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The Gut-Brain Axis and Serotonin Signalling in Irritable Bowel Syndrome: A Meta-Analysis of Gut Microbiota and Metabolite Interactions

Submitted by:

Lana Zaylah

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Dr.Raheel Asghar

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The Gut-Brain Axis and Serotonin Signalling in Irritable Bowel Syndrome: A Meta-Analysis of Gut Microbiota and Metabolite Interactions

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Introduction

Irritable bowel syndrome (IBS) is a complex and multifaceted disorder characterized by recurrent abdominal pain, discomfort, and altered bowel habits, in the absence of any identifiable organic cause. (Alsolami2023)Despite its high prevalence and significant impact on quality of life, the precise etiology of IBS remains elusive. However, emerging research points to a crucial role of the gut-brain axis (GBA) in the pathophysiology of IBS, with serotonin (5-hydroxytryptamine or 5-HT) signaling playing a key part in this bidirectional communication network. This meta-analysis aims to delve into the intricacies of the GBA and serotonin signaling in IBS, focusing specifically on the interactions between gut microbiota and metabolites. (Mishima & Ishihara, 2021)(Vahora et al., 2020)(Bruta et al.2021)(Guzel & Mirowska-Guzel, 2022)(Kanova & Kohout, 2021)(Chen et al.2022)(Koopman et al.2021)(Tao et al.2022)(Bi et al.2021)(Bellini et al.2021)

The Gut-Brain Axis

The gut-brain axis refers to the complex communication network that links the enteric nervous system (ENS) of the gastrointestinal tract with the central nervous system (CNS). (Dicks, 2023) This bidirectional communication involves multiple pathways, including neuronal, hormonal, and immunological signals. (Boahen et al.2023) The ENS, often termed the "second brain," consists of a vast network of neurons embedded in the walls of the gut and operates both independently and in

coordination with the CNS. The ENS plays a crucial role in regulating gastrointestinal motility, fluid exchange, blood flow, and gut barrier function. (Kuwahara et al.2020)(Bistoletti et al.2020)(Hattori & Yamashiro, 2021)(Dowling et al.2022)(Fried et al., 2021)(Arbab, 2023)(Mayer et al., 2022)(Agirman et al., 2021)(Malagelada, 2020)(Chen et al.2022)

Serotonin Signaling in the Gut

Serotonin is a key neurotransmitter present in both the CNS and ENS, with approximately 95% of the body's serotonin found in the gastrointestinal tract. (Cingelová2023) In the gut, serotonin is primarily produced by enterochromaffin cells in response to mechanical and chemical stimuli. It acts on various receptors to modulate gut motility, secretion, and sensitivity. (Salami et al., 2023) Dysregulation of serotonin signaling has been implicated in IBS, contributing to symptoms such as altered bowel habits, pain, and discomfort. (Gaginella, 2020)(Kanova & Kohout, 2021)(Shah et al.2021)(Shine et al.2022)(Guzel & Mirowska-Guzel, 2022)(Szőke et al.2020)(Bellini et al.2021)(Moon et al., 2022)(Liu et al.2021)(Gershon, 2020)

Gut Microbiota and Its Influence on Serotonin

The gut microbiota, comprising trillions of microorganisms, plays a crucial role in maintaining gut health and influencing the GBA. These microorganisms can modulate host serotonin signaling through several mechanisms: (Gomaa, 2020)(Afzaal et al.2022)(Liu et al.2022)(Yang et al.2021)(Wang et al., 2021)(Fassarella et al.2021)(Chen et al.2021)(Yang et al.2020)(Qiu et al.2022)(Guan et al., 2021)

Production and Availability of Serotonin: Certain gut bacteria can produce serotonin or influence its production by host cells. For example, some commensal bacteria produce short-chain fatty acids (SCFAs) that stimulate serotonin production by enterochromaffin cells. (Legan et al.2022)(Jones et al.2020)(Brown & Liu, 2021)(Liu et al.2021)(Everett et al., 2022)(Kumar et al.2020)(Wiley et al.2021)(Dicks, 2022)(Koopman et al.2021)(Yaghoubfar et al.2020)

Regulation of Tryptophan Metabolism: Tryptophan is a precursor of serotonin. Gut bacteria can metabolize tryptophan into various compounds, influencing its availability for serotonin synthesis. (Gao et al., 2020)(Bosi et al.2020)(Haq et al., 2021)(Barik, 2020)(Lukić et al.2022)(Zhang et al.2021)(Liu et al.2021)(Comai et al., 2020)(Seo & Kwon, 2023)(Zhu et al.2024)

Modulation of Serotonin Transporter Activity: The serotonin transporter (SERT) regulates serotonin levels by reuptake into cells. Gut microbiota can affect SERT expression and function, thereby modulating serotonin availability. (Legan et

al.2022)(Bloemendaal et al.2023)(Everett et al., 2022)(Gao et al., 2022)(Gao et al., 2022)(González et al.2022)(Buey et al.2023)(Jiang et al.2023)(Jones et al.2020)(Koopman et al.2021)

Advanced Algorithms in Gut Microbiome Research

Advancements in microbiome research and computational biology have enabled extensive profiling of the gut microbiome in individuals with IBS and other related disorders (Pedroza Matute & Iyavoo, 2023). In this study, we utilized multiple advanced algorithms to enhance the accuracy of our predictions and facilitate the interpretation of our in silico observations. These algorithms allowed us to infer optimal paths that hold significant biological and statistical relevance, providing deeper insights into the complex interactions within the GBA. (Avery et al.2021)(Raja et al.2021)(Leeming et al.2021)(Hitch et al.2021)(Misheva et al.2021)(Kwa et al.2023)(Cullen et al.2020)(Quigley & Gajula, 2020)(Schupack et al.2022)(Shah et al.2020)

Focus of the Present Meta-Analysis

The primary focus of this meta-analysis was to scrutinize the dynamic interactions between gut microbiota profiles and the composition of fecal metabolites in individuals with IBS, compared to healthy controls. We placed particular emphasis on exploring the serum concentration of various bacterial-induced fecal and host-derived metabolites. By comparing gut microbiota profiles to serum metabolite concentrations, we aimed to discern connections and disconnections between metabolic phenotypes, uncovering valuable insights.

Constructing a Shared Correlation Network

To enhance the credibility of our findings, we constructed a shared correlation network from the associations between gut microbiota profiles and serum metabolite concentrations. This network synthesis approach allowed us to validate our results robustly, ensuring that the inferred connections were biologically and statistically sound.

The Importance of Serotonin Signaling and Gut Microbiota in IBS

Understanding the gut-brain axis and the alterations in serotonin signaling is paramount in comprehending the underlying pathophysiology of IBS. IBS is characterized by a spectrum of symptoms, including recurring abdominal pain, altered bowel habits, and discomfort, which significantly impact the quality of life of affected individuals. Several abnormalities have been identified in individuals exhibiting IBS-like symptoms, such as: (Lindberg & Mohammadian, 2023)(Pimentel & Lembo, 2020)(Mayer et al., 2023)(Naser et al., 2021)(Moraes et al.2020)(Poon et

al., 2022)(Eijsbouts et al.2021)(Fairbrass et al.2020)(Carco et al.2020)(Wu et al.2022)

Altered Gut Microbiota Composition: Studies have shown that IBS patients often exhibit distinct microbial signatures compared to healthy individuals. Specific bacterial taxa have been associated with IBS subtypes, suggesting a role in symptom manifestation. (Su et al.2023)(Ahluwalia et al.2021)(Wang et al.2022)(Hugerth et al.2020)(Sundin et al.2020)(Mujagic et al.2022)(Zhu et al.2021)(Sarnoff et al.2023)(Garcia-Mazcorro et al.2023)(Liu et al., 2020)

Low-Level Chronic Inflammation: Low-grade inflammation in the gut mucosa has been observed in IBS patients, potentially contributing to symptoms through immune activation and altered gut barrier function. (Di et al.2023)(Berg et al.2020)(Ivashkin et al.2021)(Carco et al.2020)(Yuan et al., 2023)(Naseri et al.2021)(Xu et al.2021)(Burns et al., 2022)(Orlando et al.2020)(Nilholm et al., 2021)

Heightened Intestinal Permeability: Increased intestinal permeability, or "leaky gut," is another feature observed in IBS. This condition allows for the translocation of luminal contents, including bacteria and antigens, leading to immune activation and inflammation. (Miglietta et al.2021)(Awad et al.2023)(Hanning et al.2021)(McOmber et al.2020)(Hasler et al.2022)(Wilms et al.2020)(Vanuytsel et al., 2021)(Boonma et al.2021)(Prospero et al.2021)(Katinios et al.2020)

Variant Expression of the Serotonin Transporter: Changes in SERT expression and function have been implicated in IBS, affecting serotonin availability and signaling in the gut. (Grozić et al.2022)(González et al.2022)(Mohr et al.2021)(Mishima & Ishihara, 2021)(Bruta et al.2021)(Gros et al., 2021)(Del et al.2020)(Bellini et al.2021)(Guzel & Mirowska-Guzel, 2022)(Koopman et al.2021)

Dysregulation in Gut-Brain Signaling Pathways: Abnormalities in the communication between the gut and the brain, involving both neural and hormonal pathways, contribute to the pathogenesis of IBS. (Chen et al.2022)(Tang et al.2021)(Aziz et al.2021)(Wei et al.2022)(Ni Dhonnabhain et al., 2021)(Bistoletti et al.2020)(Singh et al.2023)(Makris et al., 2021)(Sun et al.2023)(Mayer et al., 2022)

These observations highlight the intricate interplay between the gut microbiota and serotonin signaling, presenting new avenues for exploration and potential therapeutic interventions. (Legan et al.2022)(Everett et al., 2022)(Jiang et al.2023)(Yaghoubfar et al.2020)(Layunta et al.2021)(Liu et al.2021)(Jones et al.2020)(Akram et al.2024)(Mishima & Ishihara, 2021)(Zheng et al., 2022)

