Research in Pharmaceutical Sciences, February 2025; 20(1): 1-24
Received: 20-12-2023
Peer Reviewed: 27-01-2024
Revised: 30-04-2024
Accepted: 28-05-2024
Published: 14-02-2025

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Review Article

Using metabolomics to investigate the relationship between the metabolomic profile of the intestinal microbiota derivatives and mental disorders in inflammatory bowel diseases: a narrative review

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Abstract

Individuals with inflammatory bowel disease (IBD) are at a higher risk of developing mental disorders, such as anxiety and depression. The imbalance between the intestinal microbiota and its host, known as dysbiosis, is one of the factors, disrupting the balance of metabolite production and their signaling pathways, leading to disease progression. A metabolomics approach can help identify the role of gut microbiota in mental disorders associated with IBD by evaluating metabolites and their signaling comprehensively. This narrative review focuses on metabolomics studies that have comprehensively elucidated the altered gut microbial metabolites and their signaling pathways underlying mental disorders in IBD patients. The information was compiled by searching PubMed, Web of Science, Scopus, and Google Scholar from 2005 to 2023. The findings indicated that intestinal microbial dysbiosis in IBD patients leads to mental disorders such as anxiety and depression through disturbances in the metabolism of carbohydrates, sphingolipids, bile acids, neurotransmitters, neuroprotective, inflammatory factors, and amino acids. Furthermore, the reduction in the production of neuroprotective factors and the increase in inflammation observed in these patients can also contribute to the worsening of psychological symptoms. Analyzing the metabolite profile of the patients and comparing it with that of healthy individuals using advanced technologies like metabolomics, aids in the early diagnosis and prevention of mental disorders. This approach allows for the more precise identification of the microbes responsible for metabolite production, enabling the development of tailored dietary and pharmaceutical interventions or targeted manipulation of microbiota.

Keywords: Anxiety; Depression; Gastrointestinal microbiome; Inflammatory bowel diseases; Metabolomics.

INTRODUCTION

Inflammatory bowel disease (IBD) refers to a diverse group of long-lasting inflammatory disorders, typically consisting of two distinct conditions: Crohn's disease (CD) and ulcerative colitis (UC) (1,2); this category of disease affects around 0.3% to 0.5% of the world's population (3). Along with the changes in people's lifestyles and industrialization, the global impact of IBD is felt by over 6.8 million individuals, and its incidence and prevalence are on the rise globally (4-6). IBD originates from a combination of genetic vulnerability, environmental factors (changes in diet from plant-based to animal-based, tobacco use, and the use of antibiotics), and microbial influences; all of these elements have an important function, but none of them alone can initiate the disorder (7,8). A considerable proportion of patients diagnosed with IBD experience symptoms of common mental health conditions such as anxiety and depression (9).

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Access this article online	
	Website: http://rps.mui.ac.ir
	DOI: 10.4103/RPS.RPS_273_23

Studies have shown that the occurrence of anxiety and/or depression in patients with IBD is between 13% and 44.4%, which is significantly higher than that of the general population, with a prevalence of 4.4% (10,11).

Anxiety and depression can have significant negative effects on an individual's quality of life; some of the common adverse effects include mental health deterioration, physical health complications, social isolation, impaired work and academic performance, substance abuse, financial burden, relationship strain, and increased risk of self-harm and suicide (12). It is crucial for individuals experiencing anxiety and depression to seek appropriate help and support to improve their quality of life and overall well-being, especially if it is observed in patients with IBD (13,14). The relationship between the co-occurrence of mental disorders and IBD is complex and requires a comprehensive assessment using holistic technologies (15-18). It is possible to use omics such as metagenomics and metabolomics to study how gut microbial imbalance and its metabolites exacerbate intestinal inflammation and psychiatric comorbidities, such as anxiety and depression. By employing these techniques, it is possible to gain a more precise understanding of the co-occurrence of these conditions (19,20).

Metabolomics is an expanding field that uncovers previously unknown biological processes in living organisms (21). This field of study is closely related to other omics disciplines such as genomics, metagenomics, transcriptomics, and proteomics, and collectively contributes to a better understanding of biological systems (22,23). Consequently, in our narrative review, we concentrated on demonstrating how metabolomics understanding supports the involvement of gut microbes in the concurrence of mental disorders such as anxiety and depression alongside IBD.

Anxiety and depression in IBD patients

As indicated by studies, compared with the general population, individuals with IBD may face a higher likelihood of experiencing mental health problems. However, the exact connection between these conditions and the order in which they occur is still not fully understood (24). Mental health problems refer to several conditions that affect a person's emotional, psychological, and social well-being (25). Anxiety and depression are among the most common mental health problems in patients with IBD (26,27); the prevalence of anxiety and depression in individuals with IBD is at least twice more than that in the general population. Among active IBD patients, depression accounts for almost 34.7% of cases, whereas for those in remission, it accounts for approximately 19.9%. In addition, between 19.1% and 35% of people diagnosed with IBD experience anxiety disorders (28); the occurrence of depression or anxiety in this group of patients can negatively affect their quality of life, complicate the medical management of IBD, and potentially intensify the frequency of active disease. The relationship between IBD and mental disorders appears to be bidirectional: experiencing periods of gastrointestinal disease raises the risk of anxiety and depression, whereas individuals with mood disorders have a greater risk of developing IBD (29,30).

Several factors, including biological and psychosocial elements, socioeconomic deprivation, disease flares, and severe illness, have been suggested to explain why individuals with IBD are prone to emotional disorders (31). Furthermore, there is a growing recognition of the gut-brain connection in the progression of these two conditions, indicating that alterations in the microbiome could be related to an increased probability of mental disorders. On the other hand, the chronic nature of IBD, coupled with its negative perceptions and societal implications, may play a role in the onset of depressive and anxiety symptoms (18,32). Hence, a systematic review of the publications indicated that psychiatric intervention can effectively decrease symptoms of anxiety and depression, disease activity, and gastrointestinal issues. The increasing prevalence of mental disorders in patients with IBD indicates the necessity of psychological screening. Based on this, studies suggest that patients with IBD receive psychological counseling once a year (Fig. 1) (33,34).

