment; (2) Probiotics were shown to interact with patho-physiological mechanisms believed to play an important role in MDD, including the immune system, HPA axis regulation and microbial tryptophan metabolism	[129]
C57BL/6 mice	**Immobilization stress** *Lactobacillus reuteri* NK33 and *Bifidobacterium adolescentis* NK98 (1×10^9 CFU/mouse/day) p.o. for 5 days	Elevated plus maze test	Treatment with *Lactobacillus reuteri* NK33 and/or *Bifidobacterium adolescentis* NK98, before or after immobilization stress: (a) suppressed the occurrence and development of anxiety/depression and (b) suppressed fecal *Proteobacteria* population and excessive LPS production	[130]
CD-1 mice	**LPS-induced depression** Lyophilized kefir culture with a lactic acid bacteria (15×10^9 CFU/L) p.o. for 3 weeks	Elevated plus maze test Open field test	Pubertal exposure to probiotics:(a) prevented LPS-induced depressive-like behavior in females and anxiety-like behaviors in males, (b) prevented LPS-induced increases in pro- and anti-inflammatory peripheral cytokines, (c) reduced central cytokine mRNA expression, and (d) prevented LPS-induced changes in the gut microbiota	[131]
C57BL/6J mice	**Corticosterone-induced depression** *Lactobacillus paracasei* PS23 (10^8 live or heat-killed cells/0.2 ml/day) p.o. from days 1–41	Open field test Forced swim test Sucrose preference test	(1) Depressive-like behaviors induced by corticosterone were ameliorated by treatment with live *Lactobacillus paracasei* PS23 and heat-killed PS23; (2) Live and heat-killed *Lactobacillus paracasei* PS23 reversed corticosterone-reduced protein levels of BDNF, mineralocorticoid, and glucocorticoid receptors in the hippocampus; (3) Live *Lactobacillus paracasei* PS23 reversed corticosterone-reduced serotonin levels in the hippocampus, prefrontal cortex and striatum; (4) Heat-killed *Lactobacillus paracasei* PS23 reversed corticosterone-reduced dopamine levels in the hippocampus and prefrontal cortex	[132]
Swiss mice	*Lactobacillus plantarum* 286 or *Lactobacillus plantarum* 81 (10^9 CFU) p.o. for 30 days	Open field test Forced swim test Plus maze-discriminative avoidance test	(1) Treatment with *Lactobacillus plantarum* 286 and 81 did not interfere with locomotor activity or learning and memory; (2) *Lactobacillus plantarum* 286 produced antidepressant- and anxiolytic-like behaviors in mice	[133]
PF C57BL/6 and CD-1 mice	**Chronic social defeat stress** *Clostridium butyricum* Miyairi 588 ($>5 \times 10^6$/CFU) p.o. in drinking water for 4 weeks	Social interaction test Sucrose preference test Forced swim test Tail suspension test	(1) Increased *Firmicutes* abundance in mice exposed to chronic social defeat stress treated with *Clostridium butyricum* Miyairi 588; (2) Depression-like behaviors in the mice were correlated with certain strains (i.e., *Clostridium leptum*, *Blautiacoccoides*, *Streptococcus hyointestinalis*) at the species level; (3) *Clostridium butyricum* Miyairi 588 prevented stress-induced behaviors and regulated neuroinflammation	[141]

(*continued on next page*)

Table 1 (*continued*)

Animals	Model and/or treatment	Behavioral test	Key finding (s)	Ref.
C57BL/6J mice	**Social isolation stress** Standard laboratory diet or laboratory diet containing 0.1% or 1% DHA	Open field test Elevated plus maze test Sucrose preference test	(1) Distinct microbial compositions in males and females prior to DHA supplementation; (2) DHA induced sex-specific interactions on the gut microbiota with the fatty acid producing a significant effect on the microbial profiles in males but not in females; (3) *Allobaculum* and *Ruminococcus* significantly correlated with the behavioral changes observed in male mice; (4) DHA altered commensal community composition and produced beneficial effects on anxiety and depressive-like behaviors in a sex-specific manner	[165]

Abbreviations: BDNF, brain-derived neurotrophic factor; CFU, colony-forming unit; CSC, chronic subordinate colony housing; CUMS, chronic unpredictable mild stress; CUS, chronic unexpected stress; DHA, docosahexaenoic acid; FRL, Flinders resistant line; FSL, Flinders sensitive line; GF, germ-free; HPA, hypothalamic-pituitary-adrenal; LL/resilient rats, rats with long-defeat latencies; MDD, major depressive disorder; mGluR1, metabotropic glutamate receptors 1; MS, maternal separation; OB, olfactory bulbectomy; p.o., per os; PTSD, posttraumatic stress disorder; SHC, non-stressed single-housed control; SL/vulnerable rats, rats with short-defeat latencies; PF, specific pathogen-free.

neuroinflammation [72].

The alleviating properties of FMT were tested in several preclinical studies [73,74]. Langgartner et al. [73] found that frequent FMT from unstressed mice to animals exposed to chronic psychological stress resulted in reduction of anxiety- and depression-like symptoms in the recipient rodents. Similar results were obtained by Zhang et al. [74] who transplanted the fecal microbiota into GF mice from mice lacking the NLPR3 gene, the expression of which is known to be increased in both animal models of depression and in patients with depressive disorders [75]. Furthermore, Yang et al. [76] found that mice receiving FMT from anhedonia resilient rats had improved depression-like symptoms. Likewise, a reduction of depressive- and anxiety-like symptoms in animals subjected to a spinal cord injury was observed by Schmidt et al. [77] after the FMT from healthy animals. On the contrary, Tillmann et al. [78] provided evidence against the possibility to transfer through such a procedure the resilience from rats, which were resistant to the development of depressive-like behaviors.

The effect of FMT from human with depression, but also from patients with anorexia, IBS and alcoholism with coexisting mood disorders, on the anxiety- and depressive-like behavior in GF animals was also investigated. Kelly et al. [79] prepared microbiota samples obtained from depressed patients and healthy controls and administered them via oral gavage to a microbiota-deficient rat model. The authors observed that FMT from depressed individuals to microbiota-depleted rodents induced behavioral as well as physiological changes in the acceptors, i.e., the anxiety-like behavior, anhedonia and modifications in tryptophan biotransformation. Their observations were later confirmed by two independent research teams [80,81]. Surprisingly, in the forced swim test, Kelly et al. [79] did not note any changes in the immobility duration of animals. In turn, an increase in the immobility time in the forced swim test in GF mice after FMT from humans with depression was found by Zheng et al. [80], Huang et al. [81] and Liu et al. [82]. Additionally, Zheng et al. [80] and Huang et al. [81] also found a significant reduction in the motility duration in the tail suspension test in animals after FMT from depressed patients. All of the studies mentioned above support that FMT from humans suffering from depressive disorders resulted in the depression- and anxiety-like behavior in the recipient GF animals. Besides, preclinical investigations provided evidence that depression is linked with reduced gut microbiota richness and variety [82].

Due to the abundant evidence of a close comorbid between alcoholism, anorexia, as well as, IBS with mood and anxiety disorders [83,84], a number of research teams have attempted to assess the effects of FMT from patients with these diseases on the affective behavior of laboratory animals (for review see [85]). In the preclinical studies examining the effect of FMT on depressive and anxiety-like behaviors related to alcoholism, Xu et al. [86] showed that if FMT from healthy human donors to mice started before or during the alcohol administration, the depression and anxiety-like behaviors were not developed. In turn, a year later, Zhao et al. [87] carried out a reverse-designed study, i.e., they transplanted into GF animals a microbiome derived from alcoholics and observed that such a procedure resulted in anxiety- and depression-like behaviors in recipient animals. An enhancement in anxiety-like behaviors in mice was also noted after FMT from human donors with anorexia [88], as well as, from anxious IBS patients [89]. However, such changes were not observed after FMT from non-anxious IBS donors [89].

The impact of FMT from healthy human donors on psychiatric symptoms in recipients was also assessed in clinical trials (for review see [85]). For example, Mizuno et al. [90] in open-label, non-randomized, single-center trials found that psychiatric status of IBS patients, assessed using the Hamilton Rating Scale for Depression (HAMD), was significantly improved at 1 month after FMT from healthy donors, but returned to the baseline level after 12 weeks. Also, the scores on the Hamilton Anxiety Rating Scale (HAMA) in these patients were improved, however, the changes were not statistically significant. Similarly, Huang and co-workers [91] noted significant score improvement in HAMD, as well as, in HAMA in IBS subjects at 1 and 3 months after FMT received from healthy individuals. Furthermore, at 6 months after FMT, amelioration of depressive but not anxiety symptoms was still statistically significant in comparison to baseline scores [91]. On the other hand, an improvement in HAMD and HAMA scores only at 3 weeks after FMT was found by Mazzawi et al. [92]. In turn, Xie et al. [93] in a case report presented the results of patient with IBS who received six rounds of FMT from a healthy donor. During the 18-month follow-up, his depressive symptoms improved considerably (HAMD score was lowered from 30 to 13 points). A significant improvement in mood symptoms following FMT at 6, but not at 3 and 12 months, was also found by Johnsen et al. [94] in a double blind, randomized, placebo-controlled trial. Moreover, in an open-label observational study, Kurokawa et al. [95] found a correlation between an increase of microbiota diversity after FMT procedure and improvement in depression scores. Outcomes of the cited research indicated a significant short-term relief of depressive symptoms in FMT-acceptors, whereas the results of studies revealing a long-term amelioration of depression manifestation in patients after FMT are not consistent because recovery occurred over a shorter or longer period after FMT procedure and persisted for various time. Unfortunately, all the above-mentioned studies involved small sample size and three of them used an unadjusted *P* value or no such information is shown, which raises the possibility of false-positive outcomes. Only Mazzawi et al. [92] and Kurokawa et al. [95] performed the FDR correction. Furthermore, only trials conducted by Johnsen et al. [94] were placebo-controlled.

Based on mentioned above clinical trials, but also the latest systematic review by Chinna Meyyappan et al. [85], there is strong evidence for the possibility of targeting the gut-brain axis with FMT to mitigate depression- and anxiety-like symptoms. However, subsequent studies taking into account larger study groups as well as stronger scientific protocol are warranted to fully establish the efficacy and safety of this therapeutic procedure.

2.1.3. Antibiotic-induced dysbiosis provoked anxiety- and/or depression-like behaviors

Administration of antibiotics could result in a significant dysbiosis of

the intestinal microbiota by killing most of the physiological microbiota and consequently, it could provide the space for the development of pathogens (for review see [96]). Accordingly, the influence of the intestinal microbiota on the CNS after depleting bacteria using broad-spectrum antibiotics has also been widely examined. Until the 90 s of XX century, numerous reports described psychiatric side effects, inter alia anxiety and major depression, in patients receiving antibiotics (for review see [97]). Preclinical research conducted recently confirmed that antibiotic-induced dysbiosis provoked anxiety- and/or depression-like behaviors in rodents [98,99]. Furthermore, an exposure to antibiotics for several weeks lowered diversity, changed abundance of the intestinal microbiota, and dysregulated the nerve-endocrine-immunological network in tested animals [87,100]. Likewise, the outcomes of clinical trials confirm that exposure to antibiotics, such as penicillin and quinolones, is associated with an increased risk of depression and anxiety [101]. Psychiatric events, including anxiety and depression disorder, were reported by Kaur and co-workers [102] in patients who took fluoroquinolones (72% and 62%, respectively), but also in mice. Accordingly, this might be a potential mechanism underlying abnormal psychical behaviors induced by the impaired gut microbiota. Inconsistent with the results shown above, there are preclinical data provided by Desbonnet et al. [100], as well as clinical reports presented by Murphy et al. [103].

2.1.4. Relationship between the gut microbiota composition and anxiety- and depression-like behaviors

The outcomes of animal studies confirm the relationship between the composition of the intestinal microbiota and the responsiveness to stress [62,104–107]. Additionally, Sun et al. [107] provided evidence of a strong correlation between the gut microbiota and anxiety- and depression-like behaviors, and they showed that the commonly used antidepressant – fluoxetine, both directly and indirectly attenuated stress-induced changes in the intestinal microbiota. In turn, the results of studies on microbiome alterations in depressed patients are conflicting. Serum levels of IgM and IgA against the LPS of enterobacteria were significantly elevated in depressed patients compared to healthy controls, thus suggesting that bacterial translocation or "leaky gut" may play a role in the pathophysiology of depression [108]. Jiang et al. [109] identified higher diversity in microbiota obtained from fecal samples of patients suffering from depressive disorder compared to healthy controls – the level of *Enterobacteriaceae* and *Alistipes* were enhanced, while the level of *Faecalibacterium* was reduced in depressive patients [109]. In subsequent studies, the above-mentioned authors found a markedly reduced intestinal microbial richness and diversity, as well as a marked decrease in bacteria producing SCFAs and excess of *Escherichia-Shigella*, *Fusobacterium* and *Ruminococcus gnavus* in patients with mental disorders in comparison to healthy individuals. Surprisingly, the above-mentioned changes were not revoked in patients with mood disease remission [110]. A link between improvement in symptoms of psychiatric disorders, including depression and anxiety and a decrease in gut microbiota biodiversity and severity (particularly *Firmicutes* and *Actinobacteria*) was observed in hospitalized psychiatric individuals [111]. Additionally, they demonstrated that superior greater richness and alpha diversity of the intestinal microbiota are related to remission of depression after inpatient treatment [111]. On the other hand, Naseribafrouei et al. [112] did not find any differences with respect to species richness in the fecal microbe profile in controls and depressive patients, except for *Bacteroidales* and *Lachnospiraceae,* which were overrepresented and underrepresented, respectively. In one of the newest studies, Chung et al. [113] carried out an analysis of the composition of gut microbiota and identified as many as 23 microbiota targets, which were probably related to depression and/or anxiety. In patients suffering from depressive disorders, *Actinobacteria* as well as *Firmicutes* were superabundant. The analysis at the genus level indicated an elevated abundance of *Bifidobacterium* and *Blautia* with decreased abundance of *Prevotella* in subjects with major depression. In addition, a moderate relationship between abundance of *Holdemania* and both anxiety and perceived stress level in depressed patients was shown [113]. Likewise, Coello et al. [114] found differences in the gut microbiota between patients with bipolar disorders and healthy individuals. Among the 64 bacterial genera, they identified *Flavonifractor* as a markedly more prevalent one in subjects with a newly diagnosed bipolar disorder when compared to healthy subjects [114]. It is worth to emphasize that in most of the cited studies, adjusted *P* value were used (see Table 2), what minimizes the possibility of receiving false-positive results.

To the best of our knowledge, one meta-analysis and systematic review on the association between intestinal microbiota and major depressive disorders [115] and one systematic review on the gut microbiota of the research characterizing the intestinal microbiota in depression and anxiety [116] have been published. The outcomes of them revealed: (1) inconsistencies in the alfa diversity – in most case-control trials (in 10 of 12) there are no differences in alpha diversity in depression/anxiety vs. control groups; (2) no consensus in the beta diversity – in 9 research beta diversity differed between depression/anxiety groups and controls, whereas in 6 trials were no such dissimilarity; (3) decreased abundance of *Bacteroidetes*, *Prevotellaceae*, *Faecalibacterium*, *Coprococcus*, and *Sutterella* and increased abundance of *Actinobacteria* and *Eggerthella* in individuals with depressive disorders in comparison to healthy controls; (4) a lower number of *Prevotellaceae*, *Faecalibacterium*, *Sutterella* and *Dialister*, and a higher number of *Lactobacillus* is characteristic of both depressive and anxiety disorders; and (5) an important inter-research variable is the usage of CNS acting drugs. In future studies aimed at understanding the involvement of the gut microbiota in the pathophysiology of depression/anxiety disorders this latter factor should be included) [115,116].

2.1.5. Effect of probiotic administration on the anxiety- and depressive-like behavior

Preclinical and clinical studies revealed a beneficial effect of probiotic administration on the anxiety- and depressive-like behavior in mice [117,118], rats [47], zebrafish [119], and human [47,48,120] (Tables 1 and 6). The GF mouse model was used to study the impact of chronic administration of *Lactobacillus plantarum* PS128 (PS128) on the anxiety-like and depression-like behaviors and the impact on the level of monoamine neurotransmitters in different regions of the brain, including the striatum, prefrontal cortex, and hippocampus [47,48,121]. Chronic administration of live PS128 did not induce adverse effects. Administration of live PS128 significantly extended the total distance traveled by mice in the open field test and increased the time spent in open arms in the elevated plus maze test but it did not affect the depressive-like behavior of GF mice in the forced swim test [121]. Analysis of the level of monoamine neurotransmitters showed that chronic live PS128 administration significantly increased the concentrations of both serotonin and dopamine in the striatum. No such changes were noted in the prefrontal cortex and hippocampus [121].