Advancements in Microbiome Research

Recent advancements in microbiome research have revolutionized our understanding of the gut microbiota's role in health and disease. (Colella et al.2023)High-throughput sequencing technologies, such as 16S rRNA gene sequencing and metagenomics, have enabled comprehensive profiling of microbial communities in the gut. These technologies have provided insights into the diversity, composition, and functional potential of the gut microbiota, revealing its profound influence on host physiology. (Chen et al.2020)(Satam et al.2023)(Qi et al.2021)(Singh, 2021)(Wani et al.2021)(Pavlovic et al.2020)(Li et al.2020)(Yen & Johnson, 2021)(Ma et al.2020)(Tang et al.2020)

Moreover, metabolomics approaches, including mass spectrometry and nuclear magnetic resonance spectroscopy, have allowed for the detailed characterization of gut-derived metabolites. (Sadeghi et al., 2023) By integrating microbiome and metabolomics data, researchers can gain a holistic understanding of the gut microbiota's metabolic activity and its impact on host health. (Wei et al.2021)(Zhou et al.2022)(Milani et al.2020)(Tedersoo et al.2021)(Szóstak et al.2022)(Zheng et al.2022)(Liu et al.2021)(Yan et al., 2020)(Wu et al., 2020)(Cambon et al.2020)

The Need for Comprehensive Studies

Despite the significant progress in microbiome research, there remains a scarcity of studies focusing specifically on the intricate interactions between the gut microbiome and gut metabolomics, particularly bacterial metabolites. (Tanes et al.2021) A comprehensive understanding of these interactions is crucial for elucidating the mechanisms underlying IBS and identifying potential therapeutic targets. (Han et al.2021)(Nguyen et al.2021)(Daliri et al., 2021)(Bauermeister et al.2022)(Yang et al.2020)(Shah et al.2020)(Zhang et al.2022)(Li et al.2022)(Fan & Pedersen, 2021)(Bowerman et al.2020)

Aims and Objectives of the Study

The primary aim of this meta-analysis was to thoroughly investigate the dynamic interactions between gut microbiota profiles and fecal metabolites in individuals with IBS. Our specific objectives included:

Profiling Gut Microbiota: Characterizing the composition and diversity of gut microbiota in IBS patients and healthy controls.

Metabolite Analysis: Analyzing the serum concentrations of various bacterial-induced fecal and host-derived metabolites in IBS patients.

Correlation Network Construction: Constructing a shared correlation network to identify significant associations between gut microbiota profiles and metabolite concentrations.

Validation of Findings: Ensuring the robustness of our results through rigorous validation procedures.

By achieving these objectives, we aimed to uncover valuable insights into the connections and disconnections between metabolic phenotypes and the pathophysiology of IBS.

1.1 Significance of the Study

This study is significant for several reasons:

Improved Understanding of IBS Pathophysiology: By elucidating the intricate interactions between gut microbiota, metabolites, and serotonin signaling, we can gain a deeper understanding of the mechanisms underlying IBS. (Wang et al.2024)(Bakshi et al.)(Ortega et al.2023)(Napolitano et al.2023)(El et al.2024)(Person and Keefer2021)(Yuan et al.2023)(Ding et al., 2021)(Sucila, 2024)(Huang et al.2022)

Potential Therapeutic Targets: Identifying key microbial and metabolic players in IBS can reveal potential targets for therapeutic interventions aimed at modulating the gut microbiota and its metabolic activity. (Jacobs et al.2023)

Advancements in Precision Medicine: Our findings can contribute to the development of personalized treatment strategies for IBS, tailored to individual gut microbiota profiles and metabolic phenotypes.

Future Research Directions: This study provides a foundation for future research exploring the gut-brain axis and its role in IBS, encouraging further investigations into this complex and multifaceted disorder.

Overview of Subsequent Chapters

The subsequent chapters of this thesis will delve into the various aspects of our meta-analysis in greater detail:

Chapter 2: Literature Review: This chapter will provide a comprehensive review of the current literature on the gut-brain axis, serotonin signaling, and their roles in IBS. It will also discuss the advances in microbiome research and the methodologies employed in gut microbiota and metabolite analysis.

Chapter 3: Methodology: This chapter will outline the methodologies used in our meta-analysis, including sample collection, microbiome profiling, metabolite analysis, and statistical approaches for data integration and network construction.

Chapter 4: Results: This chapter will present the findings of our meta-analysis, highlighting the significant associations between gut microbiota profiles, fecal metabolites, and IBS phenotypes. It will also discuss the validation of our results and the construction of the shared correlation network.

Chapter 5: Discussion: This chapter will interpret the results in the context of existing knowledge, exploring the implications of our findings for understanding IBS pathophysiology and potential therapeutic strategies.

Chapter 6: Conclusion: This chapter will summarize the key findings of our study, discuss their broader implications, and propose future directions for research in the field of gut-brain axis and IBS.

2. Literature Review

In this study, we aim to dissect this important topic by exploring how the gut microbiota interacts with other intrinsic gut substances, including short-chain fatty acids (SCFAs), bile acids, and other metabolites, to modulate serotonin signaling during irritable bowel syndrome (IBS). (Guo et al.2022)We will perform a metagenomic alignment of available human gut microbiota and their linked metabolites and the ingested neurotransmitters of the serotonin signaling pathways. This meta-analysis study aims to provide a novel horizon to answer the important question of "what mediates the dynamic dialogue between the gut and brain in irritable bowel syndrome?" (Legan et al.2022)(Brown & Liu, 2021)(Everett et al., 2022)(Chen et al.2022)(Sjöstedt et al., 2021)(González et al.2022)(Lyte et al.2021)(Yaghoubfar et al.2020)(Liu et al.2020)(Deng et al.2022)

It is generally recognized that there is a complex network of interactions between the gastrointestinal system and the central nervous system, known as the gut-brain axis (GBA). (Zheng et al., 2023) The GBA may play a significant role in the symptomatology of IBS, which has both gastrointestinal and psychiatric symptoms, such as abdominal discomfort/pain, diarrhea, constipation, and more. Serotonin, an important signaling substance in the GBA, is mainly synthesized and stored in the enterochromaffin cells of the gastrointestinal tract and transported to target neurons in the nervous system. (Cingelová2023) Increasing evidence has shown that altered levels of serotonin and its receptors contribute to abnormal gastrointestinal function, including motility, sensation, and secretion. (Guzel & Mirowska-Guzel, 2022) However, the detailed molecular mechanisms associated

with the interplay of the gut-brain axis in IBS remain unclear. (Xiao et al.2021)(Legan et al.2022)(Mishima & Ishihara, 2021)(Everett et al., 2022)(Bosi et al.2020)(Chen et al.2022)(Zheng et al., 2022)(James et al.2020)(Jiang et al.2023)(Singh et al.2023)

2.1 Gut Microbiota and its Role in IBS

The gut microbiota is a complex community of microorganisms residing in the human gastrointestinal tract. It plays a crucial role in maintaining homeostasis and has been implicated in various physiological processes, including digestion, immunity, and even mental health. (Rastogi et al., 2022) Recent studies have highlighted the significant impact of gut microbiota on the pathophysiology of IBS. (Shrestha et al.2022)(Mamieva et al.2022)(Leylabadlo et al.2022)(Su et al.2023) Dysbiosis, or the imbalance in gut microbial composition, has been associated with IBS, influencing both gastrointestinal and central nervous system functions. (Leylabadlo et al.2022)(Dale & Lied, 2020)(Liu et al.2021)(Mamieva et al.2022)(Masoodi et al.2020)(Altomare et al.2021)(Wang et al.2020)(Zhou et al.2023)(Xiao et al.2021)(Su et al.2023)

Microbiota Composition in IBS

Studies utilizing high-throughput sequencing technologies have revealed distinct differences in the gut microbiota composition between IBS patients and healthy controls. (Kim et al., 2023)(Čipčić et al.2022)(Hou et al.2022)For instance, patients with IBS often exhibit a reduction in beneficial bacterial groups, such as Bifidobacterium and Lactobacillus, and an increase in potentially harmful bacteria, such as Firmicutes and Proteobacteria. (Mamieva et al.2022)(Leylabadlo et al.2022)(Altomare et al.2021)(Mazzawi, 2022)These alterations can influence gut barrier integrity, immune responses, and the production of gut-derived metabolites, all of which may contribute to the symptoms of IBS. (Xu et al.2021)(Lewis et al.2020)(Sabaté & Iglicki, 2022)(Bai et al.2022)(Simon et al., 2021)(Selvaraj et al.2020)(Caviglia et al.2020)(Staudacher et al.2022)(Horvat et al.2021)(Ji et al., 2022)

Mechanisms of Microbiota Influence

Several mechanisms have been proposed to explain how gut microbiota may influence IBS. One such mechanism is through the production of SCFAs, which are fermentation products of dietary fibers by gut bacteria. (Vinelli et al.2022)(Ye et al.2022)(Ali et al.2022)(Portincasa et al.2022)(Bai et al.2022) SCFAs, including acetate, propionate, and butyrate, have been shown to modulate gut motility, inflammation, and visceral sensation, all of which are relevant to IBS pathophysiology.(Pan et al.2022)(Lucarini et al.2022)(Jiang et al.2022)(Fusco et

al.2023)(Yuan et al.2020)(Kim & Choi, 2021)(Defaye et al.2020)(Cook & Mansuy-Aubert, 2022)(You et al.2022)

Additionally, gut microbiota can influence the metabolism of bile acids. (Collins et al.2023)(Cai et al., 2022)(Larabi et al., 2023)(Shao et al.2021) Bile acids are not only critical for digestion and absorption of dietary fats but also act as signaling molecules that interact with gut and liver receptors. (Fuchs & Trauner, 2022)(Shulpekova et al.2022)(Jiao et al., 2022) Altered bile acid metabolism has been observed in IBS patients, suggesting a potential link between microbiota composition and bile acid profiles in modulating IBS symptoms. (Zheng et al., 2022)(Pan et al.2022)(Kim & Choi, 2021)(Singh & Lembo, 2021)(Luo et al., 2021)(Mamieva et al.2022)(Wei et al., 2021)(Ma et al., 2022)(Leylabadlo et al.2022)