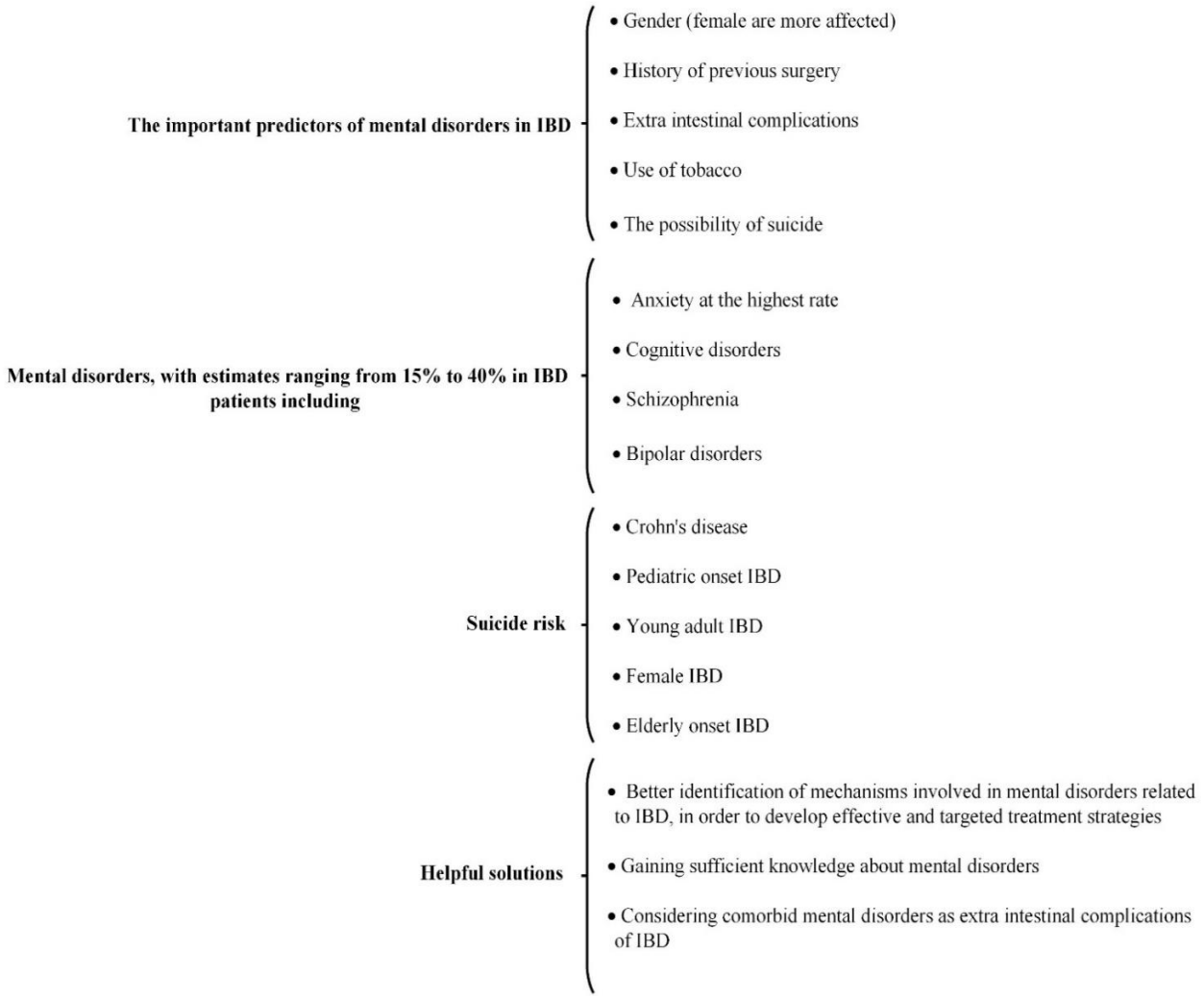

Fig. 1. Mental disorders in IBD patients. In this category, the important predictive factors in the occurrence of mental disorders in patients with IBD, the various types of mental disorders observed in IBD, the risk of suicide in these patients, and possible helpful solutions are presented. IBD, inflammatory bowel disease.

Improving the accuracy of identifying factors and mechanisms associated with the coexistence of mental disorders and IBD, and implementing methods to manage them may enhance quality of life and prevent disease progression (34). Employing omics technologies to analyze large biological data can efficiently investigate the co-occurrence of mental health disorders and IBD. The current advancements in metabolomic approaches significantly enhance the identification of metabolites across a broad spectrum, thereby facilitating a deeper understanding of their clinical application (35). Consequently, integrating metabolomics into clinical practice promises to improve disease management efficacy, ultimately leading to better patient outcomes.

Gut microbiota in healthy condition

The gut microbiota is a large and complex ecosystem of microorganisms, protozoans, fungi, and viruses that can determine the health and disease states of the host (36). The intestinal microbiota is predominantly composed of bacterial species, a fact that underscores the importance of bacterial research within the field of microbiome studies (37).

It comprises about 100 trillion microbial organisms that shape vital parts of the gut ecosystem (38); this section has about 1000 species, which mostly belong to the phyla of Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria, and the rest of the phyla, such as Cyanobacteria, Fusobacteria, and Verrucomicrobia, are less common. Functions

such as maintaining host homeostasis, providing protection against pathogens, synthesizing vitamins (such as vitamin K, vitamin B9, and vitamin B12), extracting energy from food products, enhancing immunity, producing short-chain fatty acids (SCFAs), facilitating fat storage, and potentially influencing human behavior make the microbiome an essential organ within the host organism (39-41).

The gut microbiota is pivotal in forming the initial education of microorganisms, the immune system, and immune responses through the induction of inflammatory mediators, signaling pathways, immune cells, and the development of gut-associated lymphoid tissue (GALT) (42-44).

Gut microbiota in IBD

Gut microbiota has become the focus of attention in the study of inflammatory diseases in the last two decades. In IBD patients compared to healthy individuals, a reduction in α-diversity along with the abundance of Firmicutes and increases in Bacteroidetes and Proteobacteria has been observed (45,46). Alpha diversity simplifies the quantification of gut microbial profiles by characterizing the presence and abundance of bacterial taxa within individual samples. A higher alpha diversity, indicating a more diverse and rich community of gut bacteria, is generally considered beneficial for overall health. A diverse gut microbiome can perform various functions and help maintain a healthy balance between useful and potentially pathogenic bacteria, reducing the risk of infections and other health issues (47).

Based on clinical studies, a decrease in overall diversity, in the form of an increased abundance of colitogenic microbiota, including Pasteurellaceae, adherent invasive *E. coli*, Fusobacterium spp., *Ruminococcus gnavus*, and Veillonellaceae, as well as a decreased abundance of anti-inflammatory bacteria such as Bacteroides, Bifidobacterium spp., *Feacalibacterium prausnitzii*, Roseburia, Suterella, and Clostridium classes IV and XIVa have been confirmed in patients with IBD; these alterations are characteristics of IBD (45,48-54). Microbial factors, through their impact on host metabolism, their substantial influence on the immune system, as well as their effect on gastrointestinal development, play a vital role in the pathophysiology of IBD (55,56).

Influencing factors of gut microbiota

The intestinal microbiota is less diverse at the beginning of birth and plays a decisive role in maintaining gut homeostasis under normal physiological conditions; this homeostasis can change through different stimuli such as host genetics, mode of birth, infant diet (breast or formula milk), age, type of postnatal diet (including vegetarian diets and non-vegetarian diet (Western diet), antibiotics, exogenous infections, pesticides, and toxins (56,57). In addition, probiotics, prebiotics, and fecal microbiota transplantation (FMT) can help modulate gut homeostasis. The components of these florae are different in each part of the intestinal environment, which makes the microbiota specific to each individual (38).

According to the IBD dysbiosis theory, gut microbiota composition and diversity, and the patients' localization differ from that of a healthy host microbiome, even after treatment; this imbalance between the microbiota and its host is called dysbiosis, and it is more common in people with a genetic predisposition or who are environmentally at risk (58,59).

Permanent or increased consumption of fast foods, particularly in lower socioeconomic classes, along with limited access to green spaces, are significant factors contributing to intestinal dysbiosis (60). In these people, inappropriate immune responses are more effective against the changed microbial population (61); it has been suggested that the sharp rise in cases of IBD in newly industrialized nations may be attributed to the adoption of Western-style diets containing high levels of saturated fats and simple carbohydrates, but low in dietary fiber, coupled with other lifestyle changes (62).

Understanding these complex relationships requires comprehensive and holistic technologies in analyzing big data. Applying metagenomics, metabolomics, and metatranscriptomics technologies facilitates the analysis of these relationships (46,63); for

example, the analysis of metagenomic data of mice receiving antibiotics that had gut dysbiosis by Miyoshi and colleagues enabled them to predict the onset of colitis in these mice (51).

Role of environmental factors in IBD pathogenesis and metabolite changes

Food intake plays a significant role in influencing IBD development, as research has shown that consuming fruits and vegetables can lower the risk of CD. In contrast, a diet high in fat and sugar may contribute to the increased occurrence of CD (64). Studies show that medium-chain fatty acids are more effective than long-chain fatty acids in accelerating intestinal inflammation (65). In many developed Western countries, sugary foods are identified as a risk factor for CD, and artificial additives found in Western diets can disrupt gut function and worsen inflammation (66).

Smoking can exacerbate the disease; it leads to impaired autophagy, affects cellular and humoral immune responses, and increases the production of colonic mucus. Other factors that influence the development of IBD include psychological stress, appendectomy, environmental pollution, geographical and climatic factors, and certain medications, especially non-steroidal anti-inflammatory drugs (NSAIDs) (67,68). These factors also affect the metabolomic profile of people in such a way that a diet rich in fat causes the production of pro-inflammatory metabolites, and a fiber-rich diet produces anti-inflammatory metabolites (69). Further exposure to environmental pollution increases the likelihood of generating active metabolites contributing to the escalation of oxidative stress. Stress triggers the immune system to produce specific metabolites that enhance inflammation. Moreover, NSAIDs and certain antibiotics can be metabolized into active or pro-inflammatory metabolites, potentially contributing to the onset of IBD or worsening its symptoms and complications (70).

Metabolomics

Metabolomics provides a thorough insight into the metabolic profile of samples from living systems such as serum, plasma, stool, urine, and tissues; it offers valuable information about the underlying biology and potential applications for enhancing human health and well-being. It combines advanced analytical chemistry techniques with sophisticated statistical methods to propose a comprehensive description of the metabolome, including all small molecules in a biological system (71,72).

Metabolome refers to the entire collection of small molecule chemicals, known as metabolites (as long as their molecular weight does not exceed 1500 Da), that exist within a specific cellular compartment, such as an organelle, a cell, an organ, a biofluid, or an entire organism (73). Lipids, short peptides, nucleic acids, sugars, amino acids, alcohols, and organic acids generated naturally through metabolic processes like catabolism or anabolism are known as endogenous compounds or "primary" metabolites. Some metabolites must be obtained from the diet or synthesized by genes found in the gut microflora; essential metabolites include vitamins (such as vitamin K and biotin) and essential amino acids (valine, phenylalanine, leucine, isoleucine, histidine, methionine, lysine, threonine, and tryptophan). Nutritional deficiency of these metabolites leads to diseases such as pellagra (lack of vitamin B3), rickets (lack of vitamin D), and kwashiorkor (lack of protein or essential amino acids) (74). Xenobiotic compounds, such as phytoestrogens, alkaloids, and polyphenols derived from dietary sources or the environment, as well as microbial byproducts, pollutants, chemical contaminants, and pesticides, are also considered metabolites. However, unlike endogenous compounds known as primary metabolites, essential for an organism's growth and development, these compounds are referred to as secondary metabolites and are not necessarily required for these processes; the products of these compounds may also be considered metabolites (75).

The intimate relationship between metabolites and genes has earned metabolites the nickname "the canaries of the genome". This is because a minor alteration, such as a single base change in a specific gene, can result in a significant variation of up to 10,000-fold in the levels of endogenous metabolites. Such

significant fluctuations in metabolite levels can profoundly affect various biological processes. This highlights the importance of understanding the intricate interplay between genetic changes and metabolite levels (76,77).

It reminds us that although metabolites are small, their impact on human physiology and disease is profound. In addition, due to the high sensitivity of metabolites to internal and external stimuli, they can serve as a valuable tool for assessing each individual's phenotype (78). Chen *et al*. expressed their belief that the study of serum metabolomics analysis and non-coding RNA in IBD was in its early stages but held great promise for future clinical practice; they emphasized the significance of combining various biomarkers to enhance the accuracy of disease assessment (79).

The field of metabolomics has significantly expanded and is now applied in various areas of biomedical research, animal health studies, exploratory physiological studies, food and nutritional analysis, and drug testing as a means of identifying new biomarkers (80). In the field of medicine, metabolomics has shown promise in detecting and managing diseases such as cancer, neurological disorders, cardiovascular diseases, and metabolic disorders, paving the way for a more holistic and targeted approach to healthcare (81).

Types of metabolomics experiments

Metabolomics experiments are categorized into four types, chosen based on the research question and the laboratory equipment capabilities conducting the studies; these include targeted metabolomics, untargeted metabolomics, metabolite imaging, and fluxomics (82). Targeted metabolomics is employed for biomarker detection, identification, and quantification of a small subset (between 50 and 500) of metabolites; this feature offers numerous medical and clinical applications. The untargeted metabolomics objective is to identify as many metabolites or putative metabolites as possible (often 10,000). Therefore, it is well-suited for discovering new metabolites and generating hypotheses (83).

Metabolite imaging is useful for identifying and visualizing metabolites *in vivo* or *in vitro*. Its primary purposes include assessing cellular, tissue, and organ metabolism, as well as aiding in surgical procedures. Fluxomics is a targeted metabolomics approach that monitors the movement of isotopic labels through various metabolic intermediates and measures metabolite reaction rates. In addition, it is used to understand the dynamics of metabolism and provides essential insights into both physiological and cellular metabolism (84,85).

Metabolomics and anxiety/depression

Anxiety and depression are complex disorders that are often accompanied by alterations in metabolic pathways, which can be detected using metabolomics approaches (86,87). This approach enables the identification of metabolites associated with diagnosing or predicting anxiety and depression, as well as identifying metabolites involved in neurotransmitter synthesis, degradation, or transmission (88). Moreover, it allows for exploring the functional mechanisms of these metabolites, examining interactions between gut microbiota and their metabolites with the host's central nervous system (CNS), identifying potential therapeutic targets, assessing treatment response and efficacy, and ultimately aiding in the development of personalized treatments tailored to each individual's unique metabolic profile; this approach provides valuable insights into the intricate processes governing these disorders (89,90).

The diverse benefits of metabolomics make it a potent tool for uncovering previously unknown biological mechanisms in various diseases (91). As previously stated, microbial dysbiosis is one of the key factors contributing to the occurrence of mental disorders in IBD (58).

Metabolomic studies can help elucidate the role of specific gut microbes in the onset and progression of comorbidities associated with IBD (92). It also offers the opportunity for a comprehensive and detailed investigation of the complex interactions between microbes and mental disorders in various aspects (93). Based on a review of studies, metabolomics can help identify these relationships more precisely using the following approaches (Fig. 2A-C).

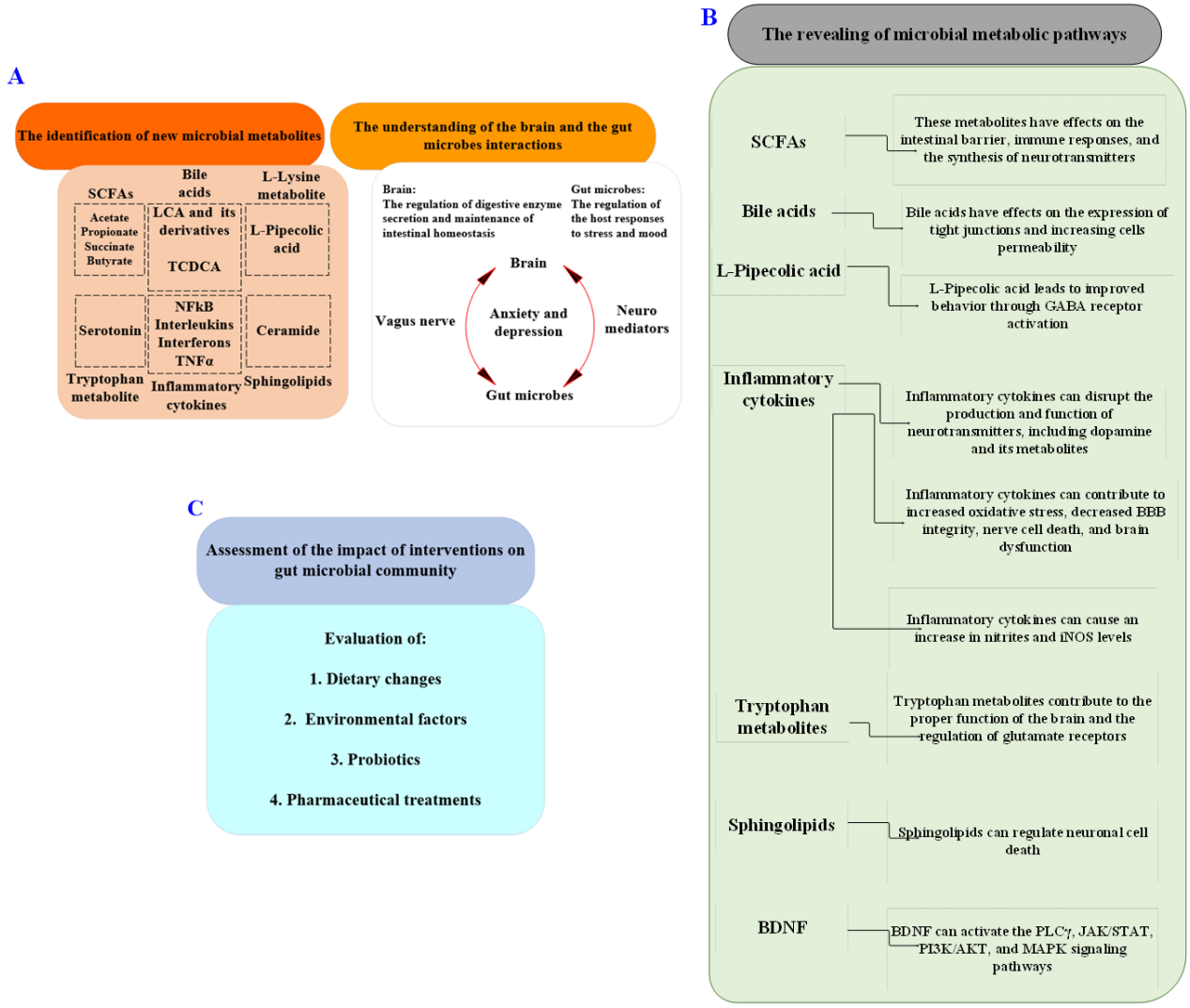

Fig. 2. (A) Application of metabolomics in identifying new biomarkers and interactions between the brain and the gut microbes in mental disorders associated with IBD. In mental disorders associated with IBD, such as anxiety and depression, the regulation of microbial metabolites shown in the left figure is disrupted. The right figure presents the connection between the brain and the gut microbes and its role in the onset of mental disorders. (B) Application of metabolomics in the revealing of microbial metabolic pathways. The microbial metabolic pathways involved in IBD-related mental disorders, such as anxiety and depression, are presented. (C) Application of metabolomics in assessing the impact of interventions on the gut microbial community. By using metabolomics, it is possible to follow the metabolites related to dietary changes, environmental factors, probiotics, and pharmaceutical agents in individuals. This methodology also facilitates the examination of changes in the gut microbiota due to the use of these factors. SCFAs, Short-chain fatty acids; NFkB, nuclear factor kappa-light-chain-enhancer of activated B; TNFα, tumor necrosis factor α; LCA, lithocholic acid; TCDCA, taurochenodeoxycholic acid; SCFAs, short-chain fatty acids; GABA, gamma-aminobutyric acid; BDNF, brain-derived neurotrophic factor; BBB, blood-brain barrier; iNOS, inducible nitric oxide synthase; PLCγ, phospholipase C-gamma; JAK/STAT, Janus kinase/signal transducer and activator of transcription; PI3K, phosphoinositide 3-kinases; AKT, protein kinase B; MAPK, mitogen-activated protein kinases.

The application of metabolomics in identifying biomarkers

Metabolomics helps identify specific metabolites altered in IBD patients compared to healthy individuals. In a study conducted by Xavier *et al*. 2700 bacterial metabolites were identified with changed levels in patients with IBD (94). The analysis revealed over 50% of previously unidentified metabolites, some of which could originate from the gut microbiota (95).

These metabolites could serve as potential biomarkers for diagnosing IBD or its consequences or monitoring the progression and response to treatment. In IBD patients who suffer from mental disorders, there is an irregularity in the intestinal metabolome, marked by an imbalanced presence of different

types of SCFAs, bile acids, intermediate metabolites of L-lysine, metabolites of tryptophan, glutamate, metabolites of dopamine including epinephrine and norepinephrine, metabolites of serotonin including melatonin, tryptamine, and 5-hydroxy indole acetic acid (5-HIAA), nitrite, sphingolipids and their metabolites, including ceramide, inflammatory metabolites, as well as metabolic pathways regulated by brain-derived neurotrophic factor (BDNF) and tryptophan (45,96-98).

The application of metabolomics in revealing microbial metabolic pathways

By analyzing the changes in metabolite levels, researchers can gain insights into the metabolic pathways affected by mental disorders with IBD. The metabolic pathways are as follows.

SCFAs signaling pathway

Microbial pectin metabolism, glycans, and other carbohydrates are negatively related to depression. Human enzymes cannot digest compounds such as pectin and glycan but gut microbes can ferment them (99). During fermentation, gut microbes break down these compounds into smaller molecules, including SCFAs such as acetate, propionate, succinate, and butyrate. SCFAs are microbial fermentation byproducts that play a vital role in gut health and overall metabolism (100). They have diverse effects on CNS functionality, such as altering neurotransmitter synthesis, improving mitochondrial performance, activating the immune system, regulating lipid metabolism, and adjusting gene expression (101).

In previous studies, it has been reported that the occurrence of major depression was associated with a decrease in the relative abundance of microbial species that produce SCFAs (102).Reduced system, such as the enteric nervous system (ENS) and the CNS (103,104). It has also been reported that depression caused by the induction of mild stress in mouse models causes a decrease in SCFA levels and the intrarectal use of propionate reduces depressive-like behaviors in these models (105).

Bile acid signaling pathway

A change in bile acid profile has been observed in patients with IBD, marked by elevated fecal-conjugated primary bile acids and reduced serum and fecal secondary bile acids (106). Bile acids are closely related to energy metabolism, immune system function, intestinal barrier function, and disease activity. Studies indicate that bile acids can influence brain function under both normal physiological and abnormal pathological conditions (107). Elevated levels of circulating serum bile acids may lead to increased permeability of the blood-brain barrier (BBB), which in turn could result in psychophysiological issues like anxiety and depression (108).

However, certain studies indicate that several bile acids, like lithocholic acid (LCA) and its derivatives, isoLCA, alloLCA, 7-keto-LCA, and 12-ketoLCA, exhibit antidepressant properties by activating the central pregnane X receptor (PXR) and vitamin D receptor (VDR) (109,110). In addition, dehydrolithocholic acid, a major metabolite of LCA, is negatively correlated with anxiety and depression levels in major depressive disorder (MDD) patients. This compound is an agonist of the farnesoid X receptor (FXR) and the PXR has recently been found to regulate adaptive immunity by inhibiting the differentiation of T helper 17 (Th17) cells (111).

Therefore, the decrease in the serum or fecal levels of this group of bile acids or other agonists may be related to the psychological issues observed in IBD. According to some studies, the binding of taurochenodeoxycholic acid (TCDCA) to the TGR5 receptor (a G protein-coupled bile acid receptor) can help alleviate depression in mice that have been treated with chronic unpredictable stress; this is achieved by reducing neuroinflammation and oxido-nitrosative stress (112). Bile acids may also be linked to mental disorders through the disruption of tight junction expression and the increased permeability of central and intestinal epithelial cells; ongoing research in this area aims at further exploring these findings (113,114).

An intermediate metabolite of the L-lysine signaling pathway

L-pipecolic acid, an intermediate metabolite of L-lysine in the brain, causes changes in behavior by activating gamma-aminobutyric acid (GABA) receptors (72,115). When GABA binds to its receptors, it causes an inflow of chloride ions into the neuron, which hyperpolarizes the cell membrane and makes it less likely for the neuron to fire an action potential; this inhibitory effect helps maintain the balance between excitatory and inhibitory neurotransmission in the brain (33,116).

BDNF signaling pathway

Lowering the level of BDNF, which may occur due to microbial dysbiosis, can lead to mental health problems such as anxiety and depression (117). BDNF, a neurotrophin, significantly influences neuroplasticity within the brain. As one of the most extensively studied molecules in the field of psychiatry, it plays a vital role in understanding and addressing various mental health disorders (118). BDNF signaling plays a critical role in neuronal development, neuronal survival, and synaptic plasticity through the activation of phospholipase C-γ (PLC-γ), Janus kinase (JAK)/signal transducer and activator of transcription (STAT), phosphatidylinositol 3-kinase (PI3K)/Akt, and mitogen-activated protein kinase (MAPK) pathways (119); the variations in BDNF levels in comorbidities with IBD are also being investigated. Some studies have suggested that decreased BDNF levels may be associated with increased symptoms of anxiety and depression in IBD patients, while others have found no such correlation. The reasons for these discrepancies are not fully understood, but they may be related to disease activity, medication use, and genetic factors. Further research is needed to clarify the relationship between BDNF, anxiety, depression, and IBD, as well as to determine whether BDNF-based interventions could be effective in managing these comorbidities (120,121).

Tryptophan signaling pathway

A review of studies revealed that the serum levels of tryptophan and the ratio of tryptophan/kynurenine were significantly lower in both subgroups of patients with UC and CD compared to the control group (122). Tryptophan can follow three main pathways in the gut: the serotonergic pathway for the production of serotonin in the enterochromaffin cells; indole, indole-3-propionic acid (IPA), indole-3-acetaldehyde (IAAld), indole-3-acid-acetic (IAA), and indole-3-aldehyde (IAld), in the gut microbiota; and kynurenine pathway in the epithelial cells, lamina propria, and immune cells (123-126). Dysbiosis can lead to abnormal activation of the three pathways involved in tryptophan metabolism in the intestines, particularly a deficiency in indole synthesis (124,127,128); individuals with IBD exhibit a significant shift in tryptophan metabolism towards the kynurenine pathway and a decrease in the activity of the indole pathway (124,129). Indole metabolites have been observed to promote mucus production in intestinal epithelial cells and modulate the inflammatory response (130). For example, the study carried out by Aoki *et al.* confirmed that indole pyruvic acid can ameliorate dextran sodium sulfate (DSS)-induced colitis symptoms in mice, reduce the abundance of Th1, and increase the production of interleukin-10 (IL10) and T regulatory cells (Tregs) (131). It is worth noting that taking indole-3 carbinol (I3C) in a dose of 400 mg twice a day for three months can significantly reduce the endoscopic score of the colon and the histological disease score in female patients with ulcerative colitis. Additionally, I3C administration decreases the levels of malondialdehyde (MDA), tumor necrosis factor α (TNF-α), and myeloperoxidase (MPO) while increasing the levels of catalase (CAT) in these patients (132).

The kynurenine pathway, a significant pathway in tryptophan metabolism plays a crucial role in distinguishing Tregs from other types of tolerogenic immune cells. This effect is protective in colitis, as Tregs help prevent excessive inflammation in the intestine. However, the same pathway also contributes to tumorigenesis, as it has been shown to promote the growth and survival of cancer cells. The exact mechanisms by which the kynurenine pathway contributes to these opposing effects are still being studied (133).

In a study conducted by Forrest and colleagues, they found that individuals with IBD who experienced mild colitis had significantly higher levels of kynurenine and kynurenic acid in their blood serum compared to healthy individuals (122). In a similar study using immunohistochemistry, the researchers found that the expression of indoleamine 2, 3-dioxygenase (IDO), an enzyme involved in tryptophan metabolism *via* the kynurenine pathway, was higher in tissue samples from individuals with IBD compared to healthy individuals (134,135). Clinical studies have observed elevated levels of kynurenine in the cerebrospinal fluid of individuals with anxiety and depression (136). This increase may be due to the increase in IDO activity. Although their precise functional mechanisms are not fully understood, it is believed that these metabolites may exert neurotoxic effects, particularly on glutamate receptors, and interfere with nerve signaling (137). Glutamate plays a vital role in normal brain function, and any disruptions in its activity can adversely affect brain health and cognitive abilities. Dysregulation of glutamate receptor function has also been observed in neurodegenerative diseases such as Alzheimer's and Parkinson's (138).

Serotonin signaling pathway

Sufficient amounts of serotonin and its metabolites such as melatonin and 5-HIAA are necessary for regulating mood, controlling anxiety, feeling happiness, modulating platelet function, controlling gastrointestinal motility, regulating the maturation of the enteric nervous system; and low serotonin levels lead to depression; extensive metabolic studies have revealed that over 90% of the body's serotonin is synthesized in the gut (139).

Interestingly, serotonin-producing cells are produced by interaction with SCFAs in the gut; as long as the production of SCFAs is within the normal range, the production of serotonin is also promoted (140). Serotonin level changes in patients with IBD and its subgroups are still a topic of debate, but most studies have confirmed an increase in this level; this increase might be caused by inflammatory mediators like IL-1β and lipopolysaccharides (LPS), which trigger the release of serotonin from enterochromaffin cells (EC) (141), while the expression of the serotonin receptor (5-hydroxytryptamine (5HT) 3 receptors) reduces in patients with IBD. This reduction may be effective in the occurrence of psychiatric diseases associated with IBD, as the correct function of this receptor plays a significant role in the regulation of intestinal motility and the effects of serotonin on brain functions (142).

Pro-inflammatory factors signaling pathway

The levels of pro-inflammatory factors, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), NOD-like receptor protein 3 (NLRP3), IL-1β, IL-6, interferon-gamma (IFN-γ), and TNFα increase in IBD, MDD, and anxiety. This rise is also linked to an increase in intestinal epithelial permeability, enabling microbes and their byproducts to enter the bloodstream and impact brain function (143,144). Pro-inflammatory factors can lead to psychological and behavioral impairment through various processes. Inflammation can disrupt the production and function of neurotransmitters such as dopamine and serotonin, which participate in cognitive and mood functions; this disruption is associated with behavioral impairment. Inflammation is also related to increased oxidative stress cognitive defects and neurodegeneration; an increase in oxidative stress with reactive oxygen species (ROS) and reactive nitrogen species (RNS) formation, which could cause loss of BBB integrity and neuronal cell death, can lead to the destruction of brain cells and the accumulation of beta-amyloid plaques which are the main hallmarks of Alzheimer's disease. Furthermore, inflammation can reduce the production of new brain cells, known as neurogenesis, associated with cognitive impairment and depression (13). Moreover, significant levels of nitrite and inducible nitric oxide synthase (iNOS) can be observed in the hippocampus and cerebral cortex because of peripheral inflammation. This increase in nitrite and iNOS contributes to the development of behavioral symptoms associated with anxiety and depression (145). Therefore, in patients with IBD, whose level of pro-inflammatory factors is higher than normal, the occurrence of accompanying psychological disorders is

more likely and is better justified. Findings also suggest that inflammation may affect the response to treatment in mental illnesses; for example, individuals with depression and higher levels of inflammation may respond less well to antidepressants (146,147).

Sphingolipids signaling pathway

Sphingolipids, which are molecules produced by both the host and microbes, frequently exhibit variations between subjects with and without IBD (148). Sphingolipids play a significant role as signaling molecules, and their involvement in the development of IBD has been suggested (149). Gut microbes can generate sphingolipids that can impact host immune responses; one notable example is the production of sphingolipids by Bacteroides, which hinder the growth of invariant natural killer T (NKT) cells and provide defense against chemically induced colitis (150). Decreased production of sphingolipids by the bacteria in patients with IBD possibly offset an elevation in host-produced sphingolipids. Research has indicated that the absence of sphingolipids from microbes led to gut inflammation and changed host ceramide pools in a mouse study. Sphingolipids could play a role in mental health issues (151). Changes in sphingolipid metabolism have been seen in people with schizophrenia, bipolar disorder, and MDD. Additionally, some studies have found that levels of certain sphingolipids, such as ceramides, are reduced in people with depression and anxiety. Ceramides have been implicated in the regulation of neuronal cell death and inflammation, both of which have been associated with mental health disorders (149,152,153).

The application of metabolomics in understanding gut-brain interactions

A notable aspect of metabolomic research is the discovery of uncommon gut-derived metabolites or atypical levels of such metabolites in the urine and blood samples of people (or animal models) affected by conditions such as autism, schizophrenia, anxiety, mood disorders, and Parkinson's disease (154).

Metabolomic studies confirmed a known bidirectional communication between the CNS of the host and microbiota through metabolites, the immune system, the autonomic nervous system, the neuroendocrine system, and the hypothalamic-pituitary-adrenal (HPA) axis. The significance of this interaction lies in activating the secretion of digestive enzymes, maintaining intestinal homeostasis, and controlling peristalsis (155). The HPA axis is a neuroendocrine regulatory network that controls various functions, including visceral sensation and stress responses in the brain-gut communication pathway, and also regulates gut epithelial permeability (156). The activation of the HPA axis by stress releases corticotropin-releasing factor (CRF) from the hypothalamus paraventricular nucleus (PVN). This process stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH) resulting in adrenal glucocorticoid release (GCs) like cortisol, the stress hormone that suppresses the immune system. Excessive production of cortisol can have detrimental effects on brain structure and function. These effects may contribute to the development and persistence of symptoms associated with mental illnesses such as anxiety disorders, depression, and post-traumatic stress disorder (PTSD) (145). The worsening of symptoms and recurrence of IBD can be attributed to adverse life events and emotional stressors, often associated with anxiety and depression (157), because the excessive production of GCs and CRH triggered by chronic psychological stress results in a decrease in the expression of tight junctions in the intestine. This reduction in tight junction expression impairs the functionality of the intestinal mucosal barrier, which is closely associated with the progression of IBD. In addition, chronic stress causes a change in the composition and function of the intestinal microbiota through the reduction of certain species of bacteria such as *Lactobacillus* spp., or an expansion of inflammatory-promoting bacteria such as *Helicobacter* and *Streptococcus* species (158). Changes in gut microbiota composition linked to HPA axis activation can heighten brain inflammatory activity. Consequently, the gut microbiota can impact stress response pathways in the

brain. Animal studies have also shown that exposure to stress before birth has long-term effects on microbiota composition and the activation of the HPA axis in adulthood (159,160).

The application of metabolomics in assessing the impact of interventions

Metabolomics plays a significant role in evaluating the impact of various interventions on the brain-gut axis function (161). By employing metabolomics and evaluating metabolites related to the gut and brain, we can analyze how dietary adjustments, environmental factors, probiotics, prebiotics (162,163), or pharmaceutical treatments influence this intricate connection between the brain and the gut (164). This valuable information helps identify the most efficient approaches to maintaining a harmonious balance between these two essential systems (165).

The application of metabolomics in the development of personalized medicine

Metabolomics holds immense promise for the development of personalized medicine (166). Metabolomics can offer a thorough insight into the distinct metabolic traits of individuals, crucial for tailoring medical treatments to their specific requirements (Fig. 3). In addition, it is possible to compare the metabolic profiles of healthy people with patients, and this approach makes it possible to identify specific biomarkers changed in each disease and the microbial species associated with them (167). Given the necessity to identify biomarkers or microbial species associated with disorders in each individual posing these methods, it can be stated that the treatment's efficacy has notably risen while endeavoring to minimize potential side effects of existing treatments (168). These biomarkers can serve as diagnostic tools for early detection or prognostic indicators guiding treatment decisions and predicting disease progression (169). Moreover, metabolomics enables researchers to gain insights into the underlying biological processes and molecular pathways involved in diseases, thereby identifying potential therapeutic targets and contributing to the development of personalized treatments (170).

As metabolomics merges with other omics data, a more thorough comprehension of the biological system being studied becomes achievable. This multidisciplinary approach aids in pinpointing stronger and dependable biomarkers, thereby enhancing the creation of efficient personalized medicine tactics. Moreover, the notable strides in high-performance metabolomics, encompassing non-targeted metabolomics, alongside sciences like machine learning and bioinformatics, offer an apt foundation for extensive data analysis, aligning well with the rapid progress of personalized medicine.

As research in this field progresses, the potential for more accurate diagnoses, improved treatment strategies, and better patient outcomes continues to grow, revolutionizing the way we approach healthcare (168,171).

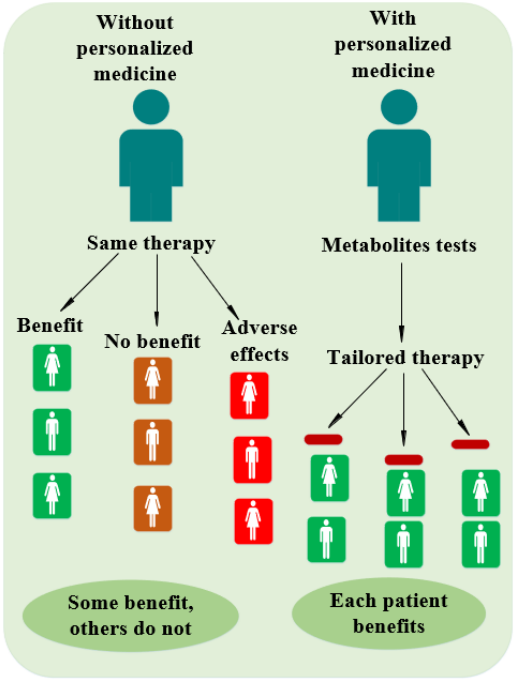

Fig. 3. The role of metabolomics in the development of personalized medicine. Applying the metabolomics approach in line with the advancement of personalized medicine makes it possible to design and implement targeted treatments based on altering the metabolite profile of each individual. Therefore, improved results can be expected. However, employing the same treatment approaches for all patients may diminish the effectiveness of the results.

Methods

This review is based on PubMed, Web of Science, Scopus, and Google Scholar databases using the MeSH terms: "Inflammatory bowel diseases", "Metabolomics", "Anxiety", "Depression", and "Gastrointestinal Microbiome"; the period of the search was from 2005 to 2023.

This study included all articles, whether about humans or animals, written in English; they were related to three sections: intestinal microbial changes in IBD, metabolite changes in IBD, and the relationship between IBD and mental disorders, included in our review. The original and review studies were considered; articles not focusing on IBD were excluded. The authors independently reviewed the articles for title and abstract eligibility. The full text of the articles was subsequently studied independently by the authors. Finally, relevant information was extracted from articles about the research objective. Following a comprehensive examination of the complete texts, we ultimately selected 90 articles for our review.

CONCLUSION

In humans, variations in behavior and neurobiological aspects are closely connected to the composition of the gut microbiome (172). Certain species of gut bacteria can increase stress reactivity, leading to a higher risk of anxiety and depression. It is well-established that individuals with IBD often experience a high rate of co-occurring mental disorders. In addition, growing research highlights the influence of the gut microbiome and microbial metabolites on anxiety and depression-related behaviors (173,174).

The study of microbial metabolites can provide good insight into the relationship between gut microbiota and mental disorders in IBD. The precise identification of these key metabolites, through identifying the signaling pathways they regulate, will better define how this complex communication is established. The metabolomics approach achieves this goal due to the examination of the metabolic profile. As metabolomics studies in this field have shown, different types of SCFAs containing acetate, propionate, succinate, and butyrate are also effective on brain function due to their effect on the function of the intestinal barrier and immune responses as well as the synthesis of neurotransmitters. A decrease in their levels causes disorders in brain function (103-105).

Certain bile acids like LCA and TCDCA have been discovered to cause brain function disorders by binding to their respective receptors, disrupting tight junction expression, and increasing cell permeability. Other metabolites such as L-pipecolic acid, derived from the breakdown of L-lysine in the brain, enhance behavior by activating the GABA receptor (33,116).

Other signaling pathways that can elucidate the link between gut microbiota and mental disorders involve the BDNF signaling pathway. Through the activation of PLCγ, JAK/STAT pathway, PI3K/Akt, and MAPK, this pathway plays a crucial role in the development, viability, and synaptic connections of the nerve cells. Decreased BDNF levels in patients with IBD may be associated with symptoms of anxiety and depression (117,119-121). Tryptophan and its metabolic pathways, like the kynurenine pathway accompanying its metabolites such as serotonin, are linked to brain function. Disorders in their production or signaling, possibly due to intestinal microbial dysbiosis, can lead to anxiety and depression symptoms in IBD patients. In addition, disruption in the signaling of tryptophan metabolites through dysregulation of the glutamate receptor leads to the development of neurodegenerative diseases (122,138).

Inflammatory factors like NF-kB, ILs, INFs, and TNFα, elevated in IBD patients, can cause behavioral disorders by affecting the synthesis and activity of neurotransmitters like dopamine and its derivatives. In addition, the increase in inflammation through the increase in oxidative stress can lead to a decrease in the integrity of the BBB, the death of nerve cells, and brain dysfunction. Increased inflammation also leads to the development of symptoms similar to anxiety and depression through increased nitrites and iNOS (143-147). Studies of sphingolipids also show that certain types of them, such as ceramide, are involved in regulating the death of nerve cells and may be related to mental disorders (148-153).

Metabolomics better describes host-microbe interactions. As the study of the metabolites involved in the two-way communication between the CNS of the host and the microbiota shows, establishing the brain-intestinal axis is necessary to regulate the secretion of digestive enzymes and maintain intestinal homeostasis. Some host responses to stress are also controlled through this bidirectional communication, including activation of the HPA axis by stress. The dysregulation of these responses may be related to the occurrence of symptoms related to anxiety and depression in IBD patients (115, 155).

Metabolomics allows for assessing the effects of interventions aimed at altering gut or brain function by analyzing associated metabolites. Dietary changes, smoking, alcohol consumption, environmental pollution, medications, and probiotic intake can all impact the gut-brain axis. Tracking the metabolites resulting from these interventions can help determine the most effective strategies to promote a healthy balance between the brain and gut (161,163-165).

Metabolomics' ability to identify each individual's metabolic profile has made it a powerful tool in advancing personalized medicine. This method enables the comparison of the metabolome between healthy individuals and patients. By identifying specific disease-related metabolites, we can potentially discover prognostic biomarkers, facilitate early diagnosis and aid in treatment follow-up. Subsequently, we can identify the microbial species associated with these metabolites. This data is essential for creating customized treatments adapted to individual needs. Ultimately, this could result in enhanced treatment approaches, precise diagnoses, and improved treatment results, all contributing to the evolution of the healthcare system (166-171).

In conclusion, the integration of metabolomics with intestinal microbiota research has provided valuable insights into the complex relationships between gut microbiota and mental disorders in IBD. This narrative review highlights the potential of metabolomics to uncover novel biomarkers and signaling pathways that may contribute to psychiatric symptoms in IBD patients such as anxiety and depression. Anxiety and depression are more prevalent in patients with IBD, and one of the most important reasons for this phenomenon is the disturbance in their metabolic profile, as well as related metabolisms. The most important of these metabolites, which have been mentioned in various studies, are different types of SCFAs, sphingolipids, bile acids, neurotransmitters, amino acids, immune and inflammatory biomarkers, and neuroprotective factors (Table 1). The balance of these metabolites is disrupted due to the dysbiosis of the intestinal microbiota, which can be caused by various reasons such as increased inflammation, side effects of drugs, or lifestyle changes in patients with IBD. As a result, other disorders such as anxiety and depression occur. A comprehensive examination of the metabolic profile of each patient and comparing it with normal people provides the possibility of predicting the occurrence of mental disorders in these patients. Today, knowledge of metabolomics has made this possibility a reality. Timely identification of metabolites related to anxiety and depression in IBD patients allows for the design and implementation of targeted treatments based on the correct nutritional or pharmaceutical interventions. In addition, by identifying the gut microbes that produce these metabolites, they can be manipulated in a targeted manner to help patients prevent the onset or development of mental disorders.

To validate these findings, future studies should aim to use larger cohorts and explore the therapeutic potential of metabolomics-based approaches in IBD patients with psychological comorbidities. Ultimately, the metabolomic discovery of biomarkers and therapeutic targets holds promise for developing novel diagnostic methods and targeted treatments.

Future directions

Considering the potential of metabolomics in discovering unknown metabolites and mechanisms involved in diseases, it is suggested that this approach be employed to investigate the metabolite profile comprehensively. This could lead to the introduction of effective biomarkers for early detection and diagnosis of diseases. Furthermore, it can help design targeted medicine by identifying appropriate therapeutic targets (175).

Table 1. The changes of microbiota derived metabolites in IBD patients

Metabolizing bacteria	Microbial metabolites	Metabolic pathways	Disorder	Findings	References
Roseburia ***Ruminococcus*** ***Salmonella*** ***Blautia*** ***Phascolarctobacterium*** ***Dialister*** ***Megasphaera***	SCFAs family Acetate Propionate Succinate Butyrate	Carbohydrate metabolism / Fermentation of fibers	CD and UC	Improvement of depressed mood	(99-105)
Bacteroides ***Streptococcus pneumoniae*** ***Pseudomonas aeruginosa***	Sphingolipids family Ceramides	de novo synthesis of ceramide, followed by the formation of various complex sphingolipids	CD and UC	Regulation of mood and neurotransmission	(148-153)
Bacteroides ***Clostridium*** ***Enterococcus*** ***Lactobacillus***	Bile acid family LCA IsoLCA AlloLCA 7-keto-LCA 12-ketoLCA Dehydrolithocholic acid TCDCA	Deconjugation of glycolithocholic acid and Deconjugation of taurocholic acid	CD and UC	Modulating of brain function	(106-114)
Lactobacillus ***Bifidobacterium***	Neurotransmitters GABA	The series of biochemical reactions that involve the synthesis, release, action, reuptake, and degradation of neurotransmitters in the nervous system.	UC and CD	Anti-depressant effect	(33,72) (115,116) (139-142) (13)
Bacillus subtilis ***Pseudomonas putida*** ***Rhodococcus rhodochrous***	L-pipecolic acid				
Enterococcus ***Akkemansia*** ***Escherchia coli*** ***Streptococcus*** ***Alistipes*** ***Roseburia***	Serotonin				
Staphylococcus aureus ***Escherchia coli*** ***Bacillus cereus*** ***Bacillus mycoides*** ***Bacillus subtilis*** ***Serratia marcescens***	Dopamine				
Lactobacillus ***Bifidobacterium***	BDNF	Growth and survival of neurons in the central and peripheral nervous system, synaptic plasticity, learning and memory	IBD	Anti-depressant effect	(117-121)
Bacteroides thetaiotaomicron ***Clostridium sporogenes*** ***Clostridium beijerinckii*** ***Escherichia coli*** ***Lactobacillus acidophilus*** ***Lactobacillus reuteri*** ***Bifidobacterium longum*** ***Bifidobacterium breve***	Tryptophan	Serotonin pathway Kynurenine Pathway Indole pathway	CD and UC	Anti-depressant effect	(122-138)

Table 1. Continued

Lactobacillus ***Bifidobacterium*** ***Clostridium*** ***Escherichia coli*** ***Streptococcus*** ***Salmonella*** ***Pseudomonas***	Inflammatory markers IL-1β, IL-6 NFkB NLRP3 IFN-γ TNFα	The activation of the JAK-STAT and MAPK signaling pathways, which in turn activate transcription factors, such as STAT3, AP-1, and CREB, which regulate the expression of genes involved in inflammation, cell survival, and apoptosis.	UC and CD	Psychological and behavioral impairment	(143-147)
Bacteroides ***Prevotella*** ***Streptococcus*** ***Pseudomonas*** ***Escherichia coli***	Nitrite	The reduction of NO through the denitrification process	IBD	Behavioral symptoms associated with anxiety and depression	(145)
Proteobacteria	iNOS	The conversion of L-arginine to NO and L-citrulline	IBD	Behavioral symptoms associated with anxiety and depression	(145)

CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; SCFAs, short-chain fatty acids; LCA, lithocholic acid; TCDCA, taurochenodeoxycholic acid; GABA, gamma aminobutyric acid; BDNF, brain-derived neu-rotrophic factor; IL, interleukin; NLRP3, NOD-like receptor protein 3; IFNγ, interferon-gamma; TNFα, tumor necrosis factor α; JAK/STAT, Janus kinase-signal transducer and activator of transcription; MAPK, mitogen-activated protein kinases; NFkB, nuclear factor kappa-light-chain-enhancer of activated B cells; AP-1, activator protein 1; CREB, cAMP response element-binding protein; NO, nitric oxide; iNOS, inducible nitric oxide synthase.

This technique can be integrated with other omics technologies, such as metagenomics and proteomics, to better understand the functions of microbes and proteins in the body. By utilizing these approaches effectively, we can gain a comprehensive understanding of living organisms, identify metabolic, microbial, and protein disorders, and ultimately lead to the provision of precise and targeted treatments. This, in turn, contributes to improving the healthcare system (167,176).

Metabolomics assesses IBD treatments by monitoring gut microbiome changes and metabolic activities. This helps determine the treatment's effectiveness and identifies side effects on the host's metabolism.

Limitation of metabolomics approach

In addition to its sensitivity and accuracy, the metabolomics approach has limitations and challenges.

Acquiring and maintaining the necessary tools for this method comes with a significant expense; proficiency and skill are essential in sample preparation. In addition, metabolomics results are affected by factors such as age, gender, diet, drug treatment, and environmental temperature and humidity (177,178). However, various techniques such as randomization, matching, stratification, multivariate analysis, and sensitivity analysis are being developed to control the impact of these confounding factors (179).

Identification of metabolites and related pathways is complex and time-consuming. However, by combining it with other omics technologies, the diagnosis and management of diseases could be improved (180).

Acknowledgments

This study was funded by the Vice-Chancellery of Research at Isfahan University of Medical Sciences through Grant No. 3400922.

Conflict of interest statement

The authors declared no conflict of interest in this study.

Authors' contributions

A. Hassanzadeh Keshteli was responsible for the conceptualization, validation, resource provision, review and editing of the article, supervision, and project administration; P. Adibi Sedeh contributed to the conceptualization, methodology, validation, and securing of funding; P. Zarei collected and

analyzed the data, interpreted the results, and drafted the article; A. Vaez participated in obtaining funding. All authors have read and agreed to the published version of the manuscript. The finalized article was read and approved by all authors.

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