Administration of *Lactobacillus rhamnosus* JB-1 and *Bifidobacterium longum* NCC3001 in mice [68,117], as well as administration of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 in rats [47] produced anxiolytic- and antidepressant-like effects or prevented anxiogenic-like effects in mice with the gut parasite *Trichuris muris* chronic infection [122]. Additionally, studied probiotics were able to increase the levels of monoamine neurotransmitters in animals' striatum [121], as well as to diminish both BDNF [122] and corticosterone [123] levels. Earlier, Gareau et al. [124] demonstrated that preparations containing either *Lactobacillus rhamnosus* or *Lactobacillus helveticus* normalized corticosterone levels in rats exposed to MS stress via improving the gut function. Moreover, reduction in the plasma corticosterone concentration corresponded with a decreased anxiety-like behavior after stress exposure in mice in the elevated plus-maze test after treatment with *Lactobacillus reuteri* [117,125]. Desbonnet et al. [126] showed that *per os* administration of *Bifidobacteria infantis* 35624

(1×10^{10} live bacterial cells in 100 ml of drinking water once daily) caused antidepressant-like effects in rats in the forced swim test, which were correlated with neurochemical changes in the brain (i.e., lower concentrations of serotonin and dopamine metabolites). Subsequent study has shown that the non-live *Lactobacillus brevis* SBC8803 in mice stimulated serotoninergic receptors located in the intestinal cells [127], which indicated that also non-viable microorganisms have the potential to modulate the gut-brain axis. Moreover, the administration of probiotics in animals, in which anxiety and depressive-like behaviors were induced experimentally, was able to overcome them [126,128]. Newly, Abildgaard et al. [129] clearly indicated that probiotic treatment (*Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19, *Lactococcus lactis* W58), independently of diet, significantly reduced depressive-like behaviors in rats. Additionally, they observed an increase in rat's hippocampal transcript levels of factors involved in HPA axis regulation and immunomodulatory properties of probiotics, which were independent of the highly pro-inflammatory LPS. Interestingly, Jang et al. [130] showed that oral administration of the probiotics *Lactobacillus reuteri* NK33 and/or *Bifidobacterium adolescentis* NK98 isolated from healthy human feces suppressed the immobilization stress-induced anxiety and depression in mice. What's more, such a treatment decreased the *Proteobacteria* population and bacterial LPS production in murine gut. More recently, Murray and co-workers [131] found that probiotics (i.e., kefir active bacterial cultures – *Lactobacillus lactis, Lactobacillus cremoris, Lactobacillus diacetylactis, Lactobacillus acidophilus*) administered to adolescent mice prevented LPS-induced: (1) depression- and anxiety-like behaviors, (2) enhancement in peripheral as well as central proinflammatory cytokine levels, and (3) changes in the gut microbiota. Apart from that, Wei et al. [132] noted that administration of live as well as heat-killed *Lactobacillus paracasei* PS23 to PF mice reduced chronic corticosterone-induced anxiety- and depression-like behaviors and highlighted possibility to use this species as a psychobiotic in the treatment of mood diseases.

Recently, McVey Neufeld et al. [123] indicated that feeding animals with *Lactobacillus rhamnosus* JB-1 for 28 days in drinking water decreased the depressive-like behavior depending on the species of mouse used. These effects were noted in BALB/c mice, but not in Swiss Webster mice, and they were similar to those observed after fluoxetine treatment. Moreover, administration of *Lactobacillus rhamnosus* JB-1 or fluoxetine to BALB/c, while not to Swiss Webster mice, decreased the plasma corticosterone level and accelerated recovery [123]. Results of these studies highlighted how important is a proper selection of an animal model for the screening of potential effects on stress-related psychiatric disorders.

Barros-Santos et al. [133] have evaluated the anxiety- and depressive-like effects of chronic administration of two new probiotic strains of *Lactobacillus plantarum*, i.e., 286 and 81 isolated from the fermentation of *Theobroma cacao* L. and *Theobroma grandiflorum*, respectively. In the case of oral administration of *Lactobacillus plantarum* 286, but not *Lactobacillus plantarum* 81, they observed the antidepressant and anxiolytic effect in mice, which was in agreement with results obtained for other *Lactobacilli* strains, i.e., *Lactobacillus rhamnosus* JB-1 [117], *Lactobacillus helveticus* NS8 [134] and *Lactobacillus acidophilus* LAB/LAB FB [135].

The positive therapeutic effect of probiotics on mood disorders has also been demonstrated in clinical trials. Benton et al. [136] showed that the use of *Lactobacillus casei* strain *Shirota* in patients with the lowest depression score at the beginning of the study contributed to the greatest benefits, i.e., there was a significant improvement in post-probiotic mood results in these patients. In addition, outcomes of two clinical studies curried out by Messaoudi et al. [47,48] indicated that a chronic co-administration of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 could also contribute to mental wellbeing of subjects with low levels of stress. In the first study, they used this probiotic formulation in the general population for 30 days and observed the reduction in both the global score of the HAMD, as well as HAMA and the global severity index (GSI) of the Hopkins symptoms checklist-90 (HSCL90). Therefore, such a therapeutic treatment has a beneficial effect on stress responses and anxiety behavior, and also contributes to an increase in mood in moderately burdened patients [47]. Next, they focused on the role of this probiotic combination in patients with the lowest urinary free cortisol levels at baseline, and concluded that the efficiency of chronic co-administration of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 may differ depending on individual's stress level [48]. Following a suggestion from preclinical studies that *Bifidobacterium* and *Lactobacillus* in the intestines have a beneficial effect on stress response and depression disorder, Aizawa et al. [137] assessed a correlation between counts of these bacteria strains and major depressive disorders. They found that people suffering from depression are characterized by markedly lower counts of *Bifidobacterium* and *Lactobacillus* versus healthy individuals. Moreover, in a randomized, double-blind, placebo-controlled trial, Lew and co-workers [138] provided evidence that administration of *Lactobacillus plantarum* P8 caused reduction in stress and anxiety symptoms through anti-inflammatory properties. Additionally, outcomes of clinical studies recently carried out by Talbot et al. [139] revealed a close relationship between microbiome balance and psychological parameters. The benefits of targeted probiotic supplementation to optimalization of the gut-brain axis balance for augmented psychical health was also emphasized.

In silico screening of animal and human metagenomic datasets prepared by Duranti et al. [140] indicated a puzzling dependence between *Bifidobacterium adolescentis* amount in the gut microbiota and mental disorders such as depression and anxiety. Moreover, in vitro trials of 82 *Bifidobacterium adolescentis* strains allowed to recognize two, which are superior GABA producers (i.e., PRL2019 and HD17T2H) and thus confirmed the ability of these bacteria to influence the CNS function via the gut-brain axis signaling [140].

Novel strategy to treat patients with depressive disorders was suggested by Tian and co-workers [141]. In preclinical experiments, they demonstrated the antidepressant-like properties of *Clostridium butyricum* Miyairi 588 that was preventively used for 28 days in mice exposed to the chronic social defeat stress. Furthermore, the chronic social defeat stress-induced enhancement in cytokines (IL-1β, IL-6, and TNF-α), as well as gut dysfunction and hippocampal microglial stimulation were partially alleviated by oral administration of *Clostridium butyricum* Miyairi 588 [141].

Effects of probiotics on depressive symptoms were also established in the recent meta-analyses prepared by Ng et al. [142] and Goh et al. [143]. In the first analysis, 10 randomized controlled trials and in the second one 19 double blind, randomized, placebo-controlled trials with a total of 1349 [142] and 1901 [143] participants, respectively, were reviewed, comparing the administration of probiotics to placebo controls. Ng et al. [142] found no overall beneficial effect of probiotic supplementation on depressed mood. Whereas, on basis of conducted subgroups analysis, they indicated slight improvement in mood after probiotic treatment in patients with pre-existing depressed mood, while the effect was negligible in healthy subjects [142]. In turn, Goh et al. [143] showed that in participants used probiotics greater improvement in depressive symptoms occurs in comparison to placebo treated groups. However, similarly to meta-analysis by Ng et al. [142], they found that probiotics possess the antidepressant activity in patients suffering from depression, but not in healthy individuals and also not in patients with other clinical conditions [143]. Additionally, Goh et al. [143] indicated more benefits after multiple strains of probiotics than a single strain of probiotics in decreasing depressive symptoms. Nonetheless, as highlighted in both meta-analyses, because of the relatively small study sample of patients with major depressive disorders and variety of the species and strains of administered probiotic in evaluated clinical trials, presented outcomes are quite preliminary. As authors emphasized, the future research with greater samples of patients diagnosed with

Table 2
Studies on the gut microbiota in patients with depression and/or anxiety.

Study design	Subjects	Treatment	Adjusted *P* value to compare gut microbiota composition	Statistically significant changes in the gut microbiota diversity/ richness	Statistically significant changes in the gut microbiota composition	Other key finding (s)	Ref.
Longitudinal, single-center, open-label, non-randomized	10 patients with IBS and 10 healthy donors	FMT	Not specified	Yes (between recipients and donors)	Yes (between effective and ineffective donors, as well as between recipients and donors)	(1) The abundance of *Bifidobacterium* in donor feces was related to the therapeutic efficacy of FMT; (2) FMT could improve depressed mood and/or anxiety via alterations in intestinal microbiota	[90]
Longitudinal	30 patients with IBS and 5 healthy donors	FMT	Not specified	Yes (between recipients and donors)	Yes (between recipients and donors)	(1) FMT from healthy donors can relieve depression and anxiety in IBS patients, which are possibly associated with changes in the gut microbiota; (2) The period for maintaining clinical response is 3–6 months after the first FMT procedure	[91]
Longitudinal	13 patients with IBS and 13 healthy donors	FMT	Holm-Sidak correction	Yes (between recipients and donors)	Yes (between recipients and donors)	(1) Donors and IBS patients had significantly different bacterial strain signals before FMT (*Ruminococcus gnavus*, *Actinobacteria* and *Bifidobacteria*) that became non-significant after 3 weeks following FMT; (2) FMT from healthy donors causes only short-term relief of depressive and anxiety symptoms	[92]
Longitudinal, randomized, single-center double blind, placebo-controlled, parallel group	83 patients with IBS (55 active and 28 placebo treatment) and healthy donors	FMT	–	Not tested	Not tested	FMT can significantly improve mood symptoms at six, but not at three and twelve months after transplantation procedure	[94]
Longitudinal, open-label observational	17 patients with IBS and 17 healthy donors	FMT	BH FDR correction	Yes (between recipients and donors)	Yes (between recipients and donors as well as between patients with and without depression)	(1) The baseline microbial diversity had a negative correlation with depression severity, and an increase of diversity after FMT correlated with improvement of depression scores; (2) Depression and anxiety symptoms in patients with functional GI disease may be improved by FMT	[95]
Longitudinal, nested case-control	202 974 patients with depression, 14,570 with anxiety, and 803 961, 57 862, matched controls, respectively	Antibiotics from different classes	–	Not tested	Not tested	Recurrent antibiotic (penicillins, quinolones, sulfonamides) exposure is associated with increased risk for depression and anxiety	[101]
Longitudinal, web-based survey	94 patients	Fluoroquinolones	–	Not tested	Not tested	Fluoroquinolones induced psychiatric events including anxiety and depression disorder.	[102]
Longitudinal	201 pregnant women	Antibiotics from different classes	–	Not tested	Not tested	(1) Antibiotic exposure was found to be independently predictive of postpartum depressive symptoms at 1- and 2-months postpartum after controlling for baseline predictors; (2) The relationship between antibiotic exposure and postpartum depressive symptoms did not maintain significance at 3- or 6-months postpartum	[103]
Cross-sectional	112 patients with depression and 28 healthy controls	None	–	Not tested	Not tested	(1) Increased IgA and IgM responses against gut commensal *Enterobacteriaceae* in depressed patents, in particular, in chronic depression; (2) Increased bacterial translocation may be involved in chronic depression by causing	[108]

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Table 2 (*continued*)

Study design	Subjects	Treatment	Adjusted *P* value to compare gut microbiota composition	Statistically significant changes in the gut microbiota diversity/ richness	Statistically significant changes in the gut microbiota composition	Other key finding (s)	Ref.
						progressive amplifications of inflammatory and cell mediated immune pathways in depression	
Cross-sectional	75 patients with depression and 30 healthy controls	None	Not specified	Yes	Yes	(1) Patients with depression had increased levels of *Enterobacteriaceae* and *Alistipes* but reduced levels of *Faecalibacterium*; (2) A negative correlation was observed between *Faecalibacterium* and the severity of depressive symptoms	[109]
Cross-sectional and prospective	40 patients with generalized anxiety disorder and 36 healthy controls	None	Bonferroni and FDR correction	Yes	Yes	(1) Patients with generalized anxiety disorder had decreased microbial richness and diversity, distinct metagenomic composition with reduced SCFAs-producing bacteria (associated with a healthy status) and overgrowth of bacteria such as *Escherichia-Shigella*, *Fusobacterium* and *Ruminococcus gnavus*; (2) These changes in the genera were not reversed in remission phase	[110]
Cross-sectional	111 psychiatric patients	None	Not specified	Yes	Yes	(1) Depression and anxiety severity shortly after admission were negatively associated with bacterial richness and diversity; (2) Intestinal microbiota richness and diversity early in the course of hospitalization was a significant predictor of depression remission at discharge	[111]
Cross-sectional, partially blinded observational	37 patients with depression and 18 healthy controls	None	FDR correction	No	Yes	(1) Several correlations between depression and fecal microbiota were found; (2) *Bacteroidales* showed an overrepresentation, while *Lachnospiraceae* showed an underrepresentation in patients with depression	[112]
Cross-sectional	36 patients with depression and 37 healthy controls	None	Taxa-wise multiple correction	Yes (beta diversity was differed between groups)	Yes	(1) 23 taxa were found to be associated with depression and beta diversity differed between depressed patients and healthy controls; (2) *Actinobacteria* and *Firmicutes* were overrepresented in depressed patients; (3) At genus level, *Bifidobacterium* and *Blautia* had relatively high abundance among depressed patients, while *Prevotella* had high abundance in healthy controls; (4) *Holdemania* exhibited moderate correlation with anxiety and perceived stress level mainly in depressed patients but not in healthy controls	[113]
Cross-sectional	113 patients with bipolar disorders, 39 unaffected relatives and 77 healthy controls	None	BH FDR correction	Yes	Yes	(1) The gut microbiota community membership of patients with bipolar disorders differed from that of healthy individuals, whereas the community membership of unaffected first-degree relatives did not; (2) *Flavonifractor* was associated with a newly diagnosed bipolar disorder	[114]

Abbreviations: BH, Benjamini-Hochberg procedure; FDR, false discovery rate; FMT, fecal microbiota transplantation; GI, gastrointestinal; IBS, irritable bowel syndrome.

depression are essential to verify the efficacy and the possible usefulness of probiotics as an adjunctive treatment in mood disorders [142,143].

The results of clinical trials in which impact of probiotics on depression and anxiety was examined have also been summarized in several systematic reviews [144]. Their outcomes are inconsistent and indicate contradictory effects of using probiotics in individuals with depressive/anxiety symptoms. Huang et al. [145], like Ng et al. [142] in a later meta-analysis, noted positive effects of probiotic supplementation

on mood in patients with pre-existing depressive symptoms. Meaningful amelioration in the anxiety symptoms after probiotic treatment was suggested by Wallace et al. [146], whereas systematic review by Pirbaglou et al. [147] showed that probiotics have a beneficial impact on both anxiety and depression behaviors. As the most effective in alleviating low mood in patients were indicated *Bifidobacterium longum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Lactobacillus helveticus*, *Lactobacillus rhamnosus* as well as *Lactobacillus casei* [144,148]. In contrast, systematic review of evidence to support the theory of psychobiotics prepared by Romijn et al. [149] indicated that there were more negative than positive findings about using probiotics for psychiatric patients. Nevertheless, this review was carried out at a time when there was still a lack of evidence on this topic.

The most recent and comprehensive meta-analysis assessing the impact of probiotics on depression and anxiety was published in 2019 [150]. The results showed overall support for an effect of probiotics on both depression and anxiety, though the largest effects were indicated for probiotics and major depression. *Lactobacillus* enjoyed the greatest interest among the studied probiotics, but when administered alone, it had no effect on depression, with a meaningful difference in the size of the effect between studies where *Lactobacillus* was supplemented alone and those in which it was used in combination with other probiotics, as well as prebiotics. Otherwise, they also noted that *Lactobacillus* had no effect on anxiety behavior, whether administered as monotherapy or polytherapy with other probiotics and/or prebiotics [150]. Numerous clinical studies have shown that *Saccharomyces boulardii* – a nonpathogenic probiotic yeast isolated from the peel of fruits [151], is more effective than other probiotics, such as *Lactobacillus* and *Bifidobacterium*, in restoring the intestinal microbiota [152,153]. However, there is limited data on the effects of supplements in depression and anxiety. In 2019, Aghamohammadi et al. [154] published the protocol of double-blind randomized controlled two-group parallel trial to investigate the effect of *Saccharomyces boulardii* supplements on, inter alia, mental health and oxidative stress in patients suffering from multiple sclerosis. They planned that the mental health and emotional distress of participants enrolled in the clinical trial would be assessed by the 28-item General Health Questionnaire [154]. Nonetheless, the outcomes of this study have not yet been published.

A unicenter, randomized, double-blind, placebo-controlled, parallel-group setting studies conducted by Karbownik et al. [155] showed that 30-day supplementation with *Saccharomyces boulardii* CNCM I-1079 did not significantly modify examination performance or increase in anxiety state and was ineffective in alleviating stress markers, such as salivary cortisol and salivary metanephrine, in healthy medical students under stress conditions. In turn, the increase in pulse rate under stress was significantly higher in the *Saccharomyces*-treated than placebo group [155].

As far as preclinical studies are concerned, there are also insufficient data to determine whether the use of yeast probiotics has a favorable or unfavorable impact or has no effect on symptoms of depression/anxiety. Recently, Constante and co-workers [156] tested the therapeutic potential of the *Saccharomyces boulardii* CNCM I-745 administered twice daily for 3-weeks in drinking water in preventing the transfer of the IBS with co-morbid anxiety phenotype to GF mice via FMT from human donors. Based on the obtained results, they concluded that *Saccharomyces boulardii* CNCM I-745 supplementation ameliorates both the behavioral and intestinal phonotype induced by FMT. Additionally, they identified regulation of indole production by bacteria and regulation of host the transient receptor potential cation channel subfamily V member 1 (*Trpv1*) gene expression as putative mechanisms of these effects [156]. Consequently, they encouraged impact of *Saccharomyces boulardii* in patients with IBS and/or mood disorders.

2.1.6. Effect of prebiotic administration on the anxiety- and depressive-like behavior

The reversal of stress effects by prebiotics has also been shown. Prebiotics can affect the composition of the intestinal microbiota, and thus affect the CNS activity. Tarr et al. [157] observed that a two-week use of human milk 3' or 6'Sialyllactose in mice prior to exposure to a social disruption stressor, prevented the development of anxiety behavior and a reduction of hippocampal immature neurons compared to group which did not receive these agents. In turn, in clinical studies, Schmidt et al. [158] explored the neuroendocrine and affective effects of two types of prebiotic supplements in healthy human volunteers. They observed that the daily use of Bimuno®-galactooligosaccharides (B-GOS®) as a prebiotic substance for 3 weeks in healthy people and in humans at high risk of depressive disorders resulted in a decrease in the salivary cortisol awakening response (a convincing indicator of the HPA axis activity which is enhanced by stressors). Such changes were not recorded after fructooligosaccharides administration. One of the recent preclinical studies indicated that administration of a polysaccharide isolated from okra (*Abelmoschus esculentus* (L) Moench) to the CUMS-induced mice alleviated anxiety as well as depressive-like behaviors and lowered parameters of the inflammatory reaction in the gut, serum and hippocampus. Additionally, such a treatment had positive effects on the intestinal dysbiosis. Otherwise, it was suggested that prebiotics might modulate activity of the HPA axis [158] and regulate the inflammation response in a similar way as probiotics in mice/rats [66,124] and in humans [47,48]. In the recent and the first quantitative data synthesis on prebiotics for depression and anxiety, Liu et al. [150] did not find an ameliorative effect for prebiotics on these diseases. However, as emphasized by the authors of this meta-analysis, presented findings should be regarded as preliminary because of the relatively small number of eligible studies included in the examination.

2.1.7. Effect of diet components on the anxiety- and depressive-like behavior

In recent years, the interest in recognizing therapeutic strategies that ameliorate mood via the regulation of the gut microbiome composition is growing. Many studies indicate that the diet significantly affects results of preclinical behavioral tests, e.g., a high-fat diet causes the anxiety- and depressive-like behavior in rodents [159–161], what is probably related to the impact of diet components on the expression of gut microbiota. Accordingly, it was recognized that dietary intervention could be a possible strategy for normalizing changes in bacterial commensals associated with neuropsychiatric diseases such as anxiety and depression. One of such strategies is the possibility of using omega-3 polyunsaturated fatty acids (PUFAs), including docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and the omega-6 (n-6) PUFA: arachidonic acid (AA). As it has been shown, their levels are reduced in patients with anxiety and depression [162,163], additionally, supplementation with these acids has a positive effect on reducing the symptoms of these illnesses [164]. Moreover, Davis et al. [165] indicated that supplementation with DHA reduced anxiety and depressive-like behaviors in a gender depending manner, i.e., in male but not female mice. Male-specific changes in the microbiota composition were found in mice in which antidepressant and anxiolytic effects were also observed, what suggests that this protective action was mediated by the microbiome [165]. Likewise, a long-term joint supplementation with DHA and EPA in young rats exposed to stress regulated the microorganism profile and impaired stress reactivity [166]. The effects observed after administration of omega-3 PUFAs result from their impact on the neurotransmission and gene expression [167]. The second possible direction of action of DHA is that it affects the structure and function of the gut microbiota. Latest data implied that omega-3 PUFAs modulate the intestinal microbiota composition and help normalize it after disrupting environmental stress [166,168].

2.1.8. Concluding remarks

Based on the cited outcomes of behavioral and biochemical preclinical studies, it could be concluded that the presence or absence of conventional intestinal microbiota influence the development of

depressive- and anxiolytic-like behavior, and is accompanied by neurochemical changes in the CNS. Further, it has been proven that FMT from donors with mental illness symptoms is able to induce similar symptoms in recipients. On the contrary, FMT from healthy subjects can mitigate depressive- and anxiety-like manifestations. The bidirectional communication of the microbiota-gut-brain axis via regulation of activity of the HPA axis as well as regulation of the BDNF level and the immune system response was proposed as a potential mechanism of the antidepressant- and anxiolytic-like effects of probiotics and prebiotics. Additionally, it should be noted, that in most of the cited preclinical as well as clinical studies no FDR adjustment was used for the *P* value. However, when comparing the results of research in which the *P* adjustment was applied with those for which this adjustment was not made, it can be concluded that the vast majority of them are congruous.

2.2. Schizophrenia

Schizophrenia is a complex psychiatric disorder with poorly understood etiology that involves interactions of genetic vulnerability with pre- and postnatal environmental factors. Epidemiological data showed significantly increased risk of developing schizophrenia after prenatal microbial infection [169]. Interestingly, schizophrenia patients have higher incidence of intestinal barrier dysfunction, increased bacterial translocation, and frequently suffer from GI comorbidities [7]. All these, along with emerging data on the role of microbiota in brain development, have contributed to preclinical and clinical studies on the gut microbiota in schizophrenia.

GF mice display increased stereotyped, repetitive, and locomotor behaviors, as well as cognitive deficits [50,51]. Hyperactivity and excessive stereotypy are often observed in animal models of schizophrenia and these behaviors are considered as mimicking positive symptoms of schizophrenia in humans [170], while cognitive impairment occurs in almost all patients with schizophrenia. Moreover, asociality is among negative symptoms of schizophrenia [171]. GF mice have also reduced social motivation and preference for social novelty. The impairment in social preference, but not social cognition, was successfully reversed by the postweaning bacterial colonization, which confirms the role of microbiota in modulation of social preference [172].

Importantly, it was demonstrated that FMT from patients with schizophrenia to GF mice may produce some schizophrenia-related changes in animal behavior [173]. GF mice transfected with microbiota from schizophrenic patients displayed increased locomotor activity, reduced anxiety, decreased depressive-like behavior, and increased startle responses as compared to mice that received microbiota from healthy subjects. The changes in animal behavior were accompanied by an increased level of glutamate and decreased levels of glutamine and GABA in the hippocampus [173] as well as with alterations of glycerophospholipid and fatty acyl metabolism [174]. In another study, FMT from unmedicated patients with schizophrenia to PF mice induced schizophrenia-like abnormal behaviors (such as psychomotor hyperactivity and cognitive impairment) and dysregulated tryptophan-kynurenine metabolism [175]. Recently, mice with antibiotic-induced microbiota depletion were transfected with only one bacteria species, *Streptococcus vestibularis*. This bacterium is present in the gut of a number of schizophrenic patients and was identified to have 11 gut-brain modules involved in the synthesis and degradation of several neurotransmitter including glutamate and GABA. *Streptococcus vestibularis* transplantation produced hyperkinetic behavior, impaired social interaction, induced changes in the expression of different immune- and inflammation-related genes, and altered neurotransmitter levels in peripheral tissues in recipient mice. In the brain, reduced tryptophan level was reported in the prefrontal cortex [176]. Lower serum tryptophan level and higher kynurenic acid level were also observed in schizophrenic patients. Thus, altered tryptophan-kynurenine metabolism may be an important link between gut microbiota and the pathogenesis of schizophrenia [175,176].

The gut microbiome profiling in a metabotropic glutamate receptor 5 (mGlu5) knockout mouse model of schizophrenia revealed a significant difference in microbial beta diversity. Specifically, a decreased relative abundance of the *Erysipelotrichaceae* family and *Allobaculum* genus in mGlu5 knockout mice were detected [177].

To date, only few studies have investigated differences in the gut microbiota between patients suffering from schizophrenia and healthy subjects (Table 3). In most of them, no changes in microbial richness/diversity were reported. There were, however, some marked differences in the abundance of specific taxa between schizophrenic patients and control groups but with much discrepancy between the reports. In the study by He et al. [178], no significant differences in microbial diversity were observed between high-risk patients, ultra-risk patients, and healthy controls. Interestingly, the orders *Clostridiales*, *Lactobacillales,* and *Bacteroidales* and genera *Lactobacillus* and *Prevotella* were significantly increased in the ultra-risk patients as compared to the other two groups. Likewise, Shen et al. [179] reported no changes in the microbiome diversity indexes between patients with schizophrenia and healthy controls. At the phylum level, the abundance of *Proteobacteria* was higher in schizophrenic patients than in controls. At the genus level, the abundance of *Succinivibrio*, *Megasphaera*, *Collinsella*, *Clostridium*, *Klebsiella*, and *Methanobrevibacter* was significantly increased in schizophrenia cohorts, whereas *Blautia*, *Coprococcus*, and *Roseburia* were higher in healthy subjects. In individuals diagnosed with first episode of schizophrenia, significantly lower numbers of *Bifidobacterium* spp., *Escherichia coli*, and *Lactobacillus* spp. were reported [180], which is in contrast to the study by Schwarz et al. [181], who demonstrated higher levels of *Lactobacillus* and *Bifidobacterium*, and a lower level of *Bacteroides* in patients with the first psychotic episode [181]. Unfortunately, all the above-mentioned studies used an unadjusted *P* value or no such information is given, which raises the possibility of false-positive discoveries. More reliable data were provided by Nguyen et al. [182] and Li et al. [183], who performed the FDR correction. Nguyen et al. [182] studied the in gut microbiota composition in schizophrenia patients with an illness of long duration. At the phylum level, *Proteobacteria* were found to be relatively decreased as compared to controls. At the genus level, *Anaerococcus* were increased in schizophrenic subjects, whereas *Haemophilus*, *Sutterella*, and *Clostridium* were decreased but there were no changes in microbial diversity. An important observation from this study is also that the increased abundance of *Ruminococcaceae* was correlated with decreased severity of negative symptoms of schizophrenia [182]. In the study by Li et al. [183] relatively more *Actinobacteria* and less *Firmicutes* at the phylum level were found, whereas at the genus level, the relative abundance of *Collinsella, Lactobacillus, Succinivibrio, Mogibacterium, Corynebacterium*, undefined *Ruminococcus* and *Eubacterium* were increased and the abundances of *Adlercreutzia*, *Anaerostipes*, *Ruminococcus* and *Faecalibacterium* were decreased in schizophrenia patients. Noteworthy, *Succinivibrio* and *Corynebacterium* were correlated with severity of schizophrenia symptoms, which may provide some new biomarkers for the diagnosis of schizophrenia [183].

Only few papers report on decreased microbial diversity/richness within patients suffering from schizophrenia [173,184,185]. In contrast, a metagenome-wide association study showed that gut microbiota diversity based on genus level taxonomy and annotated genes was much higher in patients with schizophrenia than in healthy controls [176]. It is worth noticing that all the above-mentioned changes in microbial diversity were accompanied by significant differences in the gut microbial composition between the groups [173,176,184,185]. A very interesting recent finding from a human study is that specific schizophrenia-associated microbiota was correlated with changes in the right middle frontal gyrus volume, indicating a possible link between the gut microbiota and brain structure in schizophrenia [184]. Taken together, data on gut microbiota alterations in individuals with schizophrenia are inconsistent, especially in terms of *Proteobacteria* and *Firmicutes* (at the family level) and *Clostridia* (at the class level). Increased abundance of *Lactobacilli* appears to be the most consistent finding so

far. A number of factors may contribute to the observed discrepancies. These include differences in the stage of illness, treatment status (medicated/unmediated), diet, comorbid illnesses, age, and gender of the participants, small sample sizes (less than 100 individuals), and differences in methods used across the studies.

There are also some studies focused on the role of gut microbiota in antipsychotic treatment. An altered microbial profile following olanzapine treatment was first reported in rats [186,187]. A decreased overall diversity (evidenced by reductions in *Actinobacteria* and *Proteobacteria*), increase in the relative abundance of *Firmicutes*, and decrease in *Bacteroidetes* were observed. The changes in microbial composition were accompanied by body weight gain, increased adipose tissue volume, and alterations in inflammatory and metabolic parameters. Some of the effects were gender-dependent, i.e., more pronounced in females than males [187]. Although in the two above studies microbiota composition was compared using unadjusted *P* value, similar changes in the gut microbiota and body weight gain after olanzapine treatment were shown in mice when using adjusted *P* value. Olanzapine administration decreased overall microbial diversity, lowered abundance of *Bacteroidia*, and increased abundances of *Erysipelotrichia*, *Actinobacteria*, and *Gammaproteobacteria*. Noteworthy, a lack of significant increase of the body weight in olanzapine-treated GF mice and a rapid weight gain upon microbial colonization in this study indicate that the olanzapine-induced weight gain was dependent on the presence of gut microbiota [188]. On the contrary, Kao et al. [189,190] demonstrated no significant effects of olanzapine administration on the gut microbiota in rats. Likewise, the gut microbiota composition did not change after 6 weeks of treatment with olanzapine in patients with schizophrenia [191]. A few studies also report on the role of gut microbiota in the risperidone-induced weight gain. In rats, risperidone treatment resulted in an excessive weight gain, due to reduced energy expenditure, and this effect was correlated with gut microbiota changes. Specifically, an increase of the abundance of *Firmicutes* (with fewer *Lactobacillus* species and increased *Allobaculum* compared to controls) and a concomitant decrease in *Bacteroidetes* were observed [192]. Furthermore, chronic treatment with risperidone resulted in an increase in the body mass index and lower *Bacteroidetes:Firmicutes* ratio in pediatric patients. In addition, specific taxa that correlated with risperidone-induced weight gain were identified [193]. Altered metabolism and microbiota were reported after a 24-week risperidone treatment in drug naïve subjects with the first episode of schizophrenia. *Bifidobacterium* spp. and *Escherichia coli* were increased, whereas *Clostridium coccoides* and *Lactobacillus* spp. were decreased over risperidone treatment [180]. It should be stressed out that in all the above described studies on the influence of risperidone on the gut microbiota composition, data were analyzed without adjusting *P* values or no such information is provided. Distinct changes of the gut microbial composition associated with different antipsychotic drugs were also reported by Ma et al. [184]. By contrast, Zheng et al. [173] showed that global microbial phenotypes were not affected by either sex or medications.

Several studies investigated the efficacy of treatments known to affect the gut microbiota (i.e., antibiotics, probiotics, or prebiotics) in the management of schizophrenia and/or antipsychotic-induced metabolic disturbances. A meta-analysis of randomized, double-blind controlled trials of add-on antibiotics (21), antimicrobials (4), and pre/probiotics (3) in schizophrenia showed that targeting the gut microbiome with antibiotics does not have much effect on schizophrenia symptoms [194]. In rats, antibiotic administration was shown to attenuate the olanzapine-induced body weight gain [186] and abolished the phencyclidine-induced memory deficits [195]. Data on the effects of probiotics in schizophrenia are scarce (Table 6). A randomized, placebo-controlled trial demonstrated that a 14-week probiotic supplementation (with *Lactobacillus rhamnosus* and *Bifidobacterium lactis*) did not improve psychiatric symptoms in schizophrenic patients [196]. The probiotic-treated group was, however, less likely to develop severe bowel movement difficulties, probably due to probiotic-specific immunomodulatory effects [197]. In another randomized, double-blind, placebo-controlled trial, a combination of probiotic (containing *Lactobacilli* and *Bifidobacterium bifidum)* and vitamin D was given to schizophrenic patients for 12 weeks, which improved the general and total Positive and Negative Syndrome Scale (PANSS) scores, enhanced antioxidant capacity of plasma, reduced inflammation, and improved metabolic profiles. Unfortunately, the effect of the treatment on the gut microbiota was not determined in this study. Moreover, it is uncertain which component (probiotic or vitamin D, or maybe both) was responsible for the observed changes [198]. In an open-label single-arm study, a 4-week consumption of *Bifidobacterium breve* A-1 reduced the severity of anxiety and depressive symptoms in patients with schizophrenia but the effect was not related to the changes in the gut microbiome [199]. Data on the potential benefits of prebiotics in schizophrenia treatment are also very limited. Guo et al. [200] showed that inulin ameliorated the MK-801-induced schizophrenia-like behavior in mice via modulation of the gut microbiota composition and anti-inflammatory action. In rats, administration of the B-GOS® prebiotic formulation improved cognitive flexibility [201] and attenuated the olanzapine-induced weight gain [190]. This prebiotic supplementation was also found to increase cortical neuronal responses to NMDA [201], elevate cortical expression of the NMDA receptor units [189], and increase the hippocampal BDNF level [202]. These observations are of high importance as both NMDA receptor hypofunction and reduced BDNF level appear to be implicated in the pathophysiology of schizophrenia. A pro-cognitive effect of the B-GOS® prebiotic, but without significant changes in metabolic and immune system parameters, was also reported in patients with psychosis in a double-blind, placebo--controlled cross-over study [203]. In contrast, in underweight chlorpromazine-treated schizophrenia patients, prebiotic supplementation caused a weight gain effect and changed the microbiota composition [204]. In another study, resistant starch supplementation in a cohort of patients treated with atypical antipsychotic drugs resulted in differences in the gut microbiota with no effect on the body weight [205]. However, both studies were not placebo-controlled. Recently, Liu et al. [206] presented the protocol for the first randomized, placebo-controlled, double-blinded trial investigating the effect of dietary fiber and probiotics (alone or in combination) as an add-on treatment in improving the antipsychotics-induced metabolic side effects. Altogether, some preliminary evidence suggests that patients with schizophrenia could benefit from pro- and prebiotic supplementation in terms of schizophrenia symptoms and/or adverse effects of antipsychotic medications.

To sum up, although the gut-brain interplay in schizophrenia is not a new concept, studies on the role of gut microbiota in etiopathophysiology and management of this disease are still in early stages. None of the available data allow to answer the most intriguing questions, i.e., whether dysbiosis can predispose someone to schizophrenia and what quantitative and qualitative alterations in the microbiota composition lie behind this phenomenon. It is also important to recognize the benefits of microbiota-orientated treatments in reducing the antipsychotic-induced metabolic disturbances as well as in alleviating schizophrenia symptoms.

2.3. Autism spectrum disorder

ASD is a group of neurodevelopmental disorders characterized by impairments in social interaction, verbal and nonverbal communication deficits and restricted, repetitive, and stereotyped patterns of behavior and interests. The term includes autistic disorder, Asperger disorder, and pervasive developmental disorder, not otherwise specified. The pathogenesis involves the interactions between genetic, immune system, environment and in utero factors [207]. Patients with ASD usually suffer from concomitant pathologies, including anxiety, depression, seizures [208,209] gut dysbiosis and other GI problems (such as diarrhea, constipation, abdominal pain, vomiting, bloating, reflux, or foul smelling

stools) [210]. Prevalence of GI symptoms in children with ASD is significantly greater than in control children [211]. It was estimated to range between 17% and 86%. Though it seems that dysbiosis is not dependent on the manifestation of GI symptoms in autistic children [212], GI ailments, when present, aggravate neurobehavioral symptoms in these pediatric patients [211]. A correlation between the severity of GI symptoms and the severity of ASD-related symptoms has been reported [213]. It has been suggested that aggression, self-injury or sleep disorder found in children with ASD could be a manifestation of abdominal discomfort [214]. Polymorphism detected in several genes (including *CHD8*, *MET*, *SLC6A4*, *EPHB6*) or activity of enzymes, i.e., disintegrin and metalloproteases (ADAM10 and ADAM17) have been suggested to be associated with ASD co-existing with GI problems [215–218].

GF rodents displayed abnormalities in their social behavior (i.e., reduced sociability, including diminished interaction with unfamiliar partner), increased stereotyped self-grooming, and repetitive burying behavior [172,219–221]. Abnormalities in social behavior [222] in GF animals were improved after re-colonization with the standard gut microbiota.

Elevated risk of ASD development was sugessted for neonates [223], for children born by cesarean section [224], or when pregnant mothers were given antibiotics (particularly penicillin or sulfonamides) [225]. Mothers of the autistic children were shown to be hospitalized more often during their pregnancy due to an infection [226], whereas the autistic children were breastfed for the shorter period [227] and they were treated more frequently with high doses of antibiotics [228]. These data suggest that changes in microflora induced by antibiotics might have contributed to the development of ASD. However, the epidemiological co-twin study by Slob et al. [229] showed that early-life antibiotic use was associated with increased risk of ASD, but the association disappeared when controlled for shared familial environment and genetics, thus showing that this association may be susceptible to confounding.

Nevertheless, reduced bacterial diversity and increased biomass were reported in individuals with ASD [228,230]. Generally, these alterations were accompanied by a shift from beneficial microorganisms to the spore-producing, antibiotic-resistant, and/or neurotoxin-producing ones (the exemplary results of clinical studies and information about the *P* values correction are presented in Table 4). The most important may be reduced amounts of *Prevotella*, *Corprococcus*, and *Veilonellaceae* (participating in carbohydrate ingestion and fermentation), *Bacteroidetes*, *Actinobacteria*, *Proteobacteria* [228] along with elevated levels of *Desulfovibrio* spp. (positively related to the severity of ASD) [231], *Sutterella* spp. and *Ruminococcus torques* (both involved in mucosal metabolism) [232], or *Clostridium* spp. (a neurotoxin-producing bacteria) [233]. Furthermore, abundance of *Megamonas* [234], overgrowth of *Candida* spp. that can produce ammonia and other toxins contributing to autistic behavior [235] and decrease in *Bacteroidetes: Firmicutes* ratio with elevated number of *Firmicutes* to diminished amount of *Bacteroidetes* were found by several authors [236]. According to Weston et al. [237], an imbalance between the growth of pro-inflammatory *Clostridia* and anti-inflammatory *Bifidobacterium* spp. may belong to the risk factors of development of ASD. Also, the decreased quantity of *Bifidobacterium* spp. correlated with the development of Asperger's syndrome [238].

A proper interpretation of the outcomes of the above-mentioned studies is, however, highly difficult due to their non-uniformity. Also, the existing meta-analyses on gut microbiota in ASD produced distinct conclusions. A meta-analysis, which was published in 2021, comprising 18 studies, did not show a significant association between the diagnosis of ASD and the abundance of *Bacteroidetes, Firmicutes, Proteobacteria*, and *Actinobacteria* phyla; only considerably lower amounts of *Streptococcus* and *Bifidobacterium* were demonstrated [239]. On the other hand, Iglesias-Vázquez et al. [240], based on 18 trials which were overlapping in ca. 72% with the trials included in the meta-analysis of Andreo-Martínez [239] showed a reduced quantity of *Bacteroidetes, Firmicutes*, and *Proteobacteria* phyla with elevated levels of *Bacteroides* and *Clostridium* in guts of ASD people. However, when the data analyzed by Iglesias-Vázquez et al. were recalculated using the method by Andreo-Martinez, the two analyses gave similar outcome, indicating a lack of the ASD-gut microbiota association in relation to *Bacteroidetes, Firmicutes, Proteobacteria, Bacteroides*, and *Clostridium*, thus showing that the applied synthesis method and effect size index can influence the outcome.

A role for an interplay between environmental factors and gut microbiota in the development of ASD has been suggested. The environmental levels of glyphosate, a pesticide ineffective towards *Clostridium perfringens* or *Clostridium botulinum*, may affect human microbiome by destroying sensitive *Lactobacillus* and *Bifidobacterium* and consequently, promoting the growth of *Clostridium* [241]. Thus, the relationship between environmental glyphosate and the higher abundance of *Clostridium* spp. in the GI tract in children with ASD was hypothesized. Furthermore, the relationship between *Clostridium tetani* sub-acute infection and ASD was hypothesized [242]. Similarly, association between the presence of beta2-toxin gene (produced by *Clostridium perfringens*) in the gut microbiome and development of ASD was reported [243].

Excessive use of antibiotics may result in the overgrowth of *Desulfovibrio*, i.e., bacteria resistant to common therapy, which release LPS [244]. Prenatal exposure to LPS led to the development of ASD-like behavior [245]. Elevated levels of LPS were found in the blood of autistic subjects [246,247]. Animals with maternal immune activation (MIA) presented impaired GI barrier, elevated levels of IL-6, microbial dysbiosis in the intestines, and ASD-related behaviors (e.g., decreased ultrasonic vocalization as a mode of communication, altered olfactory communication, impaired social interactions and increased repetitive marble burying and self-grooming) when compared to the control group [248]. These changes were restored by colonization with *Bacteroides fragilis*. *Lactobacillus reuteri* was also able to reverse the LPS-induced inflammation of the intestine [249]. Moreover, these bacteria stimulated release of oxytocin that positively affects social behavior and anxiety [33,248].

Abnormally high intestinal permeability has been detected in 37% of patients with ASD [248]. It may be related to the reduced number of *Lactobacillus* spp. observed in some individuals with ASD [231,232,250] as microorganisms from *Lactobacillus* spp. play a significant role in maintenance of TJs in the intestinal epithelium barrier [251,252]. Furthermore, GI abnormalities observed in autistic children corresponded with altered brain expression of CLDN-5 and CLDN-12 genes, encoding TJ proteins [37]. Increased intestinal permeability may be a marker of ASD in children with both ASD and GI problems since elevated plasma concentration of zonulin (i.e., the gut permeability-modulating protein) corresponded with the severity of autistic symptoms [253]. All the above-mentioned data show the role of the "leaky gut" in the development of ASD.

In the case of impaired BBB, which can be observed in certain (but not all) autistic subjects [37,254], LPS or SCFAs may cause brain inflammation and thus, further facilitate access to the brain for harmful substances, like heavy metals, that can accumulate there [228,246,255]. Both PET imaging and *post-mortem* studies revealed enhanced microglial activation in autistic people suggesting the presence of inflammation in the brain [226,256], whereas Erny and colleagues [257] demonstrated that proper functioning of the brain microglia needs the gut microbiome.

GI abnormalities observed in autistic children corresponded with increased brain weight (most probably due to the higher number of neurons in the prefrontal cortex) [258], reduced number of Purkinje cells in the cerebellum [242], altered BDNF levels [259], or disproportion between inhibitory and excitatory transmitters in the CNS [260]. Serotonin may be a key element that links the gut microbiome with brain responses in ASD as a murine model mimicking brain, behavioral and GI abnormalities seen in ASD harbors the most common serotonin

Table 3
Studies on the gut microbiota composition in patients with schizophrenia.

Study design	Subjects	Treatment status (antipsychotic drugs)	Adjusted *P* value to compare gut microbiota composition	Statistically significant changes in the gut microbiota diversity/richness	Statistically significant changes in the gut microbiota composition:	Other key finding (s)	Ref.
Cross-sectional	81 high-risk, 19 ultra-high risk patients, and 69 healthy controls	Unmedicated	Not specified	No	Yes (between ultra-high risk patients and the other two groups)	Elevated *Clostridiales*, *Prevotella* and *Lactobacillus ruminis* may be considered as possible biomarkers for psychosis in ultra-high-risk patients.	[178]
Cross-sectional	64 schizophrenia patients and 53 healthy controls	Medicated	FDR correction	No	Yes	Twelve significant microbiota biomarkers could be used as diagnostic factors for schizophrenia.	[179]
Longitudinal (24-week risperidone treatment)	24 first episode schizophrenia patients and 41 healthy controls	Unmedicated	Not specified	Not studied	Yes	(1) Drug naïve, first episode schizophrenia patients showed abnormalities in microbiota composition (lower *Bifidobacterium* spp., *Escherichia coli*, *Lactobacillus* spp. and higher number of *Clostridium coccoide*); (2) A 24-week risperidone treatment increased *Bifidobacterium* spp. and *E. coli* and decreased *Clostridium coccoides* and *Lactobacillus* spp.	[180]
Longitudinal (12 months)	28 first episode schizophrenia patients and 16 healthy controls	Medicated	Not specified	Not studied	Yes	Highly increased *Lactobacillus* group bacteria elevated in first episode schizophrenia patients may be significantly correlated with severity along different symptom domains.	[181]
Cross-sectional	25 schizophrenia patients and 25 healthy controls	Medicated	FDR correction	No	Yes	Increased *Ruminococcaceae* in schizophrenia patients can be correlated with decreased negative symptoms, while increased *Bacteroides* with worse depressive symptoms.	[182]
Cross-sectional, translational	63 schizophrenia patients and 69 healthy controls	Medicated	Not specified	Lower microbial richness and diversity in schizophrenia patients.	Yes	(1) Changes in the *Aerococcaceae*, *Bifidobacteriaceae*, *Brucellaceae*, *Pasteurellaceae*, and *Rikenellaceae* enabled discrimination of patients with schizophrenia from healthy subjects suggesting potential diagnostic value; (2) FMT from schizophrenia patients resulted in schizophrenia-like behavior in recipient mice, which was accompanied with lower glutamate and higher glutamine and GABA concentrations in the hippocampus.	[173]
Cross-sectional	40 first episode drug naïve schizophrenia patients, 85 antipsychotic-treated patients, and 69 healthy controls	Medicated and unmedicated	BH FDR correction	Lower α-diversity in antipsychotic-treated patients than in the first episode drug naïve schizophrenia patients and healthy patients	Yes (between the first episode drug naïve and antipsychotic-treated patients as compared to healthy controls as well as between the first episode drug naïve and antipsychotic-treated patients)	Significant associations between schizophrenia-related microbiota and brain regional grey matter volumes.	[184]
Cross-sectional, translational	90 schizophrenia patients and 81 healthy controls	Unmedicated	BH FDR correction	Increased diversities in schizophrenia patients.	Yes	Transplantation of a schizophrenia-enriched bacterium, *Streptococcus vestibularis*, affected social behaviors and neurotransmitter levels in	[176]

(*continued on next page*)

Table 3 (*continued*)

Study design	Subjects	Treatment status (antipsychotic drugs)	Adjusted *P* value to compare gut microbiota composition	Statistically significant changes in the gut microbiota diversity/richness	Statistically significant changes in the gut microbiota composition:	Other key finding (s)	Ref.
						peripheral tissues in recipient mice.	
Cross-sectional	84 schizophrenia patients and 84 healthy controls	Medicated	FDR correction	Decreased richness in schizophrenia patients.	Yes	Microbial dysbiosis index was positively correlated with microbiota-associated epitopes diversity and gut IgA levels, and negatively correlated with gut microbiota richness.	[185]
Cross-sectional	82 schizophrenia patients and 80 healthy controls	Medicated	FDR correction	No	Yes	Greater severity of schizophrenia symptoms was positively correlated with the abundance of *Succinivibrio*, whereas *Corynebacterium* was negatively related to the negative scores of PANSS.	[183]

Abbreviations: BH, Benjamini-Hochberg procedure; FDR, false discovery rate; PANSS, Positive and Negative Syndrome Scale.

transporter based mutation (SERT Ala56) found in children with ASD [261]. Increased blood serotonin and GABA concentrations were detected in autistic children [262,263], whereas their microbiome presented a lower level of enzymes implicated in metabolism of glutamate [260].

Voung and colleagues [253] reported increased levels of pro-inflammatory cytokines in astrocytes of children with ASD. Though the immune alterations are not consistent between subjects, changes in functioning and distribution of the leukocyte subtypes or the "pro-inflammatory" status, involving intensified cellular immune responses with increased levels of peripheral and brain chemokines, cytokines (including TNF-α, IL-1, IL-6, IL-12p40, IFN-γ), diminished levels of the anti-inflammatory IL-10, abnormal responses of peripheral blood macrophages and monocytes are often detected [248,264–269]. Apart from that, elevated quantity of serum antibodies against gliadin and casein that can lead to autoimmune reactions [270] along with enhanced inflammatory and phospho-NFκB signaling [271] have been noted in patients with ASD. Autistic children with GI problems had reduced amount of peripheral T cells [272] with increased levels of CD8 and/or γδ T cells in the duodenum and colon [268,273]. Gut biopsies from autistic children showed signs of infiltration of monocytes, lymphocytes, eosinophils, and natural killer cells, which indicates the inflammatory process [249].

In healthy subjects, the intestinal microbiota produces thiamine-pyrophosphate, which is a co-factor of multiple enzymes, including transketolase that is involved in the pentose phosphate oxidative pathway. Autistic people present lower concentration of the serum thiamine-pyrophosphate [274], but increased levels of ROS generating enzymes (i.e., NOX2/iNOS) in neutrophiles [271]. Altered metabolites levels were also observed in the urine of autistic children. Urinary specimens taken from those children had lower levels of antioxidants [275]. 3-(3-hydroxyphenyl)-3-hydroxypropionic acid (HPHPA) was found in higher concentrations in urine samples of children with autism compared to healthy controls. The source of HPHA are multiple species of bacteria of the *Clostridium* genus [276]. Elevated urine levels of HPHPA, 3-hydroxyphenylacetic acid, and 3-hydroxyhippuric acid found in autistic children were significantly decreased after oral therapy with vancomycin and *Bifidobacterium* supplementation. After treatment, the patients presented better eye contact behavior and reduced constipation [277].

Increased urinary and fecal concentrations of *p*-cresol and *p*-cresyl sulfate, other metabolites of *Clostridiaceae*, are also regarded as possible biomarkers of ASD. In the brain, *p*-cresol affects synthesis of noradrenaline and metabolism of dopamine, it increases lipid peroxidation and reduces activity of $Na^{(+)}$-$K^{(+)}$ ATPase. Its concentrations correspond with increased gut permeability, gut infections, autistic behavior, and severity of the disease [278]. Gevi et al. [279] found elevated concentrations of indolyl-3-acetic acid and indolyl-lactate in urine of autistic children, while De Angelis et al. [280] detected increased amounts of indole and 3-methylindole. *Achromobacter liguefaciens*, *Bacteroides* spp., *Clostridium* spp., *Escherichia coli*, *Paracolobactrum coliform* as well as *Proteus vulgaris* are well-known producers of indoles [279,280]. Indole derivatives also belong to tryptophan (i.e., the precursor of serotonin) metabolites, whose physiological pathways are changed in autistic patients [279].

Another significant metabolite associated with GI problems, whose fecal concentrations are elevated in autistic patients, is isopropanol [281]. Its metabolite (indoxylsulphate) may induce accumulation of neurotransmitters in the brain [279]. Ming and colleagues [275] found out that children with ASD present dysregulated metabolism of free amino acid that are obtained after hydrolysis of proteins and peptides. It seems that fecal levels of free amino acids are significantly higher in autistic subjects than those detected in samples taken from the healthy ones, and these data correspond with the prevalence of proteolytic bacteria [282].

Autistic individuals suffer from maldigestion and malabsorption [283]. Due to reduced expression of disaccharidases and two hexose transporters (i.e., SGLT1 and GLUT2), impaired absorption of mono- and disaccharides in the small intestine of autistic children takes place, which can contribute to the changed microbial burden in their GI tracts. These low-molecular sugars entering the large intestine in higher amounts support growth of the intestinal fermenting bacteria to the detriment of the polysaccharide-degrading ones [284]. Vitamin B1 deficiency may be a result of the reduced colonization of *Prevotella* spp. that degrades plant polysaccharides and synthesizes thiamine [228], whereas abundance of *Candida* spp. in the gut hampers recolonisation of commensal microorganisms [235]. Moreover, *Candida* yeasts induce malabsorption of minerals and carbohydrates [285]. Changes in vitamin B6, nicotinamide, tryptophan, and purine metabolism in autistic individuals were reported by Srikantha and Mohajeri [252]. Elevated levels of 3-(3-hydroxyphenyl)-3-hydroxypropionic acid, 3-hydroxyphenylacetic acid, and 3-hydroxyhippuric acid, which are suggested as indicators of dysregulated phenylalanine metabolism, are frequently observed in ASD [278]. They are most probably produced by the overgrown population of *Clostridium*.

In autistic children, abnormalities in the SCFAs concentration, i.e., significantly higher levels of acetate and propionate along with deeply reduced levels of butyrate have been observed [282]. These molecules,

which are fermentation end products of non-digested carbohydrates, act both in the brain via free fatty acid receptors FFAR2 and FFAR3, and in the gut. In the brain, they have an impact on the production of neurotransmitters and catecholamines [280,282] and partially they affect the reward system, synaptic plasticity, and memory formation [286,287]. In the intestine, they influence water and electrolytes resorption in the colon [280], modulate oxidative and inflammatory state of the mucosa, strengthen mucosal barrier by affecting expression of the tight-junction proteins (i.e., claudin-5, occludin, ZO-1), regulate visceral sensitivity along with visceral motility [288]. SCFAs can alter integrity of both the intestinal and the BBB [34].

The preclinical studies revealed that animals given propionate intracerebroventricularly presented behavioral and physiological symptoms corresponding to autism ASD, which can be used as an animal model of autism [262,289]. Autistic individuals consuming products with propionic acid or its precursors manifested more profound autistic behaviors along with GI symptoms. Propionic acid is also produced by gut bacteria closely associated with ASD, i.e., *Clostridium* spp., *Bacteroides* spp., and *Desulfovibrio* spp. [290]. On the other hand, consumption of a diet free from propionic acid or intake of antibiotics that reduce bacteria generating the propionic acid, improved the condition of autistic patients [291]. Furthermore, reactive nitrogen species, produced in higher amounts in autistic subjects interact with propionate and as a consequence, 3-nitropropionic acid, i.e., a mitochondrial neurotoxin that inhibits production of nicotinamide adenine dinucleotide (NADH), is synthesized [292]. As for butyric acid, it has both anti-inflammatory and neuroprotective effects [293,294]. Furthermore, in experiments by Rose et al. [212], it enhanced mitochondrial function during oxidative stress in cell lines from autistic boys. Most probably, SCFAs are implicated in the pathogenesis of ASD because of changes in mitochondrial functions related to the citric acid cycle, carnitine metabolism, or modulation of some genes [290]. In the colon butyrate is produced from fiber. Thus, a low-fiber diet may lead to reduced levels of gut butyrate, which in consequence may cause inflammation and other bowel diseases [295]. It is particularly important considering the fact that the recommended levels of fiber intake are not met in both the developed and developing countries [296–298].

Supplementation with prebiotics and probiotics, FMT, or antibiotic therapy are among proposed treatment strategies in ASD. Results obtained by Liu and colleagues [250] suggest that modulation of butyrate-producing bacteria (including *Eubacterium*, *Ruminococcaceae*, *Erysipelotrichaceae*, and *Lachnospiraceae*) could be beneficial in autistic patients. Administration of galactooligosaccharide to gut models inoculated with fecal samples from children suffering from this disease resulted in reduced levels of *Sutterella* spp., *Bacteroides*, Clostridial cluster IX, *Escherichia coli*, *Veillonellaceae*, *Ruminococcus* spp., *Clostridium leptum*, *Faecalibacterium prausnitzii* and in increased growth of *Bifidobacteria*. Moreover, elevated levels of butyrate along with diminished concentration of propionate were recorded [262].

In a double-blind, placebo-controlled, crossover-designed study by Parracho et al. [299], a 3-week supplementation of *Lactobacillus plantarum* changed the gut microbiota of autistic children, improved some of their GI symptoms, and had beneficial effects towards autistic behavior. Improvement in ability to concentrate and carry out orders along with decreased amounts of D-arabinitol and the ratio of D-/L-arabinitol (elevated levels of these parameters are characteristic of *Candida* infection) were observed in an open study in autistic children who had been treated with *Lactobacillus acidophilus* for 8 weeks [300].

Pärtty et al. found [301] in a randomized, double-blind, placebo--controlled prospective follow-up study that administration of *Lactobacillus rhamnosus* GG in infants in the first 6 months of their life results in reduced risk on the development of Asperger's syndrome. In an open study, a 4-month supplementation with a preparation containing *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* improved the quality of gut microbiota in autistic children, particularly shifting *Bacteroidetes: Firmicutes* ratio in favor of *Bacteroidetes* [231,302]. In another open study [303], a 3-month administration of *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, and *Bifidobacterium longum* led to significant improvements in the severity of autism and GI disturbances. Partial alleviation of autistic symptoms was also noted after a 6-month intake of a combination of immunomodulator with a set of probiotic bacteria: *Lactobacillus casei*, *Lactobacillus delbrueckii*, *Bifidobacterium longum*, *Bifidobacterium bifidum* [304]. Grossi et al. [305] published a case report presenting a significant reduction in the severity of abdominal symptoms along with improvement in autistic symptoms in a pediatric patient as a result of a 4-month treatment with a multi-strain mixture of ten probiotics (*Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus bulgaricus*, *Lactobacillus delbrueckii*, *Streprococcus thermophilus*, *Streprococcus salivarius*). These observations were confirmed in a double-blind randomized, placebo-controlled clinical trial by Santocchi et al. [306], in which a 6-month administration of a similar probiotic set to children improved their autistic symptoms even though they were not accompanied by GI problems.

A mixture of bovine colostrum product (a source of oligosaccharides) with *Bifidobacterium infantis* when given for several weeks significantly diminished frequency of some GI problems and occurrence of atypical behavior in children with ASD as assessed in a double-blind, crossover, randomized clinical trial [307]. Positive probiotic-prebiotic effects (*Bifidobacterium infantis*, *Lactobacillus rhamnosus*, *Bifidobacterium lactis*, *Lactobacillus paracasei* combined with fructooligosaccharides) in autistic children were also demonstrated in recent double blind, placebo-controlled study by Wang et al. [308]. Such a treatment significantly elevated the level of beneficial bacteria (*Bifidobacteriales* and *Bifidobacterium longum*), reduced the level of pathogenic bacteria (*Clostridium*) as well as diminished severity of both ASD and GI problems. The clinical studies on administration of probiotics in ASD are summarized in Table 6.

FMT introduced in children with ASD resulted in improvement of both bacterial diversity in the gut with amelioration of GI manifestations (such as constipation, indigestion, diarrhea, abdominal pain) and behavioral autistic symptoms that were sustained for 8 weeks post-treatment [227]. The follow-up study [309] confirmed that even two years after treatment the above-mentioned GI and autism-related symptoms were still improved when compared to the baseline. These long-term observations suggest that FMT could be a potentially safe and effective treatment strategy in children with ASD and GI problems, though further trials are needed.

Beneficial effects (though usually short-term) in relation to symptoms of ASD can also be expected after anti-*Clostridiaceae* vancomycin therapy [310] administration of neuroprotective D-cycloserine and minocycline [311–313], or vitamin B1 supplementation [228].

Additionally, patients with ASD are advised to follow a specific diet, including consumption of gluten-free and casein-free products [314, 315], monosaccharides instead of complex carbohydrates [284], reduced amount of oxalate-containing food [316], and supplementation of digestive enzymes, particularly proteases [317]. In a randomized, controlled trial, Adams and colleagues [318] reported beneficial effects (i.e., better improvement in ASD symptoms and developmental age) of the gluten-, casein-, and soy-free diet supplemented with vitamins, minerals, essential fatty acids, Epsom salt baths, carnitine, and digestive enzymes in autistic children and adults who consumed it for 1 year.

On the other hand, it was suggested that gluten- and casein-free diet may exacerbate the GI symptoms. Such a diet may lead to further reduction in the amount of the beneficial gut bacteria and to increase the number of pathogenic ones. Moreover, it decreases the amount of fiber intake, which can result in constipation, and its introduction augments the risk of protein malnutrition, reduced bone growth, and amino acid deficiencies [319–321]. Also, the ketogenic diet (i.e., a high fat diet, which is a treatment option in drug-resistant epilepsy) has been utilized in children with ASD [322]. However, such diet may lead to constipation, hypercholesterolemia, menstrual irregularities, vomiting, and

Table 4
Studies on the gut microbiota composition in ASD.

Study design	Subjects	Age/sex	Adjusted *P* value to compare gut microbiota composition	Statistically significant changes in gut microbiota composition	Ref.
Cross-sectional study	26 participants with autism and 32 healthy subjects	2–7 years/both sexes	Not specified	Increased levels in autism: *Firmicutes, Coriobacteriaceae, Peptostreptococcaceae, Rikenellaceae, Clostridium, Blautia, Roseburia* Decreased levels in autism: *Butyricimonas, Butyrivibrio, Faecalibacterium, Dialister, Bilophila, Bifidobacterium, C. perfringens*	[331]
Cross-sectional study	30 participants with autism with functional GI disease and 24 healthy subjects	3–16 years/both sexes	FDR correction	Increased levels in autism: *Firmicutes, Veillonellaceae, Lactobacillaceae, Bifidobacteriaceae, Veillonellaceae, Erysipelotrichaceae, Enterococcaceae, Desulfovibrionaceae, Bifidobacterium, Lactobacillus, Megasphaera, Mitsuokella* Decreased levels in autism: *Prevotellaceae*	[332]
Cross-sectional study	11 participants with autism and 14 healthy subjects	2–4 years/both sexes	Not specified	Increased levels in autism: *Bacteroidetes/Firmicutes* ratio, *Bacteroidetes, Proteobacteria, Parabacteroides, Ruminococcus, Lachnospira, Roseburia, Oscillospira, Faecalibacterium prausnitzii* Decreased levels in autism: *Actinobacteria, Streptococcaceae, Gemellaceae, Coriobacteriaceae, Bifidobacteriaceae, Actinomycetaceae, Actinomyces, Corynebacterium, Bifidobacterium, Eggerthella, Streptococcus, Blautia, Coprococcus*	[333]
Cross-sectional study	25 participants with autism and functional GI disease and 6 healthy subjects	3–8 years/both sexes	FDR correction	Increased in autism: *Firmicutes/Bacteroidetes* ratio, *Bacteroidetes* Decreased in autism: *Firmicutes, Veillonella, Streptococcus, Escherichia, Actinomyces, Parvimonas, Bulleida, Peptoniphilus*	[334]
Cross-sectional study	33 participants with autism with functional GI disease and 13 healthy subjects	2–9 years/ unidentified sex	Not specified	Increased in autism: *Clostridium perfringens*	[335]
Retrospective study	21 participants with autism with functional GI disease and 19 healthy subjects with functional GI disease	14.4 ± 1.1 years for participants with autism and 16 ± 1.2 years for healthy subjects/both sexes	FDR correction	Increased in autism: *Burkholderia, Oscillospira, Actinomyces, Peptostreptococcus, Ralstonia* Decreased in autism: *Neisseria, Bacteroides, Escherichia coli, Devosia, Prevotella, Streptococcus*	[336]
Cross-sectional study	40 participants with autism and 40 neurotypical subjects	Average age 11.1 ± 6.8 for participants with autism and 9.2 ± 7.9 for neurotypical subjects	FDR correction	Increased in autism: *Firmicutes/Bacteroidetes ratio, Lactobacillus, Dorea, Corynebacterium, Collinsella, Candida* Decreased in autism: *Bacteroidetes, Veillonella, Alistipes, Bilophila, Dialister, Parabacteroides*	[235]
Cross-sectional study	47 participants with autism (with or without functional GI disease) and 33 healthy subjects (with or without functional GI disease)	Average age 6.0 ± 2.8 for participants with autism and 7.3 ± 3.1 for healthy subjects	Not specified	Increased in autism: *Candida* Decreased in autism: *Lactobacillus, Clostridium*	[337]
Cross-sectional study	14 participants with autism and functional GI disease and 15 neurotypical subjects with or without functional GI disease	Participants with autism 4–13 years/males Neurotypical subjects 3–18 years/both sexes	BH FDR correction	Increased in autism: *Clostridium lituseburense, Lachnoclostridium bolteae, Lachnoclostridium hathewayi, Clostridium Aldenense, Flavonifractor plautii, Faecalibacterium prausnitzii, Roseburia intestinalis, Oscillospira valericigenes, Bilophila wadsworthia* Decreased in autism: *Blautia, Dorea, Sutterella*	[338]
Cross-sectional study	10 participants with autism and 10 healthy subjects	4–10 years/both sexes	Not specified	Increased in autism: *Bacteroidetes, Anaerofilum, Clostridium, Caloramator, Sarcina, Roseburia, Dorea, Bacteroides, Shigella, Akkermansia muciniphila, Clostridium, Porphyromonas, Prevotella, Aeromonas, Enterobacteriaceae* Decreased in autism: *Firmicutes, Fusobacteria, Verrumicrobia, Faecalibacterium, Oscillospira, Subdoligranulum, Eubacterium, Streptococcus, Turicibacter, Prevotella, Bifidobacterium, Fusobacterium, Enterococcus, Lactobacillus, Streptococcus, Lactococcus, Staphylococcus, Bifidobacterium*	[280]

Abbreviations: BH, Benjamini-Hochberg procedure; FDR, false discovery rate; GI, gastrointestinal.

dehydration.

In an open study, Brudnak et al. [317] reported that preparation containing a mixture of proteases (i.e., alpha-fetoprotein, bromelain, caso-glutenase, phytase) improved eye contact, socialization, attention, hyperactivity, comprehension, mood, anxiety/compulsion, sleep as well as digestion in children with ASD. Similarly, a randomized, placebo-controlled trial showed that intake of papain and pepsin combination resulted in alleviation of both ASD and GI symptoms [323]. According to Geier and colleagues [324], a 3-month treatment with levocarnitine may improve autistic symptoms, as assessed in a double-blind, randomized clinical trial.

Several authors suggested that deficiency of polyunsaturated fatty acids may be associated with the development of ASD [325,326]. The meta-analysis by Cheng and colleagues [327] indicated that supplementation of omega 3 fatty acids is safe and have beneficial (though small) effects on the primary symptoms of autism (i.e. social withdrawal and stereotypy) as well as on the secondary behavioral problems (i.e. hyperactivity). Though positive results of antioxidants [328], minerals, and vitamins [329,330] in autistic patients have been reported, they are not convincing, thus, further studies are needed.

In summary, the link between ASD and the gut microbiota is now a well-known phenomenon. The gut microbiota composition differs between children with ASD and healthy subjects and the alterations in the gut microbiota profile appear to be related not only to the comorbid GI symptoms but also to the severity of behavioral symptoms in ASD. Moreover, abnormalities in metabolites produced by the gut microbiota are frequently observed in ASD patients, which suggest that some microbial metabolites may be involved in the development of ASD and the severity of ASD symptomatology. As described above, a number of preclinical and clinical studies have been performed to increase our understanding on how the gut microbiota is involved in ASD and to identify potential biomarkers associated with the microbiota-gut-brain axis that may be useful for the diagnosis, prevention, and individualized treatment of ASD. Special diets, prebiotics, and probiotics have promising therapeutic potential in ASD but more randomized controlled trials are needed to find out if targeting the gut microbiota can yield therapeutic strategies for ASD.

2.4. Epilepsy

Epilepsy is a heterogeneous group of neurological diseases affecting more than 65 million people worldwide, which are characterized by an enduring predisposition to generate spontaneous, unprovoked seizures. An imbalance between neuronal excitation and inhibition has been established as a mechanism underlying seizures and is determined by systems that mediate excitation or inhibition including the glutamatergic and GABA-ergic systems, respectively [339]. The process of epilepsy development, i.e., epileptogenesis, begins following a precipitating event (e.g., brain trauma, febrile seizures, infection, stroke, status epilepticus or genetic malformation). Then, molecular and cellular alterations transform a physiological neuronal network into an epileptic state, promoting excitability, which results in chronic epilepsy. However, despite the progress in understanding the disease mechanisms, the cause is unknown in ca. 50% of cases [340]. Pharmacological treatment with anti-seizure drugs (ASDs) and non-pharmacological treatment comprising epilepsy surgery or ketogenic diet are among currently available treatment options for patients with epilepsy. It is estimated that more than one third of patients remain resistant to currently available ASDs [339,341]. In those patients, the ketogenic diet, which is a diet high in fat and low in carbohydrates, may be considered [342].

An increasing interest in the association between gut microbiota and epilepsy is reflected in the number of review/opinion articles which have been published recently [30,343–346]. An important fact is that since 2019 the results of four clinical studies on microbiota composition and/ or diversity in children with epilepsy [347–350] and three studies in adults with epilepsy [351–353] have been published. The groups evaluated in clinical studies included children or adults responsive to treatment with ASDs, patients with drug-resistant epilepsy and patients with drug-resistant epilepsy who were referred to start the ketogenic diet. These studies are summarized in Table 5.

One research area is the potential role of microbiota in drug-resistant epilepsy [354–356]. Drug resistant epilepsy is diagnosed if patient experiences seizures despite adequate trials of two ASDs, which have been chosen appropriately for the seizure type, given in a right dose alone or in combination with other ASDs [357]. In studies on microbiota, the drug-resistant epilepsy groups were either compared to drug-responsive groups [352,358] or to healthy controls [347,349,350,359]. A study assessed the microbiota profile in 42 treatment-resistant epileptic patients vs. 49 treatment-responsive patients and found significant differences in the composition of gut microbiota. The gut microbiota composition of drug-responsive patients was similar to healthy controls. Patients with four seizures per year or fewer showed an increase of *Bifidobacteria* and *Lactobacillus* compared to those with more than four seizures per year. Furthermore, increased alpha-diversity was found in drug-resistant group [358]. Another study did not find differences in alpha or beta-diversity between drug-resistant and drug-responsive patients but it did find differences in composition of microbiota [352] between these groups. In pediatric population, there were differences in diversity and composition of gut microbiota between children with drug-resistant resistant epilepsy and healthy children but both increased alpha-diversity [347] and decreased alpha-diversity [349,359] were reported.

Another research area gaining attention is the relationship between the gut microbiota and ketogenic diet [356,360–362]. Preclinical studies support the link between the ketogenic diet and epilepsy treatment.

The anti-seizure effect of ketogenic diet was mediated by microbiota in the 6-Hz induced seizure model and in Kcna1$^{-/-}$ genetic model of temporal lobe epilepsy. Mice treated with antibiotics or GF mice were resistant to ketogenic diet-mediated protection from seizures. The ketogenic diet increased the abundance of *Akkermansia muciniphila* and *Parabacteroides*. Enrichment of, and gnotobiotic cocolonization with *Akkermansia* and *Parabacteroides* restored seizure protection. Moreover, transplantation of the ketogenic diet-gut microbiota and treatment with *Akkermansia* and *Parabacteroides* each conferred seizure protection to mice fed with a control diet. Furthermore, protection from seizure correlated with hippocampal GABA/glutamate ratios [363].

In epileptic humans, there is, however, no consensus whether changes in the microbiota induced by ketogenic diet are protective or detrimental. Gut microbiota pattern differed between 30 healthy infants and 14 drug-resistant epileptic infants. *Bacteroidetes* were dominant in healthy infants. A 1-week ketogenic diet produced improvement in 64% children with drug-resistant epilepsy with a 50% decrease in seizure. At the phyla level a decrease of *Proteobacteria* and an increase of *Bacteroidetes* were observed after the ketogenic diet. At the genus level, a decrease in *Cronobacter* and an increase in *Prevotella, Bifidobacterium, and Bacteroides* were observed [359]. These observations might suggest that the ketogenic diet corrects an imbalanced gut microbiota in epileptic infants.

In another study 20 children with drug-resistant epilepsy were enrolled. After 6 months of the ketogenic diet 2 patients were seizure free, 3 had $\geq$ 90% seizure reduction, 5 had a reduction of 50–89%, and 10 had $<$ 50% reduction. Fecal microbial profiles showed lower alpha diversity, decreased abundance of *Firmicutes* and increased levels of *Bacteroidetes* after ketogenic diet. Furthermore, enrichment in *Clostridiales, Ruminococcaceae, Rikenellaceae, Lachnospiraceae,* and *Alistipes* was observed in the non-responsive group [364].

The alpha diversity was not changed after 3 months of the ketogenic diet in 12 children with drug-resistant epilepsy, compared to their parents, who did not start the ketogenic diet. Relative abundance of *Bifidobacteria* as well as *Eubacterium rectale* and *Dialister* was diminished during the intervention. An increase in relative abundance of *Escherichia*

coli was also observed after ketogenic diet [350]. Thus, the compositional changes observed in this study might not be favorable for gut or overall health.

GLUT1 deficiency syndrome (GLUT1DS) is an early-onset childhood epileptic encephalopathy, which is caused by impaired glucose transport into the brain and is treated by the ketogenic diet [365]. A pilot study showed that there were no statistically significant differences in *Firmicutes* and *Bacteroidetes*, but an increase in *Desulfovibrio* spp., a bacterial group believed to be involved in the exacerbation of the inflammatory condition of the gut mucosa associated with the consumption of fat of animal origin, was observed [366].

A case was reported whereby remission of intestinal and neurological symptoms was achieved in a girl with Crohn's disease and a 17-year history of epilepsy with the aid of FMT. During the 20 months of follow-up, the patient was seizure-free despite discontinuing treatment with the anti-seizure drug sodium valproate [367]. Based on this case, a clinical trial for FMT for epilepsy patients has been registered (NCT02889627).

Six patients with drug-resistant epilepsy attained temporary seizure freedom during antibiotic treatment. The patients were treated with antibiotics belonging to different classes: amoxicillin, amoxicillin/clavulanic acid, azithromycin, clarithromycin or piperacillin/tazobactam, ciprofloxacin and clindamycin. While the use of macrolide antibiotics may have increased the serum concentration of ASDs, thus augmenting their action, it is also possible that the observed effect was mediated by the influence on the gut microbiota [368]. On the other hand, it is known that administration of antibiotics such as penicillin may induce seizures and penicillin is used in preclinical studies to induce recurrent developmental seizure model [369].

A mixture of probiotics (*Lactobacillus rhamnosus*, *Lactobacillus reuteri*, and *Bifidobacterium infantis*) [370] as well as *Lactobacillus* (*casei, acidophilus*) and *Bifidobacterium bifidum* [371] exerted beneficial effects in an animal model of epilepsy, namely pentylenetetrazole kindling. Similarly, in a clinical trial (NCT03403907) administration of a probiotic containing *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus helveticus*, *Lactobacillus brevis, Bifidobacterium lactis*, *Bifidobacterium. lactis*, and *Streptococcus salivarius* subsp. *Thermophilus* for 4 months was beneficial in patients with drug-resistant epilepsy, resulting in $\geq$ 50% reduction in the number of seizures in 28.9% of the patients. A limitation of this study is that it was not placebo-controlled [372].

To sum up, the last several years have brought several clinical studies on microbiota diversity and composition in epilepsy. However, the fact that epilepsy is a heterogeneous group of diseases with different etiologies, may have led to inconsistency in results, in addition to methodological differences. As clinical studies included patients with drug-resistant epilepsy, patients participating in those studies were taking a different number of different ASDs. Furthermore, not all of drug-resistant patients who started a ketogenic diet responded to the ketogenic diet. Moreover, in clinical studies the control groups were either from the same household (family members [358], parents of children [350]) or from different households, which might also have an impact on microbiota profile, thus affecting the results. The conclusion of a systematic review conducted according to the PRISMA guidelines was that data cohesively support the interaction between gut microbiota and epilepsy [373]. However, this analysis included the clinical studies of Xie at al. [359], Peng et al. [358] and Şafak et al. [353], in which participated pediatric patients with drug-resistant epilepsy, adult patients with drug-resistant epilepsy and adult drug-responsive patients, respectively, thus showing the above-mentioned heterogeneity (Table 5). Hence, further studies evaluating microbiota in homogenous groups of patients may pave the way to using gut microbiota profiling as a tool in precision medicine in epilepsy.

2.5. Migraine

Migraine is one of the most disabling medical conditions. The Global Burden of Diseases, Injuries, and Risk Factors Study identifies migraine as a leading cause of disability worldwide, particularly in individuals younger than 50 years [374]. The 1-year prevalence of migraine in the general population is 12%. The annual and lifetime prevalence are 18% and 33% in women, and 6% and 13% in men, respectively. This chronic neurological disorder is characterized by attacks of headache and reversible neurological and systemic symptoms. The most characteristic symptoms include photophobia, phonophobia, cutaneous allodynia, and GI symptoms such as nausea and emesis [375]. Other GI symptoms include constipation or diarrhea. Furthermore, there is an association between migraine and GI disorders such as inflammatory bowel disease or IBS [16]. The prevalence of *Helicobater pylori* infection is also significantly greater in migraineurs than in controls (44.97% vs 33.26%, respectively) [376]. Moreover, abdominal migraine is among pediatric functional abdominal pain disorder and is currently referred to as a disorder of the gut-brain axis [377].

Increased level of proinflammatory cytokines such as TNF-α, IL-1β and IL-6, resulting from the "leaky gut", could affect nociceptive responses in the trigeminal pathway and play a role in migraine pain initiation [378]. Antibiotic treatment was shown to prolong the nitroglycerin (NTG)-induced acute migraine-like pain in wild-type (WT) mice and the pain prolongation was completely blocked by genetic deletion of TNF-α or intra-spinal trigeminal nucleus caudalis (Sp5C) injection of a TNF-α receptor antagonist. The antibiotic treatment extended the NTG-induced TNF-α up-regulation in the Sp5C. Probiotic administration significantly inhibited the antibiotic-produced migraine-like pain prolongation. Furthermore, the NTG-induced migraine-like pain in GF mice was markedly enhanced compared to that in WT mice and gut colonization with fecal microbiota from WT mice robustly reversed microbiota deprivation-caused pain enhancement. Taken together, these results suggest that gut microbiota dysbiosis contributes to chronicity of migraine-like pain by up-regulating TNF-α level in the trigeminal nociceptive system [379].

A metagenome-wide association study analyzed 108 shotgun-sequenced fecal samples obtained from elderly women who suffer from migraine and matched healthy controls. The alpha diversity was significantly decreased in the migraine group at species, genus, and Kyoto Encyclopedia of Genes and Genomes orthologous levels. *Firmicutes*, especially *Clostridium* spp., were significantly enriched in the migraine group. Conversely, the healthy controls held more beneficial microorganisms, such as *Faecalibacterium prausnitzii, Bifidobacterium adolescentis*, and *Methanobrevibacter smithii* [380]. In young females with migraine without aura who displayed dysbiosis positive correlation between dysbiosis and migraine severity and duration were found [381]. In the latter study species in stool samples were identified by matrix-assisted laser desorption ionization using the MALDI-TOF-MS method and dysbiosis was defined either as an increase or decrease in microorganism diversity [381].

Probiotic supplementation could enhance the gastric emptying rate and attenuate gastric stasis in migraineurs [378]. However, a meta-analysis of randomized placebo-controlled trials on the use of probiotics in the prophylaxis of migraine according to the PRISMA guidelines was not possible due to methodological differences. Qualitative comparison of the studies demonstrated a dichotomy of results – one trial reported no significant change in migraine frequency and intensity, while the second trial reported highly significant improvements [382]. However, concerns have been raised about the statistical analysis [383] (paired *t*-test within groups) in the study which did not show change in migraine frequency after administration of probiotics [384]. Recently, another study, which was not included in the systematic review [382], showed reduction in the mean frequency of migraine after the use of symbiotic [385]. The clinical studies on administration of probiotics in migraine are summarized in Table 6. Noteworthy is the fact

that the interventions used differed in terms of the composition as well as concentration of bacteria. Currently, the evidence supports a call to action for microbiome research in migraine, in order to build the evidence base regarding nutrition's potential impact on migraine attack prevention and treatment [386].

2.6. Parkinson's disease

Parkinson's disease is a severe neurodegenerative movement disorder which is characterized by the motor and non-motor features [387]. The motor features are primarily attributed to the loss of dopamine-containing neurons in the substantia nigra pars compacta. Progressive neuronal loss corresponds to the accumulation of intraneuronal proteinaceous cytoplasmic inclusions, named Lewy bodies, in which amyloid fibrils of the presynaptic protein α-synuclein are the main constituent [388,389].

Motor symptoms related to Parkinson's disease are often preceded by dysregulation in GI functions, which are manifested as bloating, nausea, constipation or other defecation problems, gastroparesis, or weight loss [390–392]. There are common factors in the pathophysiology of Crohn's and Parkinson's diseases, e.g., variants in the CARD15 and LRRK2 genes are involved in the pathogenesis of both diseases [393–395].

Li and colleagues [396] reported that animals deprived of dendritic cell factor 1 (i.e., a membrane protein involved in development of the nervous system) presented behavioral changes typical for Parkinson's disease and alterations in the gut microbiota. Moreover, GF rodents presented dysregulated dopamine turnover in different parts of the brain [50,67].

A large body of evidence shows the bidirectional interaction between the gut and the brain regarding α-synuclein pathology. α-Synuclein accumulates in neurons both in the brain and in the ENS. It was suggested that the GI tract may be responsible for the spread of Parkinson's disease, since inclusions of α-synuclein may at first appear in the ENS and only later they are transmitted to the CNS via the glossopharyngeal or vagal nerves [397,398]. Involvement of the vagal nerve in the propagation of α-synuclein from the gut to the brain was demonstrated by Holmqvist et al. [399]. However, Arotcarena and colleagues [400] did not find α-synuclein pathological lesions in the vagal nerve, thus arguing against the hypothesis that the vagal nerve is involved in the transmission of α-synuclein pathology. The latter study did show that patient-derived α-synuclein aggregates are able to induce nigrostriatal lesions and ENS pathology after either enteric or striatal injection in a non-human primate model (baboon monkeys), thus showing the role of the gut-brain axis in the propagation of Parkinson's disease.

Gut injection with α-synuclein fibrils (12.5 μg) in mice also systematically spread pathology "upwards", i.e., to the dorsal motor nucleus of the vagus, locus coeruleus, amygdala, dorsal raphe nucleus, and the substantia nigra pars compacta, and it induced motor and non-motor symptoms resembling Parkinson's disease [401]. Conversely, when the α-synuclein pathology firstly occurred in the olfactory bulbs, it spread further to the brain via the olfactory tract but it also went down to the ENS and it damaged its neurons [402].

Nigral overexpression of α-synuclein led to considerable neuronal loss in the ileal submucosal plexus, alterations in gut microbiome and metabolism of bile acid [403]. Mice overexpressing α-synuclein given antibiotic treatment or raised under GF conditions displayed improved motor functions and reduced amount of α-synuclein deposits. FMT from patients with Parkinson's disease to mice overexpressing α-synuclein aggravated the problems in motor functions more profoundly than gut bacteria derived from healthy subjects, which suggested that the manifestation of disease symptoms is related to the shift in gut microbiota [404].

The involvement of the gut-brain axis in the propagation of Parkinson's disease was also shown in other animal models of this disease as well as the role of gut microbiota in these models. Rotenone (a pesticide) administered intragastrically in mice (5 mg/kg, 5 days a week, up to 3 months) induced accumulation of α-synuclein in several structures of the nervous system (i.e., dorsal motor nucleus of the vagus, intermediolateral nucleus of the spinal cord, the substantia nigra) along with inflammation and α-synuclein phosphorylation in the ENS and the dorsal motor nucleus of the vagus [405]. Furthermore, oral administration of rotenone solution (10 mg/kg for 28 days) and intrastriatal infusion of rotenone (5.4 μg/mice) induced Parkinson's disease-like symptoms, including impaired motor function, elevated expression of α-synuclein, delayed intestinal transit, immune activation and colonic inflammation [406]. After gastric coadministration of paraquat (another pesticide, 1 mg/kg for 7 days) with lectin impaired nigrovagally-evoked gastric motility, reduction in tyrosine hydroxylase positive dopaminergic neurons, and misfolded α-synuclein in the myenteric plexus, dorsal motor nucleus of the vagus, and the substantia nigra pars compacta neurons were found in rats [407]. Mice exposed to 1-methyl-4--phenyl-1,2,3,6-tetrahydropyridine (MPTP) or 6-hydroxydopamine presented increased amount of *Proteus mirabilis* in their feces. After repeated oral administration of these bacteria isolated from the above-mentioned models to WT mice, the treated animals displayed Parkinson's disease-like symptoms, including impaired motor function, elevated α-synuclein aggregation in the brain and colon as well as dopaminergic neuronal loss [408].

There is evidence coming from both preclinical and clinical studies that the "leaky gut" may cause α-synuclein aggregation. Administration of LPS may be regarded as a progressive animal model of Parkinson's disease [409,410]. Stress-induced microbial dysbiosis and dysfunction of the intestinal barrier potentiated negative effects of rotenone both in the intestines (related to the intestinal hyper-permeability, disruption of TJs proteins, oxidative stress inflammation in enteric glial cells, α-synuclein, increased relative abundance of mucin-degrading Gram-negative bacteria, and endotoxemia) and in the brain (related to the lower number of resting microglia and a higher number of dystrophic/phagocytic microglia, elevated LPS reactivity in the substantia nigra, and reduced levels of dopamine and its metabolites in the striatum) [411]. Increased gut permeability with intestine α-synuclein accumulation, elevated blood and brain levels of TLR2 and TLR4, and reduced blood levels of the LPS-binding protein have been detected in subjects with Parkinson's disease [412,413]. Aggregated forms of α-synuclein can act as ligands for TLRs [414] and TLRs, particularly TLR4, have been suggested as a promising therapeutic target in Parkinson's disease. High TLR4 expression has been related to microbial dysbiosis, gut inflammation, intestinal barrier disruption, bacterial translocation, microglial activation, and neurodegeneration. Patients with Parkinson's disease presented higher expression of TLR4 in colonic biopsies [414,415].

Patients with Parkinson's disease have significantly altered gut bacteria, in relation to both its quality and quantity. A number of them present small intestinal bacterial overgrowth (increased bacterial density with dysbiosis in the small bowel) which is responsible for malabsorption, bloating, or flatulence [416], as well as worsening of motor impairment and may cause fluctuating response to treatment with levodopa. Eradication of small intestinal bacteria overgrowth improved both motor and GI symptoms. A meta-analysis of gut microbiota in 223 patients with Parkinson's disease and 137 healthy controls from five different countries revealed that Parkinson's disease is frequently associated with increased genus *Akkermansia* which increases intestinal permeability and decreased SCFA-producing bacteria of genera *Roseburia* and *Faecalibacterium* [417]. A more recent meta-analysis of ten case-control studies showed that elevated genera *Lactobacillus, Akkermansia, and Bifidobacterium* and decreased *Lachnospiraceae* family and genus *Faecalibacterium* are the most consistent alteration in the gut microbiota composition in Parkinson's disease [418]. Similar changes were reported by Shen et al. in a meta-analysis of fourteen studies. The analysis showed decreased levels of *Prevotellaceae, Faecalibacterium*, and *Lachnospiracea*e, and increased levels of *Bifidobacteriaceae, Ruminococcaceae, Verrucomicrobiaceae*, and *Christensenellaceae* [419]. Similar pattern of gut dysbiosis has been observed in rodent models of

Table 5
Studies on the gut microbiota composition in patients with epilepsy.

Study design	Subjects	Treatment status (ASDs)	Adjusted *P* value to compare gut microbiota composition	Statistically significant changes in the gut microbiota diversity	Statistically significant changes in the gut microbiota composition	Other key finding (s)	Ref.
		Children					
Cross-sectional	25 children (12 females, 13 males) with both cerebral palsy and epilepsy (CPE), 21 healthy children (9 females, 12 males)	15 CPE children on ASDs	BH FDR correction	Higher diversity in CPE	Yes	(1) Increased *Bifidobacterium*, *Streptococcus*, *Akkermansia*, *Enterococcus*, *Prevotella*, *Veillonella*, *Rothia*, and *Clostridium IV*, and decreased *Bacteroides*, *Faecalibacterium*, *Blautia*, *Ruminococcus*, *Roseburia*, *Anaerostipes*, and *Parasutterella* in CPE; (2) Negative correlations between *Bacteroides* and *Lactobacillus* and between *Intestinibacter* and *Bifidobacterium*	[348]
Prospective	8 children (5 females, 3 males) with DR epilepsy, 32 healthy children (16 females, 16 males)	ASDs (clobazam, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, valproate, topiramate)	BH FDR correction	Lower alpha-diversity in DR epilepsy	Yes	(1) Decreased *Bacteroidetes* and increased *Actinobacteria* in DR epilepsy; (2) Biomarkers for DR epilepsy: *Enterococcus faecium* group, *Bifidobacterium longum* group, and *Eggerthella lenta*	[349]
Retrospective	14 children with DR epilepsy before and after 1 week of KD (2 females, 11 males), 30 healthy children (15 females, 15 males)	ASDs	Not specified	Lower diversity in DR epilepsy	Yes	(1) Increased *Proteobacteria* (*Cronobacter*) in DR epilepsy and decreased *Proteobacteria* (*Cronobacter*) after KD; (2) Increased *Bacteroides* (*Prevotella, Bifidobacterium*) after KD	[359]
Prospective	20 children with DR epilepsy (6 females, 14 males) before and after 6 months of KD	ASDs (carbamazepine, oxcarbazepine, lamotrigine, levetiracetam, topiramate, valprotate	Not specified	KD lowered alpha-diversity	Yes	(1) Decreased *Firmicutes* and *Actinobacteria* and increased *Bacteroidetes* after KD; (2) Increased *Clostridiales*, *Ruminococcaceae*, *Rikenellaceae*, *Lachnospiraceae*, and *Alistipes* in the non-responsive to KD group	[364]
Cross-sectional (children with DR epilepsy vs healthy children) and prospective (children with DR epilepsy before and after KD)	12 children with DR epilepsy before and after 6 months of KD, 12 healthy children	ASDs	Not specified	Higher alpha-diversity in DR epilepsy	Yes	(1) Increased *Actinobacteria* (*Enterococcus*, *Anaerostipes*, *Bifidobacterium*, *Bacteroides*, and *Blautia)* in DR epilepsy; (2) Decreased *Bifidobacterium, Akkermansia, Enterococcaceae* and Actinomyces and increased *Subdoligranulum, Dialister, Alloprevotella* after KD diet	[347]
Prospective	12 children (8 females, 4 males) with DR epilepsy before and after 3 months of KD, 11 healthy parents	ASDs (clobazam, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, topiramate, valproic acid, vigabatrin)	BH FDR correction	Lower alpha-diversity in DR epilepsy (higher alpha-diversity in parents may reflect more mature gut microbiota), alpha-diversity not changed after KD	Yes	Decreased bifidobacteria as well as *Eubacterium rectale* and *Dialister,* increased *Escherichia coli* after KD	[350]
		Adults					
Cross-sectional	30 patients (16 males, 14 females) with epilepsy, 10 healthy controls (2 males, 8 females)	N/A	Not specified	N/A	N/A	Increased *Proteobacteria* (*Campylobacter*, *Delftia*, *Haemophilus*, *Lautropia*, *Neisseria)* in epilepsy *Fusobacteria* (*Leptotrichia* and *Fusobacterium)* detected in 10.6% of the patients	[353]

(*continued on next page*)

Table 5 (*continued*)

Study design	Subjects	Treatment status (ASDs)	Adjusted *P* value to compare gut microbiota composition	Statistically significant changes in the gut microbiota diversity	Statistically significant changes in the gut microbiota composition	Other key finding (s)	Ref.
						with epilepsy but not in the healthy controls	
Two cross-sectional analyses (in exploration and validation cohorts)	55 patients with epilepsy (27 males, 8 females) and 46 healthy controls (22 males, 24 females) from the same household (exploration cohort), 15 patients with epilepsy (6 males, 7 females) and 10 controls (5 males, 5 females) (validation cohort)	ASDs (carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, valproate, topiramate)	BH FDR correction	Lower alpha-diversity in epilepsy	Yes	Increased *Actinobacteria* and *Verrucomicrobia,* decreased *Proteobacteria*; increased *Prevotella_9*, *Blautia*, *Bifidobacterium*; increased *Actinobacteria*, *Verrucomicrobia, Nitrospirae* and *Blautia*, *Bifidobacterium*, *Subdoligranulum*, *Dialister*, and *Anaerostipes* in DR epilepsy:	[351]
Cross-sectional	49 patients with drug-responsive epilepsy (24 females, 25 males), 42 patients with DR epilepsy (23 females, 19 males), 65 healthy controls (33 females, 32 males) from families of the patients	ASDs (carbamazepine, clonazepam, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, valproate, topiramate)	Not specified	Increased alpha-diversity (increased richness and evenness) in DR epilepsy	Yes – between drug-responsive and DR groups	(1) *Bacteroidetes* and *Firmicutes* abundant in drug-responsive group and in healthy controls; (2) Decreased *Bacteroidetes* and increased *Firmicutes* in DR group; (3) Rare phyla in the DR group; (4) Increased *Verrucomicrobia* in DR group	[358]
Cross-sectional	20 patients (9 males, 11 females) with drug-responsive epilepsy and 20 patients (10 males, 10 females) with DR epilepsy completed the study	ASDs	Not specified	No differences in alpha-diversity (richness or evenness) or beta-diversity in DR epilepsy	Yes – between drug responsive and DR groups	(1) Increased *Bacteroides finegoldii* and *Ruminococcus_g2* in the drug-responsive epilepsy, increased *Negativicutes* (which belong to *Firmicutes)* in DR epilepsy; (2) Increased *Bacteroides finegoldii* in patients with a normal MRI, increased *Shigella genus* and *Veillonellales order* in patients with an abnormal MRI; (3) Increased *Bifidobacterium* in patients with a normal EEG, increased *Klebsiella* and *Streptococcus genus* in patients with an abnormal EEG	[352]

Abbreviations: ASDs, antiseizure drugs; BH, Benjamini-Hochberg procedure; DR, drug-resistant; FDR, false discovery rate; KD, ketogenic diet.

Parkinson's disease [420–422].

Reduced number of *Prevotella* may be associated with decreased mucin synthesis causing increased gut permeability [413]. Moreover, diminished *Prevotellaceae* count is associated with lower level of thiamine and folate biosynthesis [423] as well as lower levels of SCFAs, hydrogen sulfide, and ghrelin. Hydrogen sulfide has a protective potential towards dopaminergic neurons [424–426], whereas ghrelin is needed for physiological nigrostriatal dopamine function [427]. It is in line with observations made in subjects with Parkinson's disease, who present abnormalities in the gut microbiota accompanied by decreased levels of thiamine, folate [428,429], and ghrelin [430], along with altered concentration of SCFAs [421,431]. Paradoxically, due to altered gut microbiota coffee drinkers and smokers are at a lower risk of development of this condition [432]. Charlett et al. [433] as the first reported a high prevalence of *Helicobacter pylori* in patients suffering from Parkinson's disease, whereas other authors found out that the presence of this bacteria in the alimentary system may intensify deterioration of motor functions [434] and accelerate progression of the disease [435]. Furthermore, eradication of *Helicobacter pylori* was accompanied by improvement of motor symptoms and absorption of levodopa [434].

The significance of the gut microbiota in the development or progression of Parkinson's disease is also suggested by the observation that introduction of treatment which affects the gut-brain axis may alleviate symptoms of Parkinson's disease. In an animal model of Parkinson's disease, Ma et al. [436] demonstrated neuroprotective effects of the anti-inflammatory antibiotic minocycline, whereas Sun et al. [421] observed reduced activation of microglia and astrocytes along with decreased signaling of the TLR4/TNF-α pathway in the brain after FMT. A diet enriched in uridine, DHA, and choline improved motor symptoms, reduced α-synuclein accumulation, and diminished colonic inflammation [406]. When additionally supplemented with cofactors for phospholipid synthesis and prebiotic fibers, it was more effective in alleviation of motor and GI symptoms [437]. Similarly, Dong et al. [438] demonstrated that polymannuronic acid improved motor functions, suppressed gut, brain, and systemic inflammation as well as improved integrity of both the intestinal and BBB in mice with Parkinson's disease symptoms.

Furthermore, as it is suggested by both the preclinical and clinical studies, administration of probiotics might be among treatment strategies of Parkinson's disease. Goya et al. [439] found inhibitory effects of probiotic *Bacillus subtilis* strain towards α-synuclein aggregation in a model of synucleinopathy in *Caenorhabditis elegans*. Sun and colleagues [440] suggested that neuroprotective effects of *Clostridium butyricum* in mice with induced Parkinson's disease seem to be due to amelioration of the abnormal gut-brain axis. The authors demonstrated that oral administration of the above-mentioned strain improved gut dysbiosis, motor deficits, microglia activation, synaptic dysfunction, and loss of dopaminergic neurons. Similarly, positive effects of probiotic strains in in vitro and in vivo models of Parkinson's disease were reported by Castelli et al. [441] and Hsieh et al. [442].

Recent open-label uncontrolled study by Hegelmaier et al. [443] revealed that a 14-day ovo-lacto vegetarian diet accompanied by bowel cleansing for 8 days in patients with Parkinson's disease may ameliorate their motor impairments, reduce the need for medication, and change gut microbiome (particularly lowering the abundance of *Clostridiaceae*). In a randomized double-blind placebo-controlled clinical trial, Tamtaji et al. [444] reported that a 12-week consumption of several probiotics (*Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Lactobacillus reuteri*, and *Lactobacillus fermentum*) may improve motor impairments in subjects with Parkinson's disease, but also it has positive effects on their insulin metabolism, markers of inflammation, and markers of oxidative stress. There are also several lines of evidence demonstrating that probiotic intake can improve GI non-motor symptoms in patients suffering from Parkinson's disease (Table 6).

To sum up, the involvement of the gut-brain axis and gut microbiota in the pathophysiology of Parkinson's disease is a well-known concept today. Enrichment of *Verrucomicrobiaceae Bifidobacteriaceae, Ruminococcaceae, Christensenellaceae* and *Akkermansia* as well as depletion of *Prevotellaceae, Faecalibacterium*, and *Lachnospiracea*e in Parkinson's disease patients emerges as the most consistent gut microbiota alterations across different studies. Moreover, gut microbiota-orientated treatment may open up new avenues for the management of gastrointestinal alterations and motor symptoms in Parkinson's disease, though data from clinical studies on the beneficial effects of prebiotics, probiotics, FMT etc. are still very limited. An important observation is that human gut microbiota metabolizes levodopa and thereby may affect its bioavailability and efficacy. Identification of bacteria that metabolize levodopa to dopamine (*Enterococcus faecalis*) and dopamine to m-tyramine (*Eggerthella lenta)* [445] paves the way towards personalized medicine and discovery of biomarkers to predict levodopa effectiveness and side effects in Parkinson's disease patients.

2.7. Relationships between specific bacteria taxa and the disease

Although gut microbiota dysbiosis has been increasingly implicated in the pathophysiology of neuropsychiatric and neurological disorders, evidences regarding specific taxa involved in each disease are highly inconsistent. Integration of these rapidly expanding data to find any general patterns of changes is a challenge. Even alpha and beta diversity findings are inconsistent across microbiota studies. The limitation is also that most of the studies are not done at the species/strain level, and that level of detail is probably needed for real understanding. Nevertheless, some limited generalizations can be attempted.

A recent meta-analysis showed that decreased abundance of *Bacteroidetes, Prevotellaceae, Faecalibacterium, Coprococcus*, and *Sutterella*, as well as an increased abundance of *Actinobacteria* and *Eggerthella* are the most the most consistent findings in depressive disorder, while increased abundance *of Firmicutes, Ruminococcaceae, Subdoligranulum,* and *Dialister*, as well as decreased abundance of *Enterobacterales, Enterobacteriaceae,* and *Escherichia/Shigella* were frequently reported in anxiety. In is also noteworthy that both depression and anxiety are characterized by decreased abundance of *Prevotellaceae, Faecalibacterium, Sutterell*a, and *Dialister* along with a higher abundance of *Lactobacillus.* Overall, in depression and anxiety there is a higher abundance of proinflammatory bacteria (e.g., *Enterobacteriaceae and Eggerthella*), and decreased abundance of bacteria that secrete the anti-inflammatory SCFAs (e.g., *Faecalibacterium, Coprococcus*), which may result in dysregulated immune function [116].

The alterations in the gut microbiota composition in patients with ASD were reported in many studies but when taking into account the results of the recent two meta-analyses, the highest interest should be given only to *Bifidobacterium* and *Streptococcus* genera [239,240]. *Bifidobacteria* are one of the first bacteria that colonize the intestine of neonates and they are among the most beneficial bacteria in the intestine. A lower abundance of *Bifidobacterium* may affect neurodevelopment and contribute to the pathogenesis of ASD [239]. An association between lower abundance of *Streptococcus* and ASD is difficult to explain at the moment.

The changes in the gut microbiota profile in patients with Parkinson's disease have also been extensively studied. It appears that the Parkinson's disease-related gut dysbiosis is associated with the imbalance of SCFAs-producing bacteria (*Prevotellaceae, Faecalibacterium*, and *Ruminococcaceae*), bacteria that participate in lipid metabolism (e.g., *Christensenellaceae*) and those controlling gut permeability (e.g., *Verrucomicrobiaceae*, *Akkermansia*) [418,419,445]. Considering recent findings that levodopa is metabolized in two steps to non-therapeutic m-tyramine by *Enterococcus faecalis* and *Eggerthella lenta*, a special attention should be also given to those two genera in Parkinson's disease.

Data on the gut microbiota dysbiosis in schizophrenia and epilepsy are quite limited. In schizophrenia patients, an increased abundance of *Fusobacterium*, *Megasphaera*, *Prevotella,* and especially *Lactobacillus* genera were the most frequently reported changes but there is no meta-analysis of these data as yet. An increase in *Firmicutes* phyla and a decrease in *Bacteroidetes* and *Actinobacteria* phyla in patients suffering from epilepsy appear to be the most consistent findings across different studies. Epileptic patients were also reported to have an increase in rare bacteria phyla and genera [373]. Much less evidence implicates the gut microbiota in migraine. There in one study only showing enrichment of *Firmicutes*, especially *Clostridium* spp. in migraineurs [380].

To sum up, despite increasing evidence on the role of the microbiota dysbiosis in neuropsychiatric and neurological disorders, much more studies are needed to understand the role of specific taxa in relation to each disease.

3. Summary

The gut microbiota is increasingly recognized as an important player in the pathophysiology and treatment of neurological and psychiatric disorders. Numerous preclinical and clinical studies showed alterations in the gut microbiota composition in depression, anxiety, ASD, schizophrenia, epilepsy, or Parkinson's disease. The cause-effect relationship is, however, very inconclusive. It remains unclear whether the gut microbiota dysbiosis contributes to a specific disease or whether it is the result of a disease or maybe it is a combination of the two. Moreover, interpretation of these data is still difficult because changes in the gut microbiota profile in a specific disease entity are often inconsistent. The inconsistent findings could be attributed to many biological factors such as heterogeneous patient populations, treatment status (medicated/unmediated), differences in the stage of a given illness, diet, comorbid illnesses, physical activity, age of patients etc. Also, methodological differences may have a profound impact on the results obtained in microbiota studies. Technical factors affecting the microbiome include sample collection and storage techniques, methods of DNA extraction, selection of primers, sequencing method, and bioinformatics analysis including multiple comparisons issue [451]. However, a small sample size in most studies seems to be the main contributor to the variability of results reported. Although the association between the gut microbiota and psychiatric disorders (especially depression/anxiety, ASD, and

Table 6
Effects of probiotics in the treatment of selected neuropsychiatric and neurologic diseases.

Study design	Subjects	Treatment	Main effects	Ref.
Depression and anxiety				
Randomized, double-blind, placebo-controlled trial	26 psychiatric patients treated with probiotics and 29 treated with placebo	3×10^{11} CFU of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 for 30 days	Daily subchronic administration of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 alleviated psychological distress in volunteers	[47]
Randomized, double-blind, placebo-controlled trial	10 psychiatric patients treated with probiotics and 15 treated with placebo	3×10^{11} CFU of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 for 30 days	Daily chronic use of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 formulation could contribute to mental wellbeing of patients with low levels of stress, and could represent a prophylactic strategy against stress-related diseases in the population subject to the constraints of daily life.	[48]
Randomized, double-blind, placebo-controlled trial	132 healthy patients of the general population	6.5×10^{9} CFU of *Lactobacillus casei* for 3 weeks	The consumption of probiotic-containing products improved the mood of those whose mood was initially poor.	[136]
Randomized, double-blind, placebo-controlled trial	52 patients treated with probiotic and 51 treated with placebo	2×10^{10} CFU of *Lactobacillus plantarum* P8 for 12 weeks	*Lactobacillus plantarum* P8 administration alleviated stress, anxiety, memory and cognitive symptoms in stressed adults	[138]
Open study	33 healthy volunteers	*Lactobacillus helveticus* R0052, *Bifidobacterium longum* R0175, *Lactobacillus rhamnosus* R0011, prebiotics and for 6 weeks	Probiotics plus prebiotics supplementation optimized gut-brain axis balance for both improved metabolism and enhanced mental wellness	[139]
Schizophrenia				
Randomized, double-blind, placebo-controlled trial	33 probiotic-treated and 62 placebo-treated schizophrenia patients	10^{9} CFU of *Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* subsp. lactis Bb12 for 14 weeks	(1) No significant differences in the PANSS scores between probiotic and placebo group; (2) Probiotic-treated group was less likely to develop severe bowel difficulty over the course of the trial; (3) Reduced serum levels of vWF as well as increased MCP-1, BDNF, T-cell-specific protein RANTES, and MIP-1 beta in the probiotic-treated patients	[196, 197]
Randomized, double-blind, placebo-controlled trial	30 probiotic plus vitamin D-treated and 30 placebo-treated schizophrenia patients	2×10^{9} CFU of *Lactobacillus acidophilus, Bifidobacterium bifidum, Lactobacillus reuteri,* and *Lactobacillus fermentum* for 12 weeks plus 50,000 IU of vitamin D3 every 2 weeks	(1) Significantly ameliorated general and total PANSS scores but not negative and positive PANSS scores in the tretament group; (2) Enhanced antioxidant capacity of plasma, reduced inflammation, and improved metabolic profiles in the treatment group	[198]
Open-label single-arm study	29 schizophrenia patients with anxiety and depressive symptoms	10^{11} CFU of *Bifidobacterium breve* A-1 for 4 weeks followed by 4 weeks of observation	(1) Improved anxiety and depressive symptoms at 4 weeks; (2) No changes in the gut microbiota after probiotic treatment; (3) increased IL-22 and TRANCE expression in responders	[199]
ASD				
Double-blind, placebo-controlled, crossover-designed study	22 children with ASD aged 3–16	*Lactobacillus plantarum* WCFS1 feeding vs. placebo for 12 weeks	The introduced treatment significantly increased Lab158 counts (lactobacilli and enterococci group), significantly reduced Erec482 counts (Clostridium cluster XIVa), improved some of their gastrointestinal symptoms, and had beneficial effects towards autistic behavior	[299]
Open study	22 autistic children, aged 4–10 years	*Lactobacillus acidophilus* (strain Rosell-11, containing 5×10^{9} CFU/g) was supplemented orally twice daily for 2 months	(1) The introduced treatment significantly decreased the level of D-arabinitol and the ratio of D-/L-arabinitol in urine of autistic children; (2) Significant improvement in ability of concentration and carrying out orders were recorded	[300]
Randomized, double-blind, placebo-controlled prospective follow-up study	75 infants who were randomized to receive *Lactobacillus rhamnosus* GG (ATCC 53103) or placebo during the first 6 months of life were followed-up after 13 years	The mothers of the children were recruited in the antenatal clinics and randomized in double-blind, placebo-controlled manner to receive 1×10^{10} CFU of *Lactobacillus rhamnosus* GG or placebo (microcrystalline cellulose) daily for 4 weeks before expected delivery. After delivery, was given to the children for 6 months.	Probiotic supplementation early in life may reduce the risk of Asperger syndrome later in childhood	[301]
Open study	10 autistic children (aged 2–9 years), their 9 non-autistic siblings (aged 5–17 years), and 10 non-autistic children as a control (2–11 years old)	"Children Dophilus" capsule containing 3 strains of *Lactobacillus* (60%), 2 strains of *Bifidumbacteria* (25%) and one strain of *Streptococcus* (15%) was given orally three times a day for 4 months	Probiotic supplementation normalized the *Bacteroidetes/Firmicutes* ratio, *Desulfovibrio* spp. and the amount of *Bifidobacterium* spp. in feces of autistic children	[231]
Open study	30 autistic children, aged 5–9 years	Probiotic formula containing in each gram 100×10^{6} CFU of *Lactobacillus acidophilus, Lactobacillus rhamnosus*, and *Bifidobacteria longum* was given for 3 months	Probiotic supplementation led to significant improvements in the severity of autism and gastrointestinal symptoms	[303]
Open study	33 children with ASD	Delpro® containing probiotics (*Lactocillus acidophilus, Lactobacillus casei, Lactobacillus*	Probiotic treatment resulted in decreases in diarrhea and constipation as well as in	[304]

(*continued on next page*)

Table 6 (*continued*)

Study design	Subjects	Treatment	Main effects	Ref.
		delbruecki, Bifdobacteria longum, Bifidobacteria bifdum) formulated with Del-Immune V® containing *Lactobacillus rhamnosus* V lysate was given orally for 21 days	significant improvements in all ATEC domains (speech/language/communication, sociability, sensory/cognitive awareness, and health/ physical/behavior)	
Case study	A 12 years old boy with ASD	VSL#3 containing 9×10^{10} CFU/g of viable, lyophilized bifidobacteria (*Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis*), 8×10^{10} lactobacilli (*Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus bulgaricus, Lactobacillus delbrueckii* subsp.) and 20×10^{10} of Streptococci (*Streptococcus thermophilus, Streptococcus salivarius* subsp.) was given orally for 4 weeks followed by a four month follow-up	Probiotic treatment reduced the severity of abdominal symptoms and improved autistic core symptoms	[305]
Double-blind randomized, placebo-controlled trial	85 preschoolers with ASD (mean age: 4.2 years) randomly assigned to probiotics (n = 42) or placebo (n = 43) groups	Vivomixx® containing in each packet 450 billions of eight probiotic strains (*Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus para-casei, Lactobacillus delbrueckii* subsp. *Bulgaricus*) was given orally twice a day in the first month of treatment and once a day in the following 5 months	Probiotic supplementation improved some GI symptoms and have positive effects of on core autism symptoms	[306]
Double-blind, crossover, randomized clinical trial	9 autistic children (aged 2–11 years) randomly assigned to groups	Each participant received both treatments (orally, bovine colostrum 0.15 g/lb body weight per day + *Bifidobacterium infantis* 20 billion CFU per day or only bovine colostrum 0.15 g/lb body weight per day) but were randomized as to the order of treatment. After the first 5-week arm, participants underwent a 2-week wash out period in which no treatment was received, followed by the second 5-week arm	(1) Bovine colostrum product was well-tolerated as the only treatment or in combination with *Bifidobacterium infantis*; (2) Reduced frequency of some GI symptoms and reduced occurrence of particular aberrant behaviors were observed in patients supplemented with BCP with and without *Bifidobacterium infantis*	[307]
Double blind, placebo-controlled intervention study	26 children with ASD (aged 2–8 years) randomly assigned to probiotics (n = 16) or placebo (n = 10) groups	Placebo (maltodextrin) or mixture of probiotic (containing 10^{10} CFU/pack/day of *Bifidobacterium infantis* Bi-26, *Lactobacillus rhamnosus* HN001, *Bifidobacterium lactis* BL-04, and *Lactobacillus paracasei* LPC-37) and fructooligosaccharide were administered orally for 30–108 days	Probiotic and fructooligosaccharide treatment resulted in increased levels of beneficial bacteria (*Bifidobacteriales* and *Bifidobacterium longum*) and in suppression of suspected pathogenic bacteria (*Clostridium*)	[308]
Epilepsy				
Open-label single-arm study	43 adult patients with drug resistant epilepsy completed the study	2×10^{11} CFU of *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus helveticus*, *Lactobacillus brevis, Bifidobacterium lactis*, *Bifidobacterium lactis*, and *Streptococcus salivarius* subsp. *Thermophilus* twice a day for 4 weeks	$\geq$ 50% reduction in the number of seizures in 28.9% of patients	[372]
Migraine				
Randomized, double-blind, placebo-controlled trial	35 intervention and 34 placebo patients (women) completed the study	10^9 CFU of *Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus helveticus, Lactobacillus bulgaricus, Lactobacillus plantarum, Lactobacillus gasseri, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium lactis, Bifidobacterium bifidum,* and *Streptococcus thermophilus,* and fructooligosaccharides as prebiotic twice per day for 12 weeks.	(1) Significant reduction in the mean frequency of migraine attacks; (2) Significant reduction in the percentage change in the number of painkillers; (3) Reduction in the migraine severity and duration not statistically significant	[385]
Randomized, double-blind, placebo-controlled trial	21 intervention (17 female, 6 male) and 18 placebo (12 female, 6 male) chronic migraine patients (>15 headache days per month) completed the study 22 intervention (15 female, 7 male) and 18 placebo (13 female, 5 male) episodic migraine patients (<15 headache days per month) completed the study	2×10^9 CFU of *Bacillus subtilis PXN 21, Bifidobacterium bifidum PXN 23, Bifidobacterium breve PXN 25, Bifidobacterium infantis PXN 27, Bifidobacterium longum PXN 30, Lactobacillus acidophilus PXN 35, Lactobacillus delbrueckii ssp. bulgaricus PXN 39, Lactobacillus casei PXN 37, Lactobacillus plantarum PXN 47, Lactobacillus rhamnosus PXN 54, Lactobacillus helveticus PXN 45, Lactobacillus salivarius PXN 57, Lactococcus lactis* ssp. *lactis PXN 63*, and *Streptococcus thermophilus PXN 66* twice per day for 8–10 weeks	(1) In episodic migraineurs after a 10-week intervention: significant reduction in the mean frequency of migraine attacks/ migraine severity and the number of drugs taken per week; (2) In chronic migraineurs after an 8-week intervention: significant reduction in the mean frequency of migraine attacks/ migraine severity/ migraine duration and the number of drugs taken per day	[446]
Randomized, double-blind, placebo-controlled trial	28 intervention (28 female, 3 male) and 29 placebo (28 female, 1 male) completed the study	5×10^9 CFU of *Bifidobacterium bifidum W23, Bifidobacterium lactis W52, Lactobacillus acidophilus W37, Lactobacillus brevis W63, Lactobacillus casei W56, Lactobacillus salivarius W24, Lactococcus lactis W19 and Lactococcus lactis W58* once per day for 12 weeks	(1) No statistically significant change in migraine frequency; (2) No significant effect on drugs taken	[383]
Parkinson's disease				
	30 probiotics and 30 placebo patients with Parkinson's disease		Probiotic supplementation improved scores measured by the Movement Disorders Society-	[444]

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Table 6 (*continued*)

Study design	Subjects	Treatment	Main effects	Ref.
Randomized, double-blind, placebo-controlled trial		2×10^9 CFU/day of *Lactobacillus acidophilus*, *Bifidobacterium bifidum, Lactobacillus reuteri*, and *Lactobacillus fermentum* for 12 weeks	Unified Parkinson's Disease Rating Scale, reduced high-sensitivity C-reactive protein, malondialdehyde, and insulin levels, diminished insulin resistance, and enhanced glutathione levels as well as insulin sensitivity	
Randomized, double-blind, placebo-controlled trial	80 intervention and 40 placebo patients with Parkinson's disease	2.5×10^{11} CFU/day of *Streptococcus salivarius* subsp *thermophilus, Enterococcus faecium, Lactobacillus rhamnosus* GG, *Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus delbrueckii* subsp *bulgaricus*, and *Bifidobacterium* (*breve* and *animalis* subsp *lactis*) plus prebiotic fiber for 4 weeks	Significantly improved constipation symptoms in patients with Parkinson's disease compared with patients in the placebo group	[447]
Randomized, double-blind, placebo-controlled trial	34 probiotics and 38 placebo patients with Parkinson's disease	1×10^{10} CFU/day of *Lactobacillus acidophilus, Lactobacillus reuteri, Lactobacillus gasseri, Lactobacillus rhamnosus, Bifidobacterium bifidum, Bifidobacterium longum, Enterococcus faecalis,* and *Enterococcus faecium* for 4 weeks	Significantly improved constipation symptoms in patients with Parkinson's disease compared with patients in the placebo group	[448]
Randomized, double-blind, placebo-controlled trial	22 intervention and 26 placebo patients with Parkinson's disease	3×10^{10} CFU/day of *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus lactis, Bifidobacterium infantis,* and *Bifidobacterium longum* plus prebiotic and lactose for 8 weeks	Significantly improved constipation symptoms and gut motility in patients with Parkinson's disease compared with patients in the placebo group	[449]
Open-label, single-arm, baseline-controlled trial	25 probiotic-treated patients with Parkinson's disease	6×10^{10} CFU/day of *Lactobacillus plantarum* PS128 for 12 weeks	Improved motor score and quality of life in Parkinson's disease patients	[450]

Abbreviations: BDNF, brain-derived neurotrophic factor; CFU, colony-forming unit; GI, gastrointestinal; MCP-1, monocyte chemotactic protein-1; MDD, major depressive disorders; MIP-1, macrophage inflammatory protein-1 beta; PANSS, Positive and Negative Syndrome Scale; TRANCE, TNF-related activation-induced cytokine; vWF, von Willebrand factor.

Parkinson's disease) has been the subject of numerous studies, many of them are small-scale studies, sometimes even without adequate control groups, which may undermine the conclusions reached. Thus, further large-scale and better-standardized clinical studies are highly warranted to provide more data on the association between alterations in the gut microbiota profile and CNS diseases.

Furthermore, accumulating evidence shows that the gut microbiota is involved in the metabolism of xenobiotics and thereby it may affect the bioavailability and therapeutic efficacy of medicines. It would be of great value to study the impact of the gut microbiota on metabolism and/or activity of CNS drugs and vice versa the influence of these drugs on the gut microbiota composition. The use of medications for psychiatric and neurological disorders can adversely alter the gut microbiota, and the differences in the gut microbiota composition in those disorders may be due to medication use and not due to underlying effects of the gut microbiota in some cases. Indeed, animal studies and in vitro experiments show a relationship between such drugs and the gut microbiota but studies focused on this association in humans are very limited. Therefore, when planning the studies on the gut microbiota profile and function in human subjects, it is also important to consider medication usage.

Targeting gut microbiota with probiotics has emerged as a possible therapy for many psychiatric and neurological disorders (Table 6). Bacteria from *Bifidobacterium* and *Lactobacillus* families are the most frequently investigated, both as single- and multi-strain preparations, and *Bifidobacterium longum*, *Bifidobacterium breve, Bifidobacterium infantis*, *Lactobacillus helveticus*, *Lactobacillus rhamnosus*, *Lactobacillus plantarum,* and *Lactobacillus casei* were the most effective in improving CNS function in different preclinical studies and clinical reports. A recent meta-analysis proved the beneficial effect of probiotics only in patients with depressive symptoms. The effectiveness of probiotic supplementation in other psychiatric disorders (anxiety, stress and schizophrenia) could not be concluded from this meta-analysis [452]. Probiotics have demonstrated an overall limited efficacy in children with ASD, while clinical evidence on the beneficial effects of probiotics in schizophrenia, epilepsy, migraine and Parkinson's disease are still scarce. Thus, more randomized clinical trials on the potential benefits of probiotics and other microbiota-orientated treatment (e.g., prebiotics, FMT) in reducing symptoms of different neurological and psychiatric disorder as well as in reducing side effects of some CNS (e.g., antipsychotics) drugs are needed.

Although large-scale studies are highly warranted, such studies face a variety of challenges. Smaller but better-designed studies may also provide new insights into the relationships between the gut microbiota and the specific disease but they need to be better standardized [451]. Moreover, there is a need for more meta-analysis studies that pool together data from smaller studies and thereby allow more detailed and powerful analyses.

CRediT authorship contribution statement

KS, UD, ASz, AS, MW, AZ, EP, JF, and PW: Conceptualization, Writing – original draft, Writing – review & editing. All the authors have read and approved the final version of the manuscript.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Acknowledgments

This study was supported by Funds for Maria Curie-Skłodowska University in Lublin, Poland (MPK 502-11-30-07; ZFIN 00000010); Funds for Medical University of Lublin, Poland (DS 48/2021); Funds for Medical University of Lodz, Poland (503/1-156-04/503-11-001-19-00, to JF).

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