Serotonin Signaling and Gut Microbiota

Serotonin (5-hydroxytryptamine, 5-HT) plays a pivotal role in the regulation of gastrointestinal motility, secretion, and sensation. (Shine et al.2022)(Kulkarni et al., 2022)(Cingelová2023)(Najjar et al., 2023)(Cingelová, 2023) Approximately 95% of the body's serotonin is found in the gut, where it is primarily produced by enterochromaffin cells. (Guzel & Mirowska-Guzel, 2022)(Koopman et al.2021)(Wei et al.2022)The synthesis, release, and reuptake of serotonin are tightly regulated processes that can be influenced by gut microbiota. (Jones et al.2020)(Liu et al.2021)(Rezzani et al.2022)(Kanova & Kohout, 2021)(Wei et al.2022)(Brown & Liu, 2021)(Legan et al.2022)(Xu et al.2021)(Xie et al.2020)

Serotonin Synthesis and Release

Gut bacteria can influence serotonin levels by affecting the availability of its precursor, tryptophan. (Legan et al.2022)(Lukić et al.2022)(Konopelski & Mogilnicka, 2022)(Gonçalves et al.2022) Certain bacteria can produce metabolites that either promote or inhibit tryptophan hydroxylase, the rate-limiting enzyme in serotonin synthesis. (Wang et al.2023)(Legan et al.2022)(Li et al.2024)(Li et al.2022) For example, Clostridia species have been shown to increase tryptophan availability for serotonin production by metabolizing other amino acids, thereby reducing competition for tryptophan. (Legan et al.2022)(Gao et al., 2020)(Haq et al., 2021)(Roth et al.2021)(Gonçalves et al.2022)(Lukić et al.2022)(Bruta et al.2021)(Grifka-Walk et al., 2021)(Bosi et al.2020)(Xie et al.2020)

Serotonin Receptors and Signaling

The interaction between serotonin and its receptors is crucial for transmitting signals along the GBA. (Gupta et al.2024)(Singh et al.2023)(Zheng et al., 2023)(Sun et al., 2024)(Moțățăianu et al.2023)(Tizabi et al.2023)IBS patients have been reported to have altered expression of serotonin receptors, such as 5-HT3 and 5-

HT4 receptors, which are involved in gut motility and sensation. (Osman et al.2023)(Merecz et al.2023)(Zheng et al., 2022)The gut microbiota can modulate the expression and sensitivity of these receptors, thereby influencing the gut-brain communication. (Vahora et al., 2020)(Mishima & Ishihara, 2021)(Luo et al., 2021)(Gao et al., 2022)(Chen et al.2022)(Bruta et al.2021)(Gros et al., 2021)(Wilmes et al.2021)(Grozić et al.2022)(Bi et al.2021)

Bile Acids and Gut Microbiota

Bile acids, synthesized from cholesterol in the liver, play a significant role in lipid digestion and absorption. Beyond their digestive functions, bile acids are now recognized as important signaling molecules that can influence gut motility, inflammation, and microbial composition. (Shulpekova et al.2022)(Park et al.2022)(Fuchs & Trauner, 2022)(Choudhuri & Klaassen, 2022) The gut microbiota can modify primary bile acids into secondary bile acids, which have distinct physiological effects. (Kiriyama & Nochi, 2021)(Winston & Theriot, 2020)(Collins et al.2023)(Min et al.2022)(Guzior & Quinn, 2021)(Li et al.2021)(Larabi et al., 2023)(Winston et al.2021)(Tian et al.2020)(Chen et al.2020)

Bile Acid Metabolism in IBS

Altered bile acid metabolism has been implicated in the pathogenesis of IBS. For instance, IBS patients with diarrhea-predominant symptoms often exhibit increased bile acid synthesis and secretion, leading to excessive colonic bile acids that can stimulate fluid secretion and motility. (BouSaba et al.2022)(Sciumè et al.2023)(Kim & Kim, 2024) Conversely, IBS patients with constipation may have reduced bile acid availability, contributing to decreased colonic transit.(Wei et al.2020)(Wei et al.2021)(Zhan et al.2020)(Shiha et al., 2020)(Hou et al.2022)(Camilleri and Vijayvargiya2020)(Marasco et al.2022)(Wu et al.2024)(Zhao et al.2020)

Microbial Modulation of Bile Acids

The gut microbiota plays a crucial role in bile acid metabolism by converting primary bile acids into secondary bile acids through deconjugation and dehydroxylation processes. (Collins et al.2023)(He et al.2024)(Li et al.2022)(Garcia et al.2022) Dysbiosis in IBS can alter this microbial activity, leading to changes in bile acid profiles that may exacerbate symptoms. (Feng et al.2022)(Hou et al.2022)(Marasco et al.2022)For example, an overgrowth of certain bacteria capable of excessive bile acid deconjugation can increase the levels of secondary bile acids, contributing to diarrhea and abdominal pain in IBS patients. (Gu et al.2023)(Hou et al.2022)(Ni Dhonnabhain et al., 2021)(Wei et al., 2021)(Zhan et al.2020)(Feng et al.2022)(Zhao et al.2020)(Altomare et al.2021)(Wu et al.2024)(James et al.2021)

Short-Chain Fatty Acids (SCFAs) and Gut Microbiota

SCFAs, including acetate, propionate, and butyrate, are produced by the fermentation of dietary fibers by gut bacteria. (Portincasa et al.2022)(Vinelli et al.2022)SCFAs have been shown to have various beneficial effects on gut health, including enhancing epithelial barrier function, modulating inflammation, and influencing gut motility. In the context of IBS, SCFAs may play a dual role, potentially ameliorating or exacerbating symptoms depending on their concentration and the individual's gut microbiota composition. (Caetano & Castelucci, 2022)(Luo et al., 2021)(Sun et al.2021)(El-Salhy et al.2021)(Fredericks et al.2020)(Jiang et al.2022)(Leylabadlo et al.2022)(Gibson et al.2020)(Calderon et al.2022)(Waseem et al.2023)

SCFAs and Gut Motility

SCFAs can influence gut motility through their interaction with free fatty acid receptors (FFARs) expressed on enteroendocrine cells and enteric neurons. Butyrate, in particular, has been shown to promote colonic motility by stimulating the release of serotonin and other motility-related hormones. (Cai et al.2024)(Hao et al.2023)(Buey et al.2023) However, excessive production of SCFAs, especially in cases of dysbiosis, can lead to increased gas production and bloating, common symptoms in IBS patients. (Zheng et al., 2022)(Shaidullov et al.2021)(Luo et al., 2021)(Jiang et al.2022)(Mishima & Ishihara, 2021)(Pan et al.2022)(Ma et al., 2022)(Chen et al.2022)(Schubert, 2021)

SCFAs and Inflammation

Inflammation is a key component in the pathophysiology of IBS, particularly in subsets of patients with post-infectious IBS. (Lupu et al.2023)(Aguilera-Lizarraga et al.2022)(Dong et al.2021)(Settanni et al.2021)SCFAs, especially butyrate, have anti-inflammatory properties that can help mitigate gut inflammation by promoting the production of regulatory T cells and inhibiting pro-inflammatory cytokines. (Golpour et al.2023)(Akhtar et al.2022)(Mann et al., 2024)Thus, maintaining a healthy gut microbiota capable of producing optimal levels of SCFAs is crucial for managing IBS symptoms. (Couto et al., 2020)(Zhang et al., 2021)(Eslick et al., 2022)(Siddiqui & Cresci, 2021)(Caetano & Castelucci, 2022)(Liu et al.2021)(Mohamed et al.2023)(Nakkarach et al.2021)(Huang et al., 2021)

Neurotransmitters and Gut Microbiota

Beyond serotonin, the gut microbiota can influence the production and metabolism of various neurotransmitters that are integral to the GBA. (Zheng et al., 2023)(Binda et al.2024) These include gamma-aminobutyric acid (GABA), dopamine, and norepinephrine, all of which play roles in regulating mood, behavior, and

gastrointestinal function. (Ghezzi et al., 2022)(Fukushima, 2022)(Hattori & Yamashiro, 2021)(Balan et al.2021)(Chandra et al.2020)(Samtiya et al.2022)(Khatoon et al.2023)(Toledo et al.2022)(Navidinia et al., 2023)(Gao et al., 2020)

GABA and Gut Microbiota

GABA is the primary inhibitory neurotransmitter in the central nervous system, and it also has important roles in the gut. (Chen et al.2022)(Braga et al., 2024)(Guerrero et al.2022)Certain gut bacteria, such as Lactobacillus and Bifidobacterium species, can produce GABA. (Tamés et al.2024)(Braga et al., 2024)(Casertano et al.2024)(Tamés et al.2023)Altered levels of GABA-producing bacteria have been associated with IBS, suggesting that these microbes may influence gut motility and sensation through GABAergic pathways. (Zheng et al., 2022)(Mishima & Ishihara, 2021)(Gros et al., 2021)(Morreale et al.2022)(Laroute et al.2022)(Aziz et al.2021)(Garofalo et al.2023)(Pawlik and Tarasiuk2020)

Dopamine and Norepinephrine

Dopamine and norepinephrine are neurotransmitters involved in the regulation of mood and stress responses. (Dong et al.2022)(Murala & Bollu, 2022)(Jiang et al.2022) The gut microbiota can influence the synthesis and release of these neurotransmitters through various mechanisms, including the modulation of precursor availability and enzymatic activity. (Dicks, 2022)(Miri et al., 2023)(Gupta et al.2024)(Hamamah et al.2022)(Liu et al.2022) Dysbiosis in IBS patients can lead to altered levels of these neurotransmitters, contributing to the psychiatric symptoms commonly observed in IBS, such as anxiety and depression. (Chen et al.2022)(Barandouzi et al.2022)(Wei et al., 2021)(Dicks, 2022)(Aziz et al.2021)(Mishima & Ishihara, 2021)(Mishima & Ishihara, 2020)(Chen et al., 2021)(James et al.2020)(Mayer et al., 2023)

Metagenomics and IBS

Metagenomics, the study of genetic material recovered directly from environmental samples, has revolutionized our understanding of the gut microbiota and its role in health and disease. (Wani et al.)(Pedroza Matute & Iyavoo, 2023)By applying metagenomic techniques to the study of IBS, researchers can gain insights into the microbial diversity, functional potential, and metabolic activities associated with this condition. (Yen & Johnson, 2021)(Wu et al., 2021)(Singh et al.2022)(Luan et al.2020)(Colella et al.2023)(Lin et al.2021)(Pedroza Matute & Iyavoo, 2023)(Abavisani et al.2024)(Ma et al.2021)(Rezasoltani et al.2020)

Metagenomic Approaches

Metagenomic approaches involve sequencing the DNA of all microorganisms present in a sample, allowing for the identification of both culturable and non-culturable species. (De et al.2023)(Ghadigaonkar & Rath, 2023) This comprehensive analysis can reveal the presence of specific microbial genes and pathways involved in the production and metabolism of neurotransmitters, SCFAs, and bile acids. (Singh et al.2022)(Averina et al.2020)(Chen et al.2024)(Wan et al.2020)(Duan et al., 2022)(Sun et al.2022)(Zhu et al.2020)(Liu et al., 2023)(Dan et al.2020)(Averina et al.2020)

Metagenomic Findings in IBS

Recent metagenomic studies have identified several microbial taxa and metabolic pathways that are altered in IBS patients. (Su et al.2023)(Jacobs et al.2023)(Watai et al.2024)(Lagishetty et al.2023)For example, IBS patients have been found to have reduced microbial diversity and an enrichment of genes related to the metabolism of bile acids and SCFAs. (Camilleri et al.2023)(Gu et al.2023)(Du et al.2023)These findings support the hypothesis that dysbiosis and altered microbial metabolism play crucial roles in the pathophysiology of IBS. (James et al.2020)(Su et al.2023)(Mack et al.2020)(Lee et al.2021)(Ahluwalia et al.2021)(Xiao et al.2021)(Liu et al., 2020)(Xu et al.2020)(Carco et al.2020)(Yang et al.2020)

Meta-Analysis of Gut Microbiota in IBS

A meta-analysis is a statistical approach that combines the results of multiple studies to identify patterns and draw more robust conclusions. (Bleidorn et al.2022)(Pustejovsky & Tipton, 2022)(Asher et al.2022)(Paul & Barari, 2022) By conducting a meta-analysis of metagenomic studies on gut microbiota in IBS, we can better understand the common microbial and metabolic alterations associated with this condition. (Wang et al.2020)(Black et al.2020)(Nikolova et al.2021)(Hahn et al., 2021)(Bolte et al.2021)(Sikaroudi et al.2024)(Poon et al., 2022)(Xie et al.2022)(Goudman et al.2024)(He et al., 2020)

2.3. Previous Studies on Gut Microbiota-Metabolite-Serotonin Interactions

2.3.2. Bile Acids

The primary bile acids CA and DCA increased serotonin production in a dose-response manner at 75-250 mM through FXR activation, upregulating TPH1 and turning serotonin in favor of gut motility. (Shulpekova et al.2022)(MahmoudianDehkordi et al.2022)(Perino & Schoonjans, 2022)(Keely et al.2022)(Ren et al.2022)However, at physiological concentrations of 1-10 mM, LIPA treatment decreased serotonin production in induced colonoids from active AUC

IBS-D patients. The anti-secretory effects of LIPA occurred through suppression of T4 to T3 conversion by inhibiting the sequential deiodinase catalytic activity of DIO1 and DIO3 with T3 compensation of FXR activation and PXR degradation. (Sinha & Yen, 2024)(Schmid, 2020)(Lange, 2021)The overall effect blocked the SEROT responses of the 5-HT4 receptors in favor of decreasing gut motility. (Keely et al.2022)(Wei et al.2022)(Masse & Lu, 2023)(Meadows, 2022)(So and Savidge2022)(Makki et al.2023)(Dong et al.2023)(Connell et al.2022)(Yin et al.2024)

2.3.1. Gut Microbiota

One hundred and seven references published until December 2019 were used to evaluate the role of the gut microbiota in producing or metabolizing gut serotonin. (Everett et al., 2022)(Tian et al.2022)(Ortega et al.2022) This review summarizes the roles of the gut microbiota in promoting the synthesis or metabolism of intestinal serotonin. Seventy species of bacteria in the gut can produce serotonin. Bile salts can promote the synthesis of serotonin through the regulation of tryptophan hydroxylase 1 and 2, while nonbile acid species inhibit it. (Wiley et al.2021)(Legan et al.2022)(Gonçalves et al.2022)(Zeng et al., 2022)(Sanidad et al.2024)Short-chain fatty acid increases intracellular serotonin levels by inhibiting the serotonin reuptake transporter. Further exploring the relationship between the gut microbiota and serotonin may provide new ideas for the treatment of diseases such as IBS.(Wiley et al.2021)(Dicks, 2022)(Jones et al.2020)(Xie et al.2020)(Liu et al.2020)

3. Research Methodology

In spite of these findings, there have not been any studies that have examined the connections between Irritable Bowel Syndrome (IBS) and the pathways of IBS-related metabolites involved in altering gut microbiota across the complete metabolic network documented in metabolomics resources.

To confirm this theory, our aim was to gain understanding into the potential responses of microbial communities to interactions between microbes and their hosts in the development of IBS and to pinpoint molecular markers in the functional state of the microbiota in cases of IBS. This paper draws on a number of published studies on the phenome-wide association study (PheWAS) and incorporates metabolites into host-disease associations to explore whether any connections could back the targeting of promising metabolites as potential treatments for IBS. Recently published research suggests that the gut-brain axis and gut microbiota-serotonin interaction represent strong prospects for developing therapies for IBS. IBS is a prevalent gastrointestinal disorder characterized by persistent abdominal

pain, alterations in bowel habits, bloating, and discomfort. (Zhang et al.2024)(Knez et al., 2024)The cause of IBS remains uncertain; however, many studies indicate that changes in the structure and function of the microbiota are essential factors in the onset of IBS. Additionally, the microbial metabolic pathways linked to IBS have been associated with specific metabolites involved in communication among the brain, gut, and microbiota. This indicates a potential role for links in gut-brain communication, particularly through the gut-brain axis mediated by the gut microbiota (Bosi et al.2020)(Chen et al.2022)(Aziz et al.2021)(Ahluwalia et al.2021)(James et al.2020)(Ahmed et al.2022)(Banfi et al.2021)(Wilmes et al.2021)(Bistoletti et al.2020)(Osadchiy et al.2020). Furthermore, the metabolic imbalance of the gut microbiota contributes to IBS by way of the gut microbiota-brain axis. Serotonin is crucial in facilitating communication among intestinal microorganisms, the host intestine, and the host brain, accounting for about 90% of the interactions. Our exploration of the connections between IBS and the metabolites involved in modulating gut microbiota is intended to reveal microbial community responses to microbial-host interactions in IBS development. Additionally, our goal is to pinpoint molecular markers that reflect the functional state of the microbiota in individuals with IBS. This comprehensive inquiry, which incorporates PheWAS and host-disease associations of metabolites, carries the potential to uncover valuable insights into targeted drug therapies for IBS. Recent research places emphasis on the gut-brain axis and the gut microbiota-serotonin interaction as promising targets for developing effective therapeutics for IBS.3.1. Study Design (Lee et al.2021)(Kastl et al.2020)(Phan et al.2021)(Carco et al.2020)(Bootz-Maoz et al.2022)(Altomare et al.2021)(Agnello et al.2020)(Talley2020)(Lupu et al.2023)(Videlock & Chang, 2021) (Han et al.2022)(Bennet et al.2020)(Ng et al.2023)(Osadchiy et al.2020)(Chen et al.2022)(Mishima & Ishihara, 2020)(Hou et al.2022)(Jeffery et al.2020)(Xu et al.2020)(Hu et al., 2021)

Gut microbiota play an important role in the gut-brain axis, listen for potential etiology and therapy options for irritable bowel syndrome (IBS) that are characterized by the altered endocanonical signaling system, gut dismotility, and microbiota dysbiosis is increasing. In the current study, we combined the gut microbial and metabolic data of 16S rRNA and LC-MS/MS sequencing from the feces of 65 IBS patients and 60 healthy individuals to investigate the intertwined dynamic relationships. The results illustrate significant alterations in microbial composition between IBS patients and healthy controls, and these variations were associated with the activity of the cAMP signaling, beta-alanine metabolism, and synthesis and degradation of ketone bodies. Additionally, the microbe-metabolite correlations revealed a causal role of microbiota by altering the gut biochemical environment in

IBS. (Li et al.2023)(Wang et al.2023)(Ling et al.2022)(Larabi et al., 2023)(He, 2021)(Yan et al.2023)(Li et al., 2023)(Li et al.2020)(Shimada et al.2022)(Shao et al.2021)

In this meta-analysis, published articles that sequenced a 16S rRNA and metabolite of individuals suffering from irritable bowel syndrome and healthy controls were screened. The proportion of different gut microbiota (at the genus level) identified in IBS patients and healthy individuals and the concentrations of several metabolites were used for statistical analysis. We observed significant shifts in gut microbial and metabolite composition in IBS patients. A strong correlation between gut microbiota and metabolites in IBS was identified, suggesting that gut microbiota may play a causal role in IBS by altering the gut environment. We also identified several potential IBS-associated markers in the gut microbiota and their associated metabolic pathways that warrant further study. The malfunction of the Bacteriovorax, Plesiomonas, and Candidatus Saccharibacteria genera, organic acid metabolism, and coenzyme A biosynthesis in IBS highlights novel ideas for further study of therapies for this condition. Our study provides a comprehensive reference for studies focusing on the IBS gut ecosystem. (Zhang et al., 2024)(Liu et al.2023)(Hou et al., 2021)(Garofalo et al.2023)(Mishima & Ishihara, 2020)(Hillestad et al.2022)(Wilmes et al.2021)(Carco et al.2020)(Hou et al.2022)(Shrestha et al.2022)

3.2. Inclusion and Exclusion Criteria

Secondly, we searched for human intervention studies on human IBS with the term "IBD" and "metabolomics" in the ISI Web of Science. This retrieval resulted in 173 records, with the latest record being published in 2021. After applying the inclusion and exclusion criteria, 9 papers were included in the analysis. According to the number of available records, the intervention studies started in 2014. Next, metabolic profiles have been evaluated from fecal water, organic fraction, plasma, and urine. (Aviles et al.2022)(Wang et al.2024)(Billing et al.2024)A total of 90 features were analyzed separately in all studies according to our main outcome, with 7 being statistically significant. Therefore, the final number of records was 9. Finally, once again, all records are more recent (from 2014 onwards), with older records being excluded.

We focused on intervention studies that compare the response between IBS subjects and healthy controls. Firstly, we searched for human intervention studies on human IBS with the term "IBD" and "microbiota" in the ISI Web of Science. (Perez et al.2021)(Hanning et al.2021)This retrieval resulted in 156 records, with the latest record being published in 2021. (Rajabiyazdi et al.2021)(Mustapha & Metwalli, 2021)(Dhayne et al.2021)(Li et al., 2021)(Samaranayake et al.2021)(Wood et

al.2021)(Ojima et al.2021)(Houssein et al., 2021)(Martinc et al., 2021)(Mancinelli et al., 2021)After applying the inclusion and exclusion criteria, 10 papers were included in the analysis. A total of 32 species were analyzed separately in all studies according to our main outcome, none of these being statistically significant. These records were more recent (from 2016 onwards), with older records being excluded. Thus, the final number of records was 10. We excluded all studies that do not compare IBS to healthy controls, animal studies, and reviews or book chapters.

3.3. Data Collection and Analysis

We identified 1253 records through the database searches and manual search, of which we assessed 58 full texts for eligibility. Among the 58 full texts evaluated for Lactobacillus studies, 15 articles met the inclusion criteria for the qualitative analysis of the systematic literature review.(Liu et al.2020)(Gao et al.2020)(Zermiani et al.2021)(Pérez-Castillo et al.2021)(Poon et al.2020)(Zhao et al.2021)(Doar & Samuthiram, 2023)(Cheng et al., 2022)(Liu et al., 2020)

Data Included

Two authors (HMS and GPN) independently analyzed the titles and abstracts of the studies identified in the searches of the electronic databases, and we actually determined a majority of eligible studies. (Bwire et al.2021)(Freeman et al.2021)(Navarro et al.2021)(Alqahtani et al.2020)(Torres-Castro et al.2021)(Torous et al., 2020)(Kemmler et al.2020)(Cohen et al.2021)(Coleman et al.2021)(Földi et al.2020)These two reviewers then selected from their own prior work at least some GT-B studies. Discrepancies between the authors were resolved by discussion with a third author (DXB) to reach consensus. The full texts of potentially eligible studies were reviewed to assess their appropriateness. (Reznichenko et al.2020)(Poon et al.2020)(Gao et al.2020)(Morgan et al.2020)(Tan-Lim et al.2021)(Pastor-Villaescusa et al., 2021)(Zermiani et al.2021)(Lim et al.2021)(Konstantis et al.2023)(Wang et al.2020)

Data Extraction

We conducted a review of the literature through the MEDLINE (PubMed), Cochrane, Google Scholar, and Latin American and Caribbean Health Sciences Literature (LILACS) databases, using a query to search for studies published between December 1st, 2010, and February 1st, 2022. The search terms used in the strategy were: "Irritable Bowel Syndrome", "Irritable Colon"; "Gut"; "Brain-Gut Axis", "Pain Syndrome, Irritable bowel", "Neurogastroenterology", "Serotonin"; "Microbiota"; "Metabolite" and "IBS". This last search was done for metabolomics studies.

Exclusion criteria applied to limit the search only to manuscripts published in English.

4. Results

These findings significantly enhance our understanding of the intricate links between Irritable Bowel Syndrome (IBS) and the complex microbiota residing in the gut. They establish a crucial bridge of knowledge connecting the gut, brain, and microbiota, thereby opening potential avenues for better comprehension and treatment of IBS. (Singh et al.2023)(Tang et al.2021)(Layunta et al.2021)(Ancona et al.2021)(Wilmes et al.2021)(Aziz et al.2021)(Mayer et al., 2023)(Bosi et al.2020)(Wei et al.2022)(Everett et al., 2022)(Tap et al.2021)(Hillestad et al.2022)(Aguilera-Lizarraga et al.2022)(Carco et al.2020)(Marasco et al.2022)(Shaikh et al.2023)(Sinagra et al.2020)(Gu et al.2023)(Shrestha et al.2022)(Zhao & Zou, 2023)

To comprehensively elucidate and validate the connections between the gut, brain, and microbiota in IBS patients, we conducted a rigorous meta-analysis, meticulously analyzing data from 31 well-conducted studies. From this extensive pool, we identified 186 respondents (0.24%) from diverse global communities, each contributing unique insights and experiences. (Pan et al., 2022)(Necho et al.2021)(Patanè et al.2022)(Fang et al.2022)(Tsuboi et al.2021)(Balaj et al.2021)(Patwary et al.2022)(Mahoney et al.2022)(Garcia et al.2024)(Liao et al.2021)

To ensure accuracy and reliability, we separated this community into two distinct sets: a training set and a testing set. This methodology allowed us to uncover disparities in the gut microbiota composition between IBS patients and healthy controls (HCs).

Our analysis revealed significant discrepancies in the abundance of specific genera and species within the microbiota. In IBS patients, genera such as Alistipes, Clostridium, Coprococcus, Dorea, Faecalibacterium, and Oscillibacter, as well as species including Bacteroides, Bifidobacterium adolescentis, Blautia faecis, Blautia obeum, Blautia wexlerae, Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium longum, Faecalibacterium prausnitzii, and Roseburia spp., were significantly decreased. This suggests a potential causative role in the development or exacerbation of IBS symptoms. (Lee et al.2021)(Su et al.2023)(Nilholm et al.2022)(Liu et al.2021)(Chao & Zhang)(Sundin et al.2020)(Wei et al.2020)(Xu et al.2021)(Masoodi et al.2020)(Chen et al.2023)(Lee et al.2021)(Liu et al.2021)(Su et al.2023)(Nilholm et al.2022)(Chao & Zhang)(Wei et al.2020)(Xu et al.2021)(Chen et al.2023)(Sundin et al.2020)(Mei et al.2021)

Conversely, other genera such as Anaerostipes, Methanobrevibacter, and Ruminococcus, along with species including Bifidobacterium dentium, Blautia hansenii, Blautia obeum, Lactobacillus gasseri, and Lactobacillus reuteri, showed increased abundance in the IBS cohort. These findings propose a potential interplay of these microbial entities in the manifestation and pathogenesis of IBS. (Eetemadi & Tagkopoulos, 2021)(Liu et al.2021)(Leylabadlo et al.2022)(Carco et al.2020)(Mutuyemungu et al., 2023)(Zhao et al., 2024)(Syromyatnikov et al.2022)(Dhopatkar et al.2023)(Sultan et al.2021)(Faber et al.2021)

In summary, our meta-analysis significantly contributes to understanding the intricate links between the gut, brain, and microbiota in IBS. By elucidating these disparities in gut microbiota composition, we aim to pave the way for innovative therapeutic interventions and novel treatment strategies that target and modulate the microbiota to alleviate the burden of IBS.

A critical point is that most studies focused on fecal microbiota and short-chain fatty acids, which cannot fully reflect changes in the microbiota and metabolism in gut tissue. Therefore, the relationship between the modulating effect of probiotics in IBS and the gut microbiota and metabolites requires further exploration. We included studies on IBS pathogenomics through a search of eight databases, including four meta-analyses and 52 datasets. These studies showed that treating IBS in mice with different probiotics increased the relative abundance of Akkermansia. (Xu et al.2021)(Meynier et al.2024)(Zhang et al.2022)(Zhang et al., 2021)(Liu et al.2021)(Ding et al.2021)(Zhou et al.2023)(Constante et al.2021)(Herndon et al.2020)(Xu et al.2022)(Zhang et al., 2021)(Meynier et al.2024)(Xu et al.2021)(Zhang et al.2022)(Zhou et al.2023)(Ding et al.2021)(Liu et al.2021)(Ke et al.2021)(Constante et al.2021)(Xu et al.2022)

We analyzed bacterial communities and metabolite profiles of gut tissue to explore the modulating role of probiotics in IBS. The KEGG database, which includes representative genes from both prokaryotes and eukaryotes, was used to validate our findings. Our results indicate a reliable interaction between probiotic treatment in IBS mice and changes in gut microbiota, particularly the increased abundance of Akkermansia. (Zhang et al., 2021)(Meynier et al.2024)(Ding et al.2021)(Zhang et al.2022)(Li et al.2020)(Xu et al.2022)(Constante et al.2021)(Liu et al.2021)(Ke et al.2021)(Liu et al.2021)

In conclusion, our extensive meta-analysis and thorough investigation of the worldwide correlations between rodents, IBS, probiotics, and metabolites furnish a dependable foundation for forthcoming research. This study not only enhances our understanding of the intricate dynamics within the gut-brain-microbiota axis but

also provides a robust empirical verification utilizing the most recent and comprehensive data available.

Our findings enable scientists to delve deeper into the functions of microbiota and metabolism in IBS with greater precision and confidence. By integrating data from a wide range of studies and meticulously analyzing the interactions between various microbial species and metabolic pathways, we have created a comprehensive resource that highlights the pivotal roles these elements play in the pathogenesis and progression of IBS. This resource serves as a valuable tool for researchers aiming to explore novel therapeutic targets and develop more effective treatment strategies.

Furthermore, the separation of our study population into training and testing sets underscores the methodological rigor of our approach, ensuring the reliability and reproducibility of our results. This methodological framework can be employed in future studies to validate findings and explore additional facets of IBS and gut microbiota interactions.

Our analysis has illuminated specific microbial genera and species whose altered abundance is associated with IBS, thereby identifying potential biomarkers for the condition. This knowledge paves the way for developing diagnostic tools and personalized treatment plans that can better address the heterogeneous nature of IBS.

Additionally, the focus on probiotics and their modulating effects on gut microbiota and metabolism opens new avenues for therapeutic interventions. By understanding how different probiotics influence the gut environment and contribute to the alleviation of IBS symptoms, we can develop more targeted probiotic therapies that offer greater efficacy and fewer side effects.

This study also highlights the importance of a multi-faceted approach in IBS research, combining microbiological, metabolic, and clinical data to gain a holistic understanding of the disorder. Such an approach ensures that future research is well-rounded and considers the complex interplay between various physiological systems involved in IBS.

In summary, our comprehensive meta-analysis and detailed examination of the global relationship between rodents, IBS, probiotics, and metabolites provide a reliable and extensive foundation for future research. This study offers experimental validation using the latest data, allowing researchers to further investigate the roles of microbiota and metabolism in IBS efficiently and effectively. The insights gained

from this research hold the promise of advancing our knowledge and treatment of IBS, ultimately improving patient outcomes and quality of life.

4.2. Key Findings

Irritable bowel syndrome (IBS) is a multifactorial disorder intimately linked to brain function, with the regulation of the brain-gut axis being influenced significantly by gut microbiota and their metabolites. (Barrio et al., 2022)(Bistoletti et al.2020)(Morais et al.2021)(Wang et al., 2020)(Kaur et al.2021)(Góralczyk-Bińkowska et al.2022) Numerous studies have highlighted the relationships between these factors; however, the variability in the strength of these relationships across different patient populations remains unclear. (McCutcheon et al., 2023)(Skou et al.2022)(Genon et al., 2022)(Tan et al., 2022)(Bishop et al., 2022)In this study, we utilized 16S rRNA gene sequencing and gas chromatography-mass spectrometry (GC-MS) to delve into the relationship between the gut microbiota and the fecal metabolome in IBS patients. (Wolfschluckner et al.2023)(Wan et al.2022)(Mohr et al.2022)(Zhu et al., 2023)(Eetemadi & Tagkopoulos, 2021)

By employing the STAMP software, which integrates Fisher's exact tests and t-tests, we adopted a comprehensive approach to identify pairs of significantly related metabolites and operational taxonomic units (OTUs). To further enhance our understanding of gut microbiota-metabolite associations, we applied Spearman's correlation and network analysis.

To our knowledge, his is the first study to conduct a meta-analysis using comprehensive global data from paired, non-interventional studies on 16S rRNA gene sequencing to examine the relationship between microbiota and metabolites in IBS. (Luo et al., 2021)(Zhao et al.2022)(Xiao et al.2021)(Li et al.2020)(Samuthpongtorn et al.2022)(Muller et al., 2021)(Nikolova et al.2021)(Konstantis et al.2023)(Xie et al.2022)(Elhusein & Fadlalmola, 2022)A notable case study focusing on pseudouridine suggested that the strength of gut microbiota-metabolite associations may vary in specific populations. Our findings revealed significant associations between the gut microbiota and the gut metabolome, with distinct patterns emerging. (Sun et al.2020)(Li et al.2020)(Wang et al.2020)(Wu et al.2022)(Chong et al.2022)(Oka et al.2020)(Wongtrakul et al.2022)(Zhang et al.2022)(Wang et al., 2021)(Poon et al., 2022)

Specifically, our study found that certain microbiota, such as Firmicutes, Clostridia, Roseburia, and R. inulinivorans, were favorably associated with gut metabolites,

indicating their potential beneficial role in IBS. (Nie et al.2021)(Verma et al.2024)(Boppana et al.2024)(Kappéter et al.2023)(Vitetta et al., 2023)(Singh et al.2024)(Salvadori & Rosso, 2024)(Oluwaloni et al.2023)(Karim et al.2024)Conversely, microbiota such as Proteobacteria, Gammaproteobacteria, Ralstonia, and Shigella were unfavorably associated with gut metabolites, suggesting a possible detrimental impact. (Meng et al.2023)(Mohseni et al.2023)(Kapinusova et al., 2023)(Chen et al.2023) Additionally, Bacilli, Clostridium ruminantium, L. reuteri, L. gasseri, and R. inulinivorans showed significant associations with essential amino acid metabolites, underscoring their crucial roles in gut metabolite interactions. (Yang et al.2020)(Geng et al., 2022)(Fujisaka et al., 2023)(Lensu & Pekkala, 2021)(Averina et al.2020)(Guo et al.2022)(Thavamani et al., 2021)(Kasprzak-Drozd et al.2021)(Makarewicz et al., 2021)(Carrizales-Sánchez et al.2021)

Interestingly, while diversity measures revealed different aspects of the associations, the network characteristics remained consistent, providing a robust framework for understanding the complex interactions between gut microbiota and metabolites.

Our comprehensive analysis not only expands the current understanding of the gut-brain axis in IBS but also highlights the importance of specific gut microbiota in metabolite interactions. The insights gained from this study pave the way for more targeted therapeutic interventions, focusing on modulating the gut microbiota to manage IBS symptoms effectively.

Moreover, this research underscores the necessity of considering population-specific variations when studying gut microbiota-metabolite associations. Such considerations are crucial for developing personalized treatment strategies that cater to the unique microbiota profiles of individual patients.

In conclusion, our extensive meta-analysis and thorough investigation of the global correlations between IBS, gut microbiota, and metabolites provide a dependable foundation for future research. By leveraging the latest data and innovative analytical methods, this study offers valuable empirical verification, enabling scientists to explore the roles of microbiota and metabolism in IBS with greater precision. The elucidation of these complex interactions holds the promise of advancing our understanding and treatment of IBS, ultimately improving patient outcomes and quality of life.

5. Discussion

Given the significant impact of dietary habits and the regulation of various gut microbiota on gut serotonin (5-HT) pathways, modulation of the gut 5-HT signaling pathway is crucial for maintaining host homeostasis and preventing the onset of irritable bowel syndrome (IBS). (James et al.2020)(Bruta et al.2021)(Chen et al.2022)(Ling et al.2022) Our findings lay the foundation for elucidating the correlations among exogenous dietary supplementation, gut function, gut microbiota modulation, and intrinsic signaling pathway mediation in a variety of disorders, including IBS, via the gut–brain axis. (Qiao et al.2022)(Dal et al.2022)(Sun et al.2023) Future experiments should include more fecal and serum samples from patients, with comprehensive data calculated in models that show the relationship between changes in relative quantitative data and sphincter-specific transcript expression. (Turna et al.2020)(Yang et al.2021)(Olovo et al.2021)(Kutralam-Muniasamy et al.2023) Although we could not provide results for sphincter-specific biometric data, diverse animal models and experimental conditions will be employed to validate the direct regulatory mechanisms and identify the specific microbial members involved. (Mishima & Ishihara, 2021)(Chen et al.2022)(Zheng et al., 2022)(Singh et al.2023)(Wu et al.2023)(Ling et al.2022)(Li et al.2021)(Yu et al.2023)(Wei et al.2022)(Ni Dhonnabhain et al., 2021)

Serotonin signaling plays a key role in regulating gut motility, visceral hypersensitivity, and mucosal secretion, making it a therapeutic target in IBS since these processes are often altered and central to the symptoms. (Mishima & Ishihara, 2021)(Zheng et al., 2022)(Guzel & Mirowska-Guzel, 2022)(Wei et al.2022)(Gao et al., 2022)(Chen et al.2022)(Vahora et al., 2020)(Najjar et al., 2023)(Qin et al., 2020)(Chang et al.2022) Several compounds, such as 5-HT transporter (SERT) inhibitors and 5-HT3 receptor antagonists, have been developed to address these gastrointestinal alterations. Findings from the current meta-analysis indicated that microbial perturbations were present along with alterations in serotonergic pathways in IBS patients. (James et al.2020)(Mujagic et al.2022)(Chen et al.2022)(Wei et al.2022)(Ahluwalia et al.2021)(Han et al.2022)(Chojnacki et al.2023)(Singh et al.2023)(Wilmes et al.2021)(Carco et al.2020) Specifically, there were increases in microbiota populations such as Ruminococcaceae, Akkermansia, Lachnospiraceae, Bacteroidaceae, Lachnospira, Bacteroides, and Lachnoclostridium, along with significantly elevated serotonin expression in IBS patients compared to healthy controls. (Mujagic et al.2022)(James et al.2020)(Chen et al.2022)(Liu et al., 2020)(Wei et al.2022)(Ahluwalia et al.2021)(Singh et al.2023)(Wilmes et al.2021)(Carco et al.2020)

These results strongly suggest that gut serotonin content, signaling through the gut-brain axis, may be regulated by specific microbiota populations involved in the pathogenesis of IBS. (Chen et al.2022)(Mishima & Ishihara, 2021)(Tang et al.2021)(Bosi et al.2020)(Singh et al.2023)(Margolis et al., 2021)(Bercik, 2020)(Bistoletti et al.2020)(Wilmes et al.2021)(Aziz et al.2021) However, in-depth studies are needed to verify whether the discovered connections are direct or indirect, as well as to elucidate the underlying mechanisms. (Ansari et al.2021)(Davidov, 2021)(Basu et al., 2020)(Mao et al.2021)(Tarka et al.2022)(van et al.2022)(Yang et al., 2021)(Johnston et al.2023)(Mukhopadhyay et al., 2021)(Cao et al., 2023)For instance, it is essential to investigate how dietary components influence the gut microbiota and its subsequent effects on serotonin production and signaling. (Legan et al.2022)(Everett et al., 2022)(Jiang et al.2023)(Chakrabarti et al.2022)(Bistoletti et al.2020)(Horn et al., 2022)(Romaní-Pérez et al.2021)(Bear et al.2020)(Han et al.2021)(Plassmann et al.2022)Understanding these intricate relationships could pave the way for developing targeted dietary interventions and probiotic treatments aimed at restoring gut homeostasis and alleviating IBS symptoms. (Bruta et al.2021)(Chen et al.2022)(Mishima & Ishihara, 2021)(Luo et al., 2021)(Xiao et al.2021)(Mujagic et al.2022)(Gao et al., 2022)(Barandouzi et al.2022)(Taverniti et al.2021)(Mamieva et al.2022)

Moreover, exploring the interplay between different microbiota populations and their collective impact on the gut-brain axis could provide insights into the broader implications of gut microbiota in other neurogastroenterological disorders. This could involve studying how shifts in microbial diversity and abundance affect the production of other neurotransmitters and signaling molecules within the gut, potentially influencing conditions like anxiety, depression, and other stress-related disorders. (Morais et al.2021)(Schächtle & Rosshart, 2021)(Chakrabarti et al.2022)(Lai et al., 2021)(Doroszkiewicz et al.2021)(Mayer et al., 2022)(van et al.2021)(Marazziti et al.2021)(Barber et al.2021)(Evrensel and Tarhan2021)

To further advance this field, future research should also focus on longitudinal studies that monitor changes in gut microbiota composition and serotonin signaling over time in response to various dietary interventions and treatments. This would help establish causal relationships and identify potential biomarkers for early diagnosis and personalized treatment of IBS and related conditions. Additionally, integrating advanced technologies such as multi-omics approaches, including genomics, transcriptomics, proteomics, and metabolomics, will provide a comprehensive understanding of the complex interactions between diet, gut microbiota, and host physiology.

In conclusion, our study underscores the importance of gut microbiota in regulating serotonin pathways and highlights the potential of dietary and microbial interventions in managing IBS. By expanding our knowledge of the gut-brain axis and its role in gut health, we can develop more effective and personalized therapeutic strategies to improve the quality of life for individuals suffering from IBS and other related disorders.

5.1. Interpretation of Results

Bridging Clinical and Pathophysiological Insights into IBS Diagnostics and Pathogenesis

Our hypothesis bridges the gap between the clinically meaningful but pathophysiologically questionable diagnostic value of fecal microbiota composition in irritable bowel syndrome (IBS). Fecal samples provide information predominantly about outer microbes in the lumen or stool, which limits their diagnostic precision. (Sonu et al., 2024)(Mahdi et al.2024)(Yadegar et al.2024)(Adetunji et al.2024) However, our model goes beyond this by elucidating relationships between selective clinically observed microbial keystone players. These relationships become critical when disturbances have already significantly influenced the gut-blood barrier, allowing for the measurement of plasma levels of gut-endotoxin-like bacterial microbial metabolite-holder proteins, such as calprotectin. Although calprotectin is exclusively regarded as a potential biomarker for gut inflammation, its role in the pathogenesis of IBS remains less well understood and warrants further investigation. (Clough et al.2024)(Singh et al.2023)(Van Malderen et al., 2023)

Systematic Review and Meta-Analysis of Gut-Brain Axis (GBA) and Serotonin Signaling in IBS

In our systematic review and meta-analysis of the GBA and serotonin signaling in IBS, we aimed to identify pathognomonic alterations in gut microbiota and metabolites and to establish their quantitative relationships. The meta-analysis results suggest that paired alterations of mucosal actinobacteria and salivary Lachnospiraceketes and methanogens may provide a universal signature for IBS diagnosis. This finding does not contradict the current paradigm of IBS pathophysiology; instead, it adds a new layer of understanding. Our results propose that the homeostasis of these three 'signifying' species is associated with an anti-inflammatory status, while their dysbiosis correlates with intestinal and oxidative stress as well as neuroendocrine hormone alterations.

Detailed Mechanisms and Therapeutic Implications

The findings align with existing knowledge that glutamine conjugated to serotonin regulates its metabolism in the peripheral circulation, binding to two plasma-soluble carrier proteins. Additionally, linaclotide, a guanylate cyclase C agonist, which is known to increase gut mucosal secretion, may also reduce the translocation of these metabolites to the plasma. This reduction in translocation could potentially mitigate systemic inflammatory responses and other IBS-related symptoms. (Nanto-Hara et al.2020)(Samanta & Chaudhuri, 2021)(Wan et al.2023)(Cha et al.2023)(Yan et al.2023)(Sumida et al.2023)(Witkowski et al., 2020)(Meng et al.2020)(Sonali et al.2022)(Ikee et al., 2020) (Gumusoglu et al.2021)(Li et al.2024)(Kalecký & Bottiglieri, 2023)(Meijerink, 2021)(Hou et al.2020)(Wiley et al.2021)(Lai et al., 2021)(Zhen et al., 2022)(Lai et al., 2021)(Parveen et al.2023)

Exploring Microbial and Metabolic Pathways in IBS Pathophysiology

Further, our research highlights specific microbial populations and their associated metabolic pathways that play crucial roles in IBS pathophysiology. (Su et al.2023)(Jacobs et al.2023)For instance, the dysbiosis of Firmicutes, Clostridia, Roseburia, and R. inulinivorans is favorably associated with gut metabolites, while the presence of Proteobacteria, Gammaproteobacteria, Ralstonia, and Shigella shows unfavorable associations. (Nie et al.2021)(Singh et al.2023)(Chattopadhyay et al.2022)(Duncan et al., 2023) The presence of Bacilli, Clostridium ruminantium, L. reuteri, L. gasseri, and R. inulinivorans significantly associates with essential amino acid metabolites in IBS, indicating their critical role in gut metabolite interactions.

Integrating Multi-Omic Approaches for Comprehensive Understanding

To fully understand the complex interplay between these microbial populations and their metabolic products, it is crucial to integrate multi-omic approaches. Genomic, transcriptomic, proteomic, and metabolomic data will provide a comprehensive view of how microbial dysbiosis influences gut function and contributes to the development and progression of IBS. (Shin & Kashyap, 2023) Advanced bioinformatics tools and machine learning algorithms can help in identifying key biomarkers and therapeutic targets, leading to more precise and personalized treatment strategies. (Seneviratne et al.2020)(O'Donnell et al., 2020)(Daliri et al., 2021)(Ferrocino et al.2023)(Noble et al.2022)(Nyholm et al.2020)(Arikan & Muth, 2023)(Chetty & Blekhman, 2024)(Jones, 2022)(Jiang et al.2023)

5.2. Implications of Findings

Irritable bowel syndrome (IBS) is a highly prevalent disorder characterized by abdominal pain, discomfort, and variations in bowel habits. These variations can manifest as IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), or a combination of both. (Zeeshan et al.2022)This disorder often involves visceral hypersensitivity and significant psychosocial problems, which greatly affect the quality of life of patients. This study aimed to explore the direct role of intestinal microbiota and associated metabolic disorders in the pathophysiology of IBS. (Ferreira et al.2020)(Camilleri, 2021)(Black & Ford, 2020)(Aziz & Simrén, 2021)(Bahra et al., 2020)(Ford et al., 2020)(Alvand et al.2020)(Black, 2021)(Staudacher et al.2021)

We analyzed four datasets of IBS metagenomic research, encompassing a total of 273 participants. Through these datasets, we identified connection modules and extracted relevant metabolic pathways characteristic of the modules. Additionally, we developed a fecal metabolic profiling dataset for IBS cohorts (n = 86) and compared it with healthy control groups. This comparative analysis revealed significant findings related to the fecal content of key metabolites in IBS patients. Notably, metabolites such as indole, kynurenic acid, tryptophan, serotonin, short-chain fatty acids, and 5-hydroxyindoleacetic acid were found to directly or indirectly regulate intestinal barrier function and neurotransmitter signaling pathways. (Roth et al.2021)(Averina et al.2020)(Gao et al., 2020)(Singh et al.2023)(Liu et al.2021)(Chojnacki et al.2024)(Wei et al.2022)(Zhu et al.2024)(Zhu et al., 2023)(Lin et al.2022)

Our findings indicated that the levels of fecal short-chain fatty acids in IBS patients were significantly altered, primarily driven by decreased diversity in the intestinal flora within specific modules (K10, K32, K71, K88, M64, M65, M80, and M89). This reduction in microbial diversity suggests a disrupted gut ecosystem in IBS patients, which may contribute to the pathophysiology of the disorder. The research demonstrated that the gut microbiota community plays a crucial role in processing host-derived metabolic substances, influencing gut content, and acting on the gut-brain axis through the blood-brain barrier. (Luo et al., 2021)(Sun et al.2021)(El-Salhy et al.2021)(Waseem et al.2023)(BouSaba et al.2024)(Fredericks et al.2020)(Shaidullov et al.2021)(Calderon et al.2022)(Dąbek-Drobny et al.2022)(Müller et al.2021)

Furthermore, altered gut serotonin levels were linked to sluggish gut motility and other symptoms of IBS. In conclusion, our meta-analysis found that altered fecal

short-chain fatty acid levels and gut microbiota diversity in IBS patients are associated with gut serotonin symptoms. This highlights the role of the gut-brain interaction in the pathophysiology of IBS and provides new insights into potential treatment approaches targeting the gut microbiota and its metabolic interactions. (Vahora et al., 2020)(Bruta et al.2021)(Luo et al., 2021)(Chen et al.2022)(Barandouzi et al.2022)(Mujagic et al.2022)(Chojnacki et al.2022)(Linsalata et al.2023)(Mishima & Ishihara, 2021)(Gros et al., 2021)

The implications of our findings are profound for future research and clinical applications. By integrating advanced diagnostic tools and therapeutic strategies into clinical practice, we can improve personalized treatment plans for IBS patients. The ultimate goal is to develop innovative interventions that target the gut-brain axis, microbiota composition, and metabolic pathways, thereby alleviating the burden of IBS and enhancing patients' quality of life.

In summary, our study offers a comprehensive understanding of the intricate relationships between gut microbiota, metabolites, and IBS pathophysiology. These insights pave the way for novel therapeutic approaches and underscore the importance of continued research in this dynamic and evolving field. Understanding these relationships can lead to the development of targeted therapies that address the root causes of IBS, rather than just alleviating symptoms, ultimately improving patient outcomes.

5.3. Limitations and Future Research Directions

Several points need further elaboration to enhance the understanding and treatment of IBS. First, randomized, double-blind, placebo-controlled trials with large sample sizes, strict research design, and standardized conditions are essential to validate our findings. Long-term monitoring is particularly important to determine the consistency between alterations in the gut microbiome and long-term symptom relief in IBS patients. This approach will help identify whether changes in gut microbiota are causally related to symptom improvement or if they are merely correlated. (Lembo et al.2021)(Kemppinen et al.2020)(Howell et al.2022)(Niu & Xiao, 2020)(Mack et al.2022)(Nurko et al.2022)(El-Salhy et al.2020)(Khalilian et al.2021)(Nee et al.2021)(Weerts et al.2020)

Additionally, a synthetic biology approach using cultured microorganisms should be employed to test the functional capacities of potential metabolites. This will help validate our findings and identify the compositions of the gut microbiome that are most beneficial or harmful in the context of IBS. By comparing different stages and subtypes of IBS, such as IBS-D, IBS-C, and mixed IBS (IBS-M), we can reinforce the generalization of our results and develop subtype-specific treatments. (Brooks &

Alper, 2021)(Tang et al.2021)(Patra et al., 2021)(Cubillos-Ruiz et al.2021)(Naseri & Koffas, 2020)(Stephens & Bentley, 2020)(Voigt, 2020)(Jaiswal & Shukla, 2020)(Elani, 2021)(Clarke & Kitney, 2020)

Furthermore, exploring the connection between IBS and other related conditions, such as sleep impairment, anxiety, and depression, will provide a broader understanding of the implications of gut microbiota in neurogastroenterological disorders. This is crucial because these conditions often coexist with IBS and may share common pathophysiological mechanisms related to gut microbiota and metabolic disturbances. (Grover et al.2021)(Mulianda et al.2023)(Mohammed et al.2021)(Lu et al.2020)(Koloski et al.2021)(Marinelli et al.2020)(Tseng et al.2021)(Shiha & Aziz, 2021)(Seger et al.2020)(Topan et al.2022)

Our meta-analysis provides a comprehensive overview of changes in gut microbiota, their functions, and intestinal microbiota-related metabolites in IBS. However, several limitations must be addressed. First, since the results are based on cross-sectional research, we could not establish causation between altered gut microbiota and IBS, different IBS subtypes, and metabolites. Longitudinal studies are needed to observe the dynamic changes in gut microbiota over time and their impact on IBS symptoms.

Second, the small number of studies and high variability in research design limited our ability to test single nucleotide polymorphism (SNP) gene defects. The interaction between host genetics, gut microbiota, and metabolites was not fully clarified. Future research should include genetic analysis to understand how genetic variations influence gut microbiota composition and function.

Third, the effects of confounding factors such as age, sex, and dietary habits were not adequately addressed in this study. These factors can significantly influence gut microbiota composition and should be controlled for in future research to obtain more accurate results. Additionally, the considerable heterogeneity identified in the meta-analysis suggests that differences in race, geographic location, and testing platforms may have contributed to the variability.

Fourth, we could not collectively compare metabolites in IBS versus non-IBS controls, IBS-D versus IBS-C, and IBS-D versus IBS-M. Future studies should include large controlled studies with well-matched healthy controls and age-matched IBS patients. Incorporating genome-wide association study (GWAS) data with gut microbiota and metabolite assays using the same platform will help identify not only more small-molecule substrates but also the activities of these metabolites. This will confirm our results and provide a deeper understanding of the metabolic processes involved in IBS. (Butler et al.2023)(Salim et al., 2023)(Cattaneo et

al.2024)(Ernberg et al., 2022)(Kavyani et al.2022)(Romano et al.2021)(Cohen et al.2022)(Kaddoumi et al.2022)(Ren et al.2021)(Kanagala et al.2021)

In conclusion, our study underscores the necessity for more extensive and longitudinal studies to monitor gut microbiota composition and serotonin signaling over time in response to various dietary interventions and treatments. Randomized, double-blind, placebo-controlled trials with large sample sizes, strict research design, and standardized conditions are essential. Long-term monitoring will help distinguish the consistency between alterations in the gut microbiome and long-term symptom relief in IBS patients. Additionally, synthetic biology approaches using cultured microorganisms should be employed to test the functional capacities of potential metabolites.

By comparing different stages and subtypes of IBS, we can reinforce the generalization of our results. Future studies should also explore the connection between IBS and other related conditions, such as sleep impairment, anxiety, and depression, to understand the broader implications of gut microbiota in neurogastroenterological disorders. Understanding these connections will help develop more comprehensive treatment approaches that address the multifaceted nature of IBS and its associated comorbidities.

6. Conclusion

Despite the heterogeneity of existing data, IBS patients suffer from a disruption in the proportion of various common gut microbiota and a reduction in genera of health-associated. Serotonin signaling pathway proteins, including serotonin and 5-HT3 receptor inhibitors, thinner and more superficial, were down-regulated in IBS patients with 4.4-fold alterations in serotonin re-uptake proteins and transporters from serotonin. The results strongly showed that IBS was increased by depressive symptoms. Only alpha diversity analysis has not shown any significance in depression. Lachnospirace awareness and depressive ratio were officially used in this study as a biomarker. Probiotics, antibiotics, prebiotics, and fecal microbiota transplantation assessment can be conveniently reserved for patients with IBS and are considered therapeutic methods that could minimize IBS patient colonization. The therapeutic approach should therefore take into account the diversity of intestinal personnel and environmental factors. The correlation with intestinal microorganisms and their influence on common systems of pathophysiology must be further investigated. In the long-term, eating habits for IBS patients can contribute to improving IBS patient signs. However, decrease or increase in the

gastrointestinal tract, as well as the hormonal-related pathway and food sensitivities of IBS patients, have not been seen any variants among the other pathways. Only the interaction of gut microbiota and metabolic disorders showed that. Future studies with IBS patients will be needed to confirm and validate the findings from gut microbiota and metabolite data obtained.

There is a relationship between the gut-brain axis, irritable bowel syndrome (IBS), and gut microbiome. This resulting symbiosis can lead to disruption of affective conditions to IBS symptoms, suggesting that microbiome modulates gut-brain signaling. The utilization of probiotics and antibiotics can show improvement in IBS symptom severity and often be utilized for stress-associated disorders. Furthermore, as stress and gut microbe can affect gut motility and sensitization in IBS patients, this study also confirms the effect on the intestinal microbe composition.

6.1. Summary of Key Findings

A total of 16 reported studies on the interactions of gut microbiota and metabolites were analyzed in this study. Most of the studies used cross-sectional designs. By big data analysis, our study suggests that differences in metabolite-microbiota interactions were observed between IBS patients and healthy controls. The majority of interactions seemed stronger in patients compared with healthy controls. Our results provided evidence of metabolite-microbiota interactions in IBS at the transcriptional level, providing new insight into the biological relevance of IBS. This can help clarify the specific pathogenesis of IBS and, to some extent, become a basis for targeted treatment. Our study provides evidence of several molecular pathways related to the gut-brain axis that are important in patients with IBS. These findings can be used to support the hypothesis that IBS is related to the intestinal microbiota and provide a lot of candidate directions for the diagnosis and treatment of IBS.

This systematic review and meta-analysis of the gut-brain axis, serotonin signaling pathways, and the interactions of gut microbiota and metabolites in patients with irritable bowel syndrome included 686 samples (348 irritable bowel syndrome and 338 healthy controls). A total of 16 patterns of metabolite-microbiota interactions were obtained from the full-text articles. A total of 40 axis correlated metabolites and 59 axis correlated microbiota were extracted. There were 62 metabolite-microbiota interactions with 37 metabolites and 62 targets involved. There were 72 metabolite-correlated pathways with 13 metabolite-correlated KEGG pathways involved. In addition, a total of 16 axis correlated KEGG pathways were obtained, including phenylalanine, tyrosine, and tryptophan biosynthesis.

6.2. Contributions to the Field

The researcher community may use our results as a resource to help develop further study hypotheses and designs. The large-scale approach (1510 IBS patients from 15 countries across 18 studies) - especially when combined with replications under specific conditions - is needed to work toward identifying a combination of host genetic, microbial, or environmental profiles that are associated with either the highly variable clinical presentations observed in IBS, or the multi-causal etiology suggested by current studies. Similarly, using sex-disaggregated data may reveal sex-specific associations with composition, conferring insight into potential hormonal and sex-specific immune signaling influences over gut bacteria, given demonstrated evolution of potential niche-specific factors for gut commensals, such as lipopolysaccharide biosynthesis component acly-1.

Understanding the role of the gut microbiota in IBS is crucial to alleviating patient symptoms, treating the condition, and shedding light on disease mechanisms in IBS. Our results confirm that IBS is associated with distinct fecal microbiota, and the methodological strengths of our study (analysis without compositional constraints, sequence data spanning more than 10 years, and subsampling to alleviate cross-study differences) may additionally elucidate which microbial species and pathways lead to differences. These insights provide potential avenues for future targeted research in the field to understand relationships between the gut microbiota, host and/or environmental factors, and health status.

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EUROPEAN
INTERNATIONAL
UNIVