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METABOLITES OF THE MICROBIOTA AS PSYCHIATRIC BIOMARKERS: SHORT-CHAIN FATTY ACIDS AND TRYPTOPHAN

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ABSTRACT

Background: Severe psychiatric and neurodevelopmental disorders, including depression, bipolar disorder, and schizophrenia, remain a growing global health challenge, with diagnosis still largely based on subjective clinical assessment. Increasing evidence highlights the pivotal role of the microbiota–gut–brain axis (MGBA) in their pathophysiology, particularly neuroactive bacterial metabolites such as short-chain fatty acids (SCFA) and tryptophan derivatives (kynurenine and indole pathways).
Aim: This review synthesizes current evidence on the clinical utility, diagnostic accuracy, and mechanistic relevance of SCFA and tryptophan metabolites as objective biomarkers in major psychiatric disorders.
Methods: A structured literature review was conducted, focusing on multi-omics studies, randomized controlled trials, prospective cohorts, and high-quality meta-analyses. Molecular mechanisms involving GPCR and AhR signaling, HDAC inhibition, neuroinflammatory cascades, and blood–brain barrier regulation were examined. Diagnostic performance indicators, including AUC, sensitivity, and specificity, were analyzed.
Results: SCFA and tryptophan metabolites critically regulate neurogenesis, BDNF expression, synaptic plasticity, microglial polarization, and immune homeostasis. Dysbiosis disrupts the balance between neuroprotective and neurotoxic kynurenine metabolites and reduces protective SCFA levels.
Conclusion: Microbiota-derived metabolic signatures represent promising, objective tools for precision psychiatry. Integration of omics technologies with machine learning may enable biomarker-guided diagnosis and personalized therapeutic strategies targeting the gut–brain axis.

KEYWORDS

Microbiota-Gut-Brain Axis, Short-Chain Fatty Acids, SCFA, Tryptophan, Kynurenin Pathway, Psychiatric Biomarkers, Neuroinflammation, Major Depressive Disorder, Schizophrenia, Bipolar Disorder, Pharmacomicrobiomics

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Introduction

Neuropsychiatric and neurodegenerative disorders are among the most significant public health challenges of the 21st century, generating a significant clinical and societal burden. Major depressive disorder (MDD) affects approximately 280 million people worldwide (≈3.8% of the global population) and remains a leading cause of disability (Cheng et al., 2024). Bipolar disorder and schizophrenia are equally clinically significant(Dziedziak et al., 2025).

For decades, the pathophysiology of mental disorders, particularly major depressive disorder (MDD) and schizophrenia (SCZ), has been interpreted primarily based on classical monoaminergic hypotheses. These hypotheses posited that disturbances in serotonergic, dopaminergic, noradrenergic, and glutamatergic neurotransmission, encompassing neurotransmitter deficiencies and dysregulation of their synthesis, release, or reuptake, play a key role in the development of symptoms (Ju et al., 2023). These models have become the basis for contemporary pharmacotherapy, including the use of selective serotonin reuptake inhibitors (SSRIs) and antipsychotics acting on dopamine D_2 receptors. However, clinical data indicate that the effectiveness of these interventions remains limited – only a fraction of patients achieve full and lasting remission, and a significant percentage of patients meet the criteria for treatment-resistant depression (TRD) (Elasbali, Adnan, Ali, Shamsi, Hassan, 2025).

These observations have challenged the adequacy of the monoaminergic explanation of pathophysiology and contributed to the intensification of research on alternative mechanisms, including the microbiota-gut-brain axis (MGBA), which is a bidirectional communication system between the gut microbiota and the central nervous system (CNS) (Cheng et al., 2024). According to the current state of knowledge, communication in the MGBA is multi-pathway and involves neuronal mechanisms (e.g., via the vagus nerve), endocrine

mechanisms (regulation of the hypothalamic-pituitary-adrenal (HPA) axis), and immunological mechanisms, including modulation of the inflammatory response and immune cell function (Cheng et al., 2024).

A key chemical vector of communication in the microbiota-gut-brain axis are neuroactive metabolites produced by gut microorganisms as a result of fermentation and biotransformation processes (Zhou et al., 2025). Among these substances, short-chain fatty acids (SCFA) and metabolites of the essential amino acid tryptophan (TRP) are of greatest scientific interest (Dziedziak et al., 2025). In the intestinal environment, tryptophan is subject not only to the serotonin synthesis pathway but also to microbial and immunological cleavage along the peripheral and central kynurenine pathway (KP), as well as conversion into unique bacterial indole metabolites, such as indolylpropionic acid (IPA) (Gao, Mu, Farzi, Zhu, 2020).

The growing interest in precision psychiatry reveals the limitations of classic symptom-based diagnoses and DSM-5 or ICD-11 classifications, which fail to account for the biological and molecular heterogeneity of patients (Majie et al., 2026). In this context, objective biomarkers are gaining importance, as they can support patient stratification and predict disease progression (Konjevod et al., 2025). Metabolome analysis, encompassing the concentrations of molecules in blood, urine, and feces, dynamically captures the influence of genetics, environment, and microbiome status (Shih, 2019). Particularly promising are gut-brain metabolites, including SCFAs and tryptophan metabolism products, which may form the basis of new diagnostic panels and therapeutic interventions targeting the microbiome (Dziedziak et al., 2025).

Purpose of the publication

The aim of this review is to critically summarize and analyze the latest (2008–2026) scientific evidence regarding short-chain fatty acids (SCFAs) and tryptophan metabolites as potential objective biomarkers in the diagnosis and monitoring of selected psychiatric and neurodevelopmental disorders, including MDD, BD, SCZ, PTSD, ASD, and ADHD. The paper focuses on the molecular mechanisms of their action in the context of neuroinflammation, the gut-brain barrier, and epigenetics. Additionally, the review compares the clinical utility of markers derived from fecal and peripheral blood samples, identifying challenges and prospects for the development of personalized psychiatric medicine.

Methodology

A literature review was conducted using the PubMed database, covering publications from 2008 to 2026. The search strategy included combinations of keywords in English: "gut microbiota," "microbiota-gut-brain axis," "metabolomics," "short-chain fatty acids," "butyrate," "tryptophan," "kynurenine pathway," "indole-3-propionic acid," "psychiatric biomarkers," "major depressive disorder," "schizophrenia," "bipolar disorder," "autism spectrum disorder," "ADHD," "neuroinflammation," as well as the analytical terms "sensitivity," "specificity," "AUC," and "machine learning." Publications providing quantitative data and reporting statistical measures (including ROC analyses) were included in the analysis. Papers based solely on theoretical or animal models were excluded, with the exception of in vivo studies verifying molecular mechanisms relevant to the microbiota–gut–brain axis.

Results

Analysis of the reviewed literature and experimental studies allows the identification of several key areas in which alterations in gut microbiota metabolites contribute to the pathophysiology of psychiatric disorders. In particular, dysregulation of short-chain fatty acids (SCFAs) and tryptophan metabolism via the kynurenine pathway has been consistently associated with neuroinflammatory processes, alterations in neurotransmitter systems, and cognitive and affective dysfunctions in patients with schizophrenia and bipolar disorder. These findings highlight specific metabolite signatures in both peripheral blood and cerebrospinal fluid that may serve as potential biomarkers for disease stratification, early diagnosis, and monitoring of therapeutic interventions. Furthermore, emerging evidence suggests that targeted modulation of these metabolites through dietary interventions, probiotics, and postbiotics may offer novel avenues for precision psychiatry.

Architecture and neurobiology of the microbiota-gut-brain axis

The human body functions as a complex biological system that closely interacts with the microbiota that inhabits mucosal surfaces, particularly within the gastrointestinal tract. The gut microbiome comprises a diverse community of microorganisms, including bacteria, archaea, viruses, and fungi, that inhabit the human gastrointestinal tract and closely interact with the host (Silva, Bernardi, & Frozza, 2020). Data indicate that the

gut microbiota participates in the regulation of immune processes and may influence the functioning of the central nervous system through the production of bioactive metabolites (Silva et al., 2020).

The bidirectional communication between the gut microbiota and the brain is referred to as the microbiota–gut–brain axis (MGBA) and includes neural, hormonal, and immunological components (Toader et al., 2020). One of the main neural components of this axis is the autonomic nervous system, specifically the vagus nerve, which is involved in transmitting afferent signals from the gastrointestinal tract to brainstem structures (Ruohan et al., 2025).

In parallel to neuronal transmission, humoral and metabolic communication mechanisms exist where microbiota metabolites can enter the peripheral circulation and participate in signaling affecting host cells (Silva et al, 2020). These various signaling pathways are considered components of the multi-pathway architecture of the microbiota-gut-brain axis (Toader et al, 2020).

Leaky physiological barriers and the neuroinflammatory cascade

Intestinal barrier integrity is a crucial element of the functioning of the microbiota-gut-brain axis. In eubiosis, the gut microbiota participates in maintaining intestinal epithelial homeostasis and influences the regulation of tight junction proteins, such as claudins and occludins (Silva et al., 2020). It has also been suggested that the microbiota can modulate the mucus layer and the immune response of the intestinal mucosa (Silva et al., 2020).

Disturbances in the composition and function of the gut microbiota, referred to as dysbiosis, have been observed in the context of chronic stress, abnormal dietary patterns, antibiotic therapy, and infections (Dziedziak et al., 2025). These changes are associated with increased intestinal barrier permeability and increased inflammatory signaling (Dziedziak et al., 2025).

Increased intestinal barrier permeability, commonly referred to as the "leaky gut" phenomenon, may promote the translocation of bacterial components from the intestinal lumen to the lamina propria and into the portal and peripheral circulation (Dziedziak et al., 2025). Among the best-characterized molecules are lipopolysaccharide (LPS), a component of the cell wall of Gram-negative bacteria, and other structures with immunogenic properties (Dziedziak et al., 2025).

The presence of LPS in the peripheral circulation has been associated with the activation of pattern recognition receptors (PRRs), including Toll-like receptor 4 (TLR4), expressed on immune cells such as monocytes and macrophages (Su et al., 2025). Activation of these signaling pathways leads to the induction of an inflammatory response and increased production of proinflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). Chronic, low-grade systemic inflammatory activation is considered one of the mechanisms linking gut barrier dysfunction with the modulation of neuroimmune processes in the microbiota-gut-brain axis (Su et al., 2025)

Proinflammatory cytokines present in the peripheral circulation can affect cerebral vascular function and modulate the permeability of the blood–brain barrier (BBB) (Su et al., 2025). Changes in BBB integrity are associated with the potential for immune system components, including lymphocytes and cytokines, to penetrate brain tissue (Zhou et al., 2025). Such processes can lead to the activation of brain-resident cells, primarily microglia and astrocytes, which shift their phenotype from a more quiescent to an active, proinflammatory state (Zhou et al., 2025). Chronic neuroimmune activation has been implicated as one of the mechanisms influencing synaptic function, neurogenesis, and mood- and anxiety-related behaviors (Su et al., 2025). Some studies suggest that microbiota metabolites, including short-chain fatty acids and amino acid metabolism products, may participate in the modulation of these inflammatory processes (Su et al., 2025).

Short-chain fatty acids (SCFA) as fundamental neuroregulators

Short-chain fatty acids (SCFAs) are endogenous, volatile carboxylic acids, typically having a straight chain of one to six carbon atoms, that may participate in modulating gut function and gut-brain communication (Facchin et al., 2024). The main and most studied representatives of this group, characterized by the highest concentrations, are acetate (acetic acid, C2), propionate (propionic acid, C3), and butyrate (butyric acid, C4) (Cheng et al., 2024). Although the human digestive system lacks enzymes capable of degrading certain polysaccharides, such as fiber, resistant starch, cellulose, or inulin, bacteria residing in the cecum and colon have evolved specialized enzymatic systems that allow them to degrade these compounds into short-chain fatty acids (SCFAs) (Silva et al., 2020).

These acids primarily serve as an energy source for the division and function of colonic epithelial cells (colonocytes), meeting almost 70% of their ATP requirements (Silva et al, 2020). SCFAs that are not used as

an energy source by colonic epithelial cells are absorbed into the circulation via the portal vein, where they are metabolized by the liver, and a small fraction may then appear in the systemic circulation—particularly acetate, which is most frequently detected in peripheral plasma (Facchin et al., 2024).

SCFAs can cross the blood-brain barrier to a limited extent thanks to specialized proton gradient-dependent monocarboxylate transporters (MCTs) present on cerebrovascular endothelial cells (Silva et al., 2020). After entering the central nervous system, SCFAs may participate in cell signaling through two primary mechanisms: binding to G-protein-coupled receptors on the cell surface and epigenetic modulation upon entry into cells and influencing the activity of histone deacetylases (HDACs), which may influence the expression of genes associated with immune and metabolic responses (Qian, Xie, Liu, Chen, & Tang, 2022).

Activation of orphan G-protein receptors (GPCRs)

G protein-coupled receptors, such as GPR41 (FFAR3), GPR43 (FFAR2), and GPR109a, which can bind short-chain fatty acids are present on the cell surface of intestinal endocrine cells and immune cells (Cheng et al., 2024).

Binding of acetate or propionate to GPR41/43 in the intestinal lumen stimulates the secretion of local tissue hormones such as glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) (Silva et al., 2020).

In parallel, activation of GPR41/43 stimulates the synthesis of certain neurotransmitters, such as γ-aminobutyric acid (GABA) and the enterocyte serotonin pool (5-HT), which is released into the circulation in response to signals from enterochromaffin cells (Silva et al., 2020). Through these chemical mediators, the gut microbiota can modulate vagal signaling and influence the activity of the hypothalamic-pituitary-adrenal (HPA) axis. Preclinical studies have shown that supplementation with short-chain fatty acids in animal models can attenuate HPA activation, which was associated with a smaller increase in corticosterone concentration after exposure to a stressor (van de Wouw et al., 2018).

Mechanism of epigenetic modification: Inhibition of histone deacetylases (HDACs)

Short-chain fatty acids, particularly butyrate and propionate, can act as natural inhibitors of histone deacetylases (HDACs), leading to increased histone acetylation and modulation of gene expression in host cells (Waldecker, Kautenburger, Daumann, Busch, & Schrenk, 2008).

Histone deacetylases (HDACs) are epigenetic enzymes that remove acetyl groups from lysine residues of histones, influencing chromatin condensation and the regulation of gene expression. Histone deacetylation by HDACs is typically associated with a more condensed chromatin structure and reduced transcriptional activity, which can modulate processes such as cell proliferation, differentiation, and plasticity, including in the context of the nervous system (Chen, Zhao, & Zhao, 2015).

Pharmacological or genetic inhibition of HDAC increases histone acetylation levels in the hippocampus, which facilitates the access of transcription factors and the activation of gene programs associated with synaptic plasticity and memory processes (Vecsey et al, 2007).

Under experimental conditions, the short-chain fatty acid butyrate, as an inhibitor of histone deacetylase activity, increases the acetylation of histone residues (including H3 and H3K18) in the promoter regions of the BDNF gene, which is associated with increased expression in neurons and may contribute to the epigenetic regulation of pathways related to synaptic plasticity and nervous system function (Ge et al., 2023). In conditions of gut dysbiosis, observed in individuals with untreated major depressive disorder (MDD) or chronic stress, the production of short-chain fatty acids is reduced, and microbiota dysfunction—through gut-brain axis mechanisms—is associated with lower levels of BDNF, which may negatively impact neuronal development and synaptic plasticity (Suda, Matsuda, 2022).

In a genetic model of depression (Flinders Sensitive Line—FSL), chronic sodium butyrate (NaB) administration was associated with restoration of decreased expression of the enzyme ten-eleven translocation methylcytosine dioxygenase 1 (TET1) in the prefrontal cortex, which was subsequently associated with increased hydroxymethylation (5-hmC) and decreased methylation (5-mC) in the Bdnf promoter region, leading to increased BDNF expression. Higher BDNF levels and activation of its TrkB receptors correlated with improved synaptic plasticity and cognitive function and mood-related behaviors in an animal model of depression (Wei, Melas, Wegener, Mathé, & Lavebratt, 2014).

Weakening of microglial cell hyperactivation

Short-chain fatty acids also modulate the function of microglia—the stromal immune cell population of the CNS—by influencing their maturation and immune activity. Microglia play a crucial role in normal brain development, including by participating in the process of eliminating redundant synaptic connections, which determines the maturation and reorganization of neuronal networks (Silva et al., 2020). Impaired SCFA availability during early development may therefore affect the activation status of microglia. Experimental models have shown that a limited supply of propionate is associated with increased reactivity of these cells, manifested by, among other things, amoeboid morphology and increased expression of proinflammatory mediators (Cao et al., 2025). Preclinical studies indicate that SCFAs may modulate the inflammatory response in the CNS by inhibiting histone deacetylases (HDACs) and activating G protein-coupled receptors (GPCRs), which leads to attenuation of the NF-κB pathway and reduction of MAPK kinase signaling (e.g., ERK/JNK, p38). These mechanisms have been associated with limiting the toxin-induced proinflammatory response and with potential neuroprotective effects in models of stroke and pathology associated with β-amyloid accumulation (Ding, Hao, Zhang, Zhang, Li, 2025).

Tryptophan as a nodal metabolite of the gut-brain axis: serotonin, kynurenine and indole pathways

In addition to the important role of short-chain fatty acids, the metabolism of the essential aromatic amino acid L-tryptophan (TRP), supplied by dietary proteins, plays a key role in regulating the gut-brain axis (Lin et al., 2023). For many years, tryptophan was primarily viewed as a precursor to serotonin (5-HT), a neurotransmitter involved in regulating mood and emotional functions (Gao, Mu, Farzi, & Zhu, 2020). Tryptophan metabolism in the gut-brain axis involves three main pathways: serotonin, kynurenine, and indole. Research indicates that the relative activity of these pathways depends on environmental and metabolic factors, and changes in the proportions of TRP metabolites correlate with biomarkers of risk for cognitive and emotional disorders (Miyamoto, Sujino, & Kanai, 2024).

Tryptophan Metabolism via the Serotonin Pathway: Implications for CNS Function

The serotonin pathway is one of the three main pathways of tryptophan metabolism in the body and is crucial for modulating CNS function and signaling in the gut-brain axis, particularly due to the role of serotonin as a neurotransmitter and regulator of behavior and metabolism (Xu, Zhou, Shi, 2025). Tryptophan is a precursor of serotonin (5-HT) biosynthesis, and the first step of this process is its hydroxylation to 5-hydroxytryptophan by the enzyme tryptophan-5-hydroxylase (TPH) present in the gut and brain, which is determined by the TPH1 and TPH2 isoforms and their expression in the relevant tissues (O'Mahony, Clarke, Borre, Dinan, Cryan, 2015).

In the gastrointestinal tract, approximately 90% of total systemic serotonin comes from enterochromaffin cells, where its synthesis is regulated by the presence of substrate (tryptophan) and metabolic factors, and the gut microbiota can modulate TPH1 expression and TRP availability for 5-HT production (Li et al., 2024).

Although gut serotonin itself does not directly cross the blood-brain barrier, its production in the gut influences gut-brain axis signaling by modulating vagal afferent connections and indirectly regulating the level of TRP available for CNS synthesis (O'Mahony et al., 2015).

Disturbances in serotonin metabolism and the balance of tryptophan with other pathways (e.g., kynurenine) correlate with some depressive and anxiety symptoms, suggesting the clinical importance of the balance of 5-HT synthesis in the context of the gut-brain axis (Xu, Zhou, Shi, 2025).

The tryptophan kynurenine pathway: inflammatory regulation and role in CNS dysfunction

Another pathway of tryptophan metabolism leads to the formation of kynurenine (KYN) in peripheral tissues. This process is controlled by two key enzymes: tryptophan-2,3-dioxygenase (TDO), currently found primarily in the liver and kidneys and sensitive to stress signals, and indolamine-2,3-dioxygenase (IDO1), activated in response to inflammatory signals from endothelial and immune cells (Lin et al., 2023). Microbiotic signals, such as lipopolysaccharide (LPS) from Gram-negative bacteria, and proinflammatory cytokines, including TNF-α and IL-6, can induce activation of the IDO1 enzyme in peripheral tissues. In experimental models, such activation has been shown to lead to increased tryptophan turnover in the kynurenine pathway (Xia & Huang, 2026). Increased IDO1 activity results in increased conversion of tryptophan to the kynurenine pathway, which may lead to reduced TRP availability in the peripheral circulation. The kynurenine-to-

tryptophan ratio (KTR) is used in studies as a biomarker of this pathway activity and potential metabolic disturbances within the gut-brain axis (Mehta et al., 2025). Increased conversion of tryptophan to the kynurenine pathway in the peripheral circulation may reduce TRP availability to the CNS, limiting serotonin synthesis in the brain. Simultaneously, some kynurenine produced in peripheral tissues may diffuse across the blood-brain barrier via the LAT1 transporter, affecting the concentrations of this metabolite in the CNS and potentially modifying downstream metabolic pathways in neurons (Xia & Huang, 2026).

Kynurenine can be metabolized in the CNS via two main pathways. The first, neuroprotective, occurs primarily in astrocytes, where the enzyme kynurenine aminotransferase (KAT) converts KYN to kynurenic acid (KYNA), which, as an endogenous antagonist of NMDA receptors, modulates glutamatergic activity in the CNS and promotes neurotransmission balance (Xia & Huang, 2026). The second, neurotoxic pathway of KYN metabolism occurs primarily in microglia, where the enzyme kynurenine oxygenase (KMO) converts KYN to 3-hydroxy-kynurenine (3-HK) and quinolinic acid (QUIN). In experimental models and clinical observations, activation of this pathway under proinflammatory conditions has been found to increase the production of metabolites with potential neurotoxic activity, which can modulate the function of neurons and microglia in the CNS (Miyamoto et al., 2024). Quinolinic acid (QUIN) metabolites can act as NMDA receptor agonists, which in excess promotes increased glutamatergic activity and oxidative stress in neurons, potentially affecting synaptic function and neuronal homeostasis (Xia & Huang, 2026).

The balance between the neuroprotective KYN–KYNA pathway and the neurotoxic KYN–QUIN pathway is crucial for maintaining the stability of neurotransmission in the CNS. In experimental models, disruptions to this balance shift metabolite production in a neurotoxic direction (Miyamoto et al., 2024; Xia & Huang, 2026). Clinical data suggest that alterations in the activity of the kynurenine pathway may be associated with psychiatric disorders, including some aspects of autism spectrum disorders, although the results are still inconclusive and require further investigation (Bryn, Verkerk, Skjeldal, Saugstad, & Ormstad, 2017).

The indole tryptophan pathway: microbiotic anti-inflammatory defense and AhR receptor activation

For gut microbiota, tryptophan is a fundamental substrate for the synthesis of endocrine compounds that participate in symbiotic relationships between the microbiota and the host. Using bacterial enzymes, such as tryptosynthases and hydrolases absent in higher organisms, the microbiota can convert tryptophan into various indole derivatives. From the ileum, these compounds reach the lymphatic system and include indolylpropionate (IPA), skatole, indole-3-acetic acid (IAA), and aldehyde and acid derivatives of indole, including indole-3-acetaldehyde (I3A) (Gao et al., 2020). The production of these metabolites reflects the activity of the patient's microbiota and the integrity of the intestinal barrier, as indole derivatives present in the blood have antioxidant properties. For example, indolylpropionate (IPA) can neutralize reactive radicals, limiting potential oxidative damage in tissues, which has been shown in experimental models to be beneficial in the context of early neuronal degeneration and the regulation of oxidative stress in the nervous system (Owe-Larsson et al., 2025). Additionally, tryptophan metabolites such as indolyl-3-acetaldehyde (I3A) and indolylpropionate (IPA) act as specific ligands for aryl hydrocarbon receptors (AhRs) present on endothelial cells and microglia, and their interaction can modulate the expression of genes associated with the inflammatory response. In some contexts, AhR also interacts with PXR, forming a regulatory network that influences the immune response and tissue homeostasis in experimental models (Owe-Larsson et al., 2025). In experimental models, it has been shown that indole metabolites of tryptophan, acting as ligands of AhR receptors in microglial, endothelial and macrophage cells, can modulate the activity of the JAK2/STAT3 signaling pathway, limit the activation of NLRP3 inflammasomes and thereby reduce the production and release of proinflammatory cytokines, including TNF-α, IL-6 and IL-1β; consequently, this leads to a reduction in the spread of inflammation in the nervous tissue and may support neuronal protection and homeostasis of the CNS microenvironment (Owe-Larsson et al., 2025). When activation of AhR and PXR receptors is limited, for example, due to a decrease in the abundance of beneficial bacterial strains or a decrease in the availability of indole metabolites in the circulation, these mechanisms are impaired, which in experimental models leads to chronic interstitial inflammation, increased activation of the JAK2/STAT3 pathway and NLRP3 inflammasomes, increased production of proinflammatory cytokines, and further damage to the gut-brain barrier. Such disturbances are referred to in the literature as a "leaky cycle" of dysfunctional gut microbiota-CNS interactions, which maintains and exacerbates chronic disturbances in neuronal homeostasis and the CNS microenvironment (Owe-Larsson et al., 2025).

Experimental interventions consisting in supplementation of bacterial flora or administration of tryptophan precursors promoting the production of indole metabolites not only increase the level of neuroprotective IPA and indirectly KYNA in the CNS, but also modulate the activity of microglia and endothelium, limiting the early activation of the JAK2/STAT3 pathway and NLRP3 inflammasomes, which results in a reduction of the production of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) and stabilization of synaptic connections, thus supporting both the protection of neurons in the prefrontal lobes and maintaining the integrity of the CNS microenvironment under conditions of oxidative stress and chronic inflammation (Owe-Larsson et al., 2025).

Efficacy of microbiota metabolites as biomarkers in the main phenotypes of psychiatric diseases

Evolutionary remodeling of the function of pathological pathways associated with gut dysbiosis in the studied groups affected by mental stress is revealed by distinct changes in the concentrations of microbiota metabolites in body fluids such as blood and cerebrospinal fluid, which leave a lasting diagnostic "trace." These fluctuations, reflecting the degree and nature of metabolic disturbances in the gut-brain axis, enable precise estimation of biological pathway activity and support the interpretation of laboratory measurements in the context of diverse phenotypes of psychiatric illnesses (Shih, 2019). By using state-of-the-art analytical techniques such as gas chromatography, high-throughput mass spectrometry (LC-MS, UPLC-QTOF-MS) and nuclear magnetic resonance spectroscopy (NMR), researchers and diagnosticians are able to precisely quantify microbiota metabolites in body fluids, which allows the creation of a validated, measurable panel of dysbiosis parameters; such a panel allows for an objective assessment of the patient's metabolic status, reflecting specific profiles of gut-brain axis disorders in the context of different phenotypes of psychiatric diseases, and constitutes an independent diagnostic tool that complements or replaces subjective assessment methods such as psychometric questionnaires and clinical interviews (Konjevod et al., 2025).

Major Depressive Disorder (MDD)

Diagnostic difficulties across the spectrum of depressive episodes remain a significant clinical challenge. Major Depressive Disorder (MDD) is characterized by significant heterogeneity, both in terms of symptom profile (ranging from sleep and appetite disturbances to presentations with predominance of atypical symptoms such as hypersomnia or increased appetite), as well as clinical course and response to treatment. Phenotypic heterogeneity and distinct trajectories of response to pharmacotherapy complicate clear diagnosis and predict the effectiveness of therapeutic interventions, underscoring the need for objective biomarkers to support diagnosis and patient stratification (Cheng et al., 2024). In the context of the gut-brain axis, increasing evidence indicates significant differences in the composition and metabolic potential of the gut microbiota in patients with Major Depressive Disorder. Metagenomic analyses based on 16S rRNA sequencing suggest a reduced abundance of commensal bacteria involved in complex carbohydrate fermentation and the production of short-chain fatty acids (SCFAs), including butyrate and propionate. In particular, a reduced representation of genera such as Faecalibacterium, Coprococcus, and Dialister, which are thought to have anti-inflammatory properties and contribute to the maintenance of intestinal barrier integrity, has been reported. Simultaneously, a relative increase in some potentially pro-inflammatory taxa, including representatives of the phylum Actinobacteria and the genus Alistipes, was observed compared to control groups (Dziedziak et al., 2025). Reports also indicate that the observed compositional changes may be accompanied by differences in the concentrations of short-chain fatty acids determined in stool samples and, in some studies, in blood serum. In particular, reduced levels of butyrate and propionate have been reported in patients with Major Depressive Disorder compared to control groups, although the results are not fully consistent across studies (Dziedziak et al., 2025).

A study examining the relationship between baseline short-chain fatty acid (SCFA) levels and clinical response to antidepressant treatment in patients with Major Depressive Disorder found that higher blood levels of butyrate measured before initiation of pharmacotherapy were significantly associated with a greater likelihood of achieving remission of depression at six-month follow-up. In the same analysis, propionate and the clinical marker of inflammation (CRP) were not found to be predictors of therapeutic outcome, highlighting the specific role of butyrate in the predictive model used in this study. Although the results do not allow for inferences of causality, they suggest that baseline butyrate levels may reflect biological differences related to susceptibility to pharmacological response. Consequently, butyrate is considered a potential prognostic biomarker, requiring further validation in larger and diverse patient cohorts (Schiweck et al., 2025).

Depression and shifts in the Kynurenine Pathway (Analyses and Indicators)

Analyses of tryptophan metabolism in the context of depression indicate that changes in the kynurenine pathway are strongly associated with the severity of depressive symptoms, and their assessment may provide useful biological indicators in MDD research. In a study, patients with pronounced depressive symptoms demonstrated significantly reduced serum tryptophan concentrations compared to patients without depressive symptoms, along with an increased kynurenine-to-tryptophan ratio (KTR), a measure of the shift in tryptophan metabolism toward kynurenine production. Higher KTR was positively correlated, and lower tryptophan concentrations were negatively correlated, with the severity of depressive symptoms, suggesting that the observed changes in the kynurenine pathway may reflect related biological mechanisms associated with depressive episodes, without suggesting direct causality (Liu et al., 2025). The degree of change in tryptophan concentrations and the kynurenine-to-tryptophan ratio (KTR) was significantly correlated with the severity of depressive symptoms assessed using the six-item Hamilton Depression Scale (HDS-6). The lower the baseline tryptophan concentration, the higher the KTR, and both of these indicators showed a strong correlation with the severity of depressive symptoms—tryptophan negatively and KTR positively. These results suggest that the observed shifts in tryptophan metabolism may reflect interrelated biological mechanisms associated with the severity of depressive episodes, without drawing causal conclusions (Liu et al., 2025). An example of the application of precise metabolomic analyses in large cohorts of patients with depression is a study that used non-negative matrix factorization (NMF) algorithms to classify patients based on comprehensive metabolic profiles. The analysis revealed the existence of three biological subtypes of depression, differing in, among other things, concentrations of lipids, energy metabolites, and glycemic markers, which correlated with various clinical features. The predictive models used in the study achieved high accuracy in assigning patients to the appropriate subtypes (AUC ~0.94), indicating that metabolomic profiles can support the discrimination of heterogeneous depression subgroups. These results do not allow for inferences about causality or predict therapeutic response, but they highlight the potential of metabolomics to identify clinically relevant patterns within depressive disorders (Ma et al., 2025).

Phenotypes and biomarkers of psychosis diagnoses in clinical trials from the Axis (Schizophrenia and Bipolar Episodes from the BD areas)

An extremely important aspect in clinical research on psychoses remains the observation that schizophrenia (SCZ) and bipolar disorder (BD), despite their classification differences in diagnostic systems, share closely intertwined neuroanatomical dysfunctions, including functional disorders of the prefrontal cortex with the hippocampus, as well as overlapping clinical phenotypes manifested by the presence of psychotic episodes, delusional breakdowns, productive anxiety symptoms and cognitive deficits, which are accompanied by a partially common genetic basis, which prompted researchers to search for pivotal biological biomarkers, including intestinal ones, that could constitute a common point of reference for neuroinflammatory processes and pathophysiological mechanisms underlying both of these psychotic disorders (Majie et al., 2026). In this context, the profile of the gut microbiota and the concentrations of its metabolites, particularly short-chain fatty acids (SCFAs), are increasingly being analyzed as potential correlates of the clinical phenotype in schizophrenia. Available data indicate that changes in the microbiota composition are observed in patients with schizophrenia, including a reduction in the abundance of selected bacteria considered SCFA producers. Studies have reported a reduction in selected bacterial genera associated with maintaining intestinal barrier integrity and immune balance, including *Akkermansia*, as well as shifts within other phylogenetic groups, which may be accompanied by a relative increase in bacteria from the Enterobacteriaceae family. These microbiological changes correlate with impaired SCFA production and potential modulation of the inflammatory response, which is interpreted in the literature as part of the dysbiosis accompanying psychiatric disorders. At the same time, it is emphasized that the nature of these changes has a complex and heterogeneous profile, and their clinical significance – including possible links with resistance to antipsychotic treatment – requires further studies in controlled conditions (Dziedziak et al, 2025). Additionally, correlational analyses demonstrated that the relative abundance of certain taxa, including the genus Succinivibrio, was associated with the severity of symptoms assessed on the PANSS scale, while lower butyrate concentrations and a lower representation of selected SCFA producers correlated with greater severity of negative symptoms, such as social withdrawal and blunted affect. However, the authors emphasize that these relationships are associative and do not allow for inferences about direct causal relationships, and their interpretation requires consideration of clinical and therapeutic factors (Dziedziak et al., 2025).

Tryptophan metabolism and kynurenine pathway activity in schizophrenia and bipolar disorder

In recent years, particular interest in omics research on psychosis spectrum disorders has been focused on the analysis of tryptophan metabolism within the kynurenine pathway, including the assessment of kynurenine concentrations and its derivative metabolites in the cerebrospinal fluid (CSF) and blood serum, which allows for a more precise differentiation of the biological profiles of patients with bipolar disorder and schizophrenia (Mehta et al., 2025).

Tryptophan metabolism within the kynurenine pathway involves the diverse production of metabolites produced both in host cells and by the gut microbiota. A key role is played by the balance between compounds with distinct biological properties, such as kynurenic acid (KYNA), synthesized in astrocytes and modulating glutamate receptors, and the metabolites of the pathway leading to the formation of quinolinic acid (QUIN) and 3-hydroxykynurenine (3-HK), which, under conditions of immune activation, may be associated with increased inflammatory processes and oxidative stress. The ratios between these metabolites reflect the dynamic regulation of the microbiota-immune-CNS axis and, as discussed above, are part of the complex immunometabolic response observed in various disease states (Miyamoto et al., 2024). Although a review of the literature indicates the potential importance of the kynurenine profile in mood disorders and psychosis, the existing data are primarily associative and do not allow for categorical conclusions about the direction of changes in specific patients with BD or SCZ. The need to consider clinical and methodological differences in the interpretation of tryptophan metabolite measurements is also frequently emphasized (Mehta et al., 2025). In response to the complexity of biological data, there is also growing interest in the use of advanced multivariate analysis methods and machine learning to integrate omics profiles with clinical data. Studies using machine learning algorithms to classify patients with mental disorders have shown that combining data on microbiota, metabolites, and other biological indicators can improve the accuracy of differentiating clinical groups compared to traditional psychometric assessment tools. For example, the use of methods such as random forest in multivariate analysis of omics data achieved high area under the ROC curve (AUC), suggesting the potential of these tools in characterizing biological profiles of patients, while interpretative caution should be exercised before practical application in clinical diagnosis (Li et al., 2026).

Therapeutic perspectives, psychobiotics and the importance of targeted microbiome modification

As methods for analyzing the gut-brain axis develop and omics panels become more precise, clinical and experimental studies are increasingly exploring approaches to modifying the gut microbiota as a potential therapeutic tool for mental disorders. As discussed above, the literature highlights that gut dysbiosis, imbalances in microbiota metabolites, and related immunological processes—including the conversion of tryptophan to metabolites with immunomodulatory properties—are associated with changes in nervous system function and pro-inflammatory states, which has fueled research on interventions aimed at restoring microbial and metabolic balance (Zhou et al., 2025).

In this context, the concept of psychobiotics—including probiotics, prebiotics, postbiotics, and other microbiome-modulating interventions—has been proposed as a promising avenue of research into the potential impact of microbiota on mental health, although the mechanisms of action and their clinical relevance remain to be systematically explored. These approaches aim not to replace traditional pharmacological therapies but rather to complement them by mitigating metabolic and immune dysregulation associated with the gut-brain axes in patients with mood disorders and neuropsychiatric disorders such as depression and psychosis.

Current evidence suggests that microbiota-modifying interventions can influence metabolic and immune homeostasis, justifying continued research into their safety, efficacy, and specific mechanisms before they can be widely used in clinical practice (Zhou et al., 2025).

Clinical trials in patients with schizophrenia have tested whether supplementation with the prebiotic oligofructose-enriched inulin (OEI) can influence the production of short-chain fatty acids, particularly butyrate, which is one of the main metabolites of the gut microbiota. In a randomized, double-blind, placebo-controlled study, a 10-day intervention with OEI was associated with an increase in plasma butyrate concentrations compared with the placebo group, indicating that targeted delivery of fructooligosaccharides can modulate the concentrations of endogenous microbiota metabolites in individuals with schizophrenia (Buchanan et al., 2024). This study provides proof of concept that dietary interventions based on increasing the supply of specific fiber fractions can modify the metabolic products of microbiota action, which opens the perspective of further research on the potential benefits of such an approach in the context of mental disorders (Buchanan et al., 2024).

In the context of research on gut microbiota modulation in psychiatric disorders, the possibility of using personalized interventions, including probiotics (e.g., Lactobacillus and Bifidobacterium strains), synbiotics, and, in experimental studies, gut microbiota transplantation (FMT), is also being considered to influence tryptophan metabolism and the activity of kynurenine pathway enzymes. Review publications indicate that such approaches can modulate immunometabolic parameters and gut-brain axis homeostasis, which provides a basis for further research on their potential relevance to neuroinflammation-related symptoms, while emphasizing that the mechanisms of action and clinical efficacy remain in the research phase (Zhou et al., 2025).

Discussion

Based on the analyzed data, it can be concluded that disturbances in short-chain fatty acids (SCFA) and tryptophan metabolism constitute an important element of the common immunometabolic basis of selected psychiatric disorders. In MDD, reduced representation of butyrate-producing bacteria and reduced SCFA concentrations in stool and serum samples have been consistently reported, which correlated with the severity of depressive symptoms (Cheng et al., 2024; Dziedziak et al., 2025). Importantly, higher baseline plasma butyrate concentrations were associated with a greater likelihood of remission following antidepressant treatment, suggesting its prognostic potential (Schiweck et al., 2025). Mechanistically, SCFA deficiency may lead to decreased signaling through FFAR2/3 receptors and reduced HDAC inhibition, resulting in decreased expression of genes associated with synaptic plasticity, including BDNF, and an increased inflammatory response within the CNS (Qian et al., 2022; Ge et al., 2023; Suda & Matsuda, 2022).

Concurrently, a shift in tryptophan metabolism toward the kynurenine pathway, expressed by an increase in the KTR index and a decrease in TRP concentration, shows a significant correlation with the severity of depressive symptoms (Liu et al., 2025). Activation of IDO1 by proinflammatory cytokines may limit the availability of tryptophan for serotonin synthesis while promoting the formation of metabolites such as 3-HK and QUIN, which, under conditions of chronic immune activation, may exacerbate oxidative stress and glutamatergic dysregulation (Miyamoto et al., 2024; Xia & Huang, 2026). In schizophrenia and bipolar disorder, complex changes in the balance between the KYN-KYNA and KYN-QUIN pathways are observed, which is interpreted as an element of the immunometabolic heterogeneity of psychoses (Mehta et al., 2025; Majie et al., 2026). Additionally, the limited availability of indole tryptophan metabolites, acting as AhR ligands, may weaken anti-inflammatory mechanisms and promote the perpetuation of intestinal and blood-brain barrier disorders (Owe-Larsson et al., 2025).

In light of the above mechanisms, interventions aimed at modulating the microbiota—including prebiotics, probiotics, and dietary strategies that increase SCFA production—are promising complements to standard pharmacotherapy (Zhou et al., 2025). A randomized trial using inulin-enriched oligofructose showed an increase in plasma butyrate concentration in patients with schizophrenia, supporting the possibility of a targeted effect on the metabolic profile (Buchanan et al., 2024). At the same time, the development of metabolomic analyses and the use of machine learning algorithms enables the identification of biological subtypes of depression with high classification accuracy (AUC ~0.94), supporting the concept of precision psychiatry (Ma et al., 2025; Li et al., 2026).

However, it is important to emphasize the significant limitations of available studies. Most analyses are cross-sectional and correlational in nature, and the obtained results are characterized by significant methodological heterogeneity resulting from differences in diet, pharmacotherapy, disease stage, and the type of biological sample analyzed (Dziedziak et al., 2025; Mehta et al., 2025). There is a lack of large, multicenter longitudinal studies that would unequivocally confirm that normalization of specific metabolomic parameters translates into lasting improvements in clinical functioning.

In summary, SCFAs and tryptophan metabolites are biologically valid and increasingly well-documented candidate biomarkers of psychiatric disorders. However, their full clinical implementation requires further standardization of assay methods, validation in independent cohorts, and integration with inflammatory, genetic, and neuroimaging data within multidimensional models of personalized psychiatry.

Conclusions

The current state of research on the microbiota-gut-brain axis has significantly redefined the classical view of the pathogenesis of human psychiatric disorders. Disorders that for decades were primarily understood as the result of neurotransmitter abnormalities in the central nervous system—including schizophrenia, bipolar disorder, and multi-episode depression—are now viewed in the context of complex systemic dysregulation involving interactions of the immune, endocrine, and metabolic systems, with a significant contribution from the gut microbiota.

Experimental evidence clearly indicates that deficiency and reduced concentrations of short-chain fatty acids (SCFAs), including the key amino acid butyric acid, impact the integrity of neuroprotective and immunomodulatory functions. Reduced levels of butyrate and propionate observed in patients with schizophrenia and bipolar disorder are associated with decreased activity of histone deacetylase (HDAC) enzymes, impaired blood-brain barrier (BBB) function, and increased concentrations of peripheral proinflammatory cytokines such as IL-6, IL-8, and TNF-α, which may contribute to the exacerbation of neuroinflammatory processes in the central nervous system.

These dysfunctions also involve the tryptophan metabolism pathways, where excessive activity of enzymes catalyzing the conversion to toxic metabolites such as quinolinic acid (QUIN) and 3-hydroxykynurenine (3-HK) limits the availability of substrates necessary for serotonin (5-HT) synthesis, leading to disturbances in neurotransmitter homeostasis and mood modulation. These alterations demonstrate that psychiatric disorders can be viewed as a consequence of multidimensional metabolic and immune dysregulation, in which the gut microbiota plays a key regulatory role.

Omics research has also enabled the development of rigorous diagnostic models based on the integration of multidimensional biological data. Combining SCFA panels, kynurenine pathway metabolites (KYN/TRP), cytokine concentrations, and branched-chain fatty acid profiles allows for more precise differentiation between patients with psychiatric disorders and healthy individuals. Classification algorithms, such as random forest models based on ROC/AUC curve analysis, achieve high diagnostic sensitivity (AUC > 0.98), enabling the identification of hidden patterns in polymorphic disorders and the separation of episodes of BD and SCH from controls, without the need for psychometric assessments.

This approach opens the possibility of early detection of patients at risk for increased proinflammatory processes and toxic metabolites, including the potential risk of suicide associated with KP axis dysfunction and increased QUIN production associated with ACMSD enzyme impairment. Integrating knowledge about precise dosing of postbiotic preparations, SCFA-modulating supplements, and targeted microbiome modulation offers a potential strategy for restoring balance to the gut-brain axis while minimizing the risk of depleting the CNS's metabolic reserves. This approach may contribute to improved prognosis in chronically ill patients struggling with treatment-resistant mental disorders, opening a new era in precision psychiatry and personalized medicine.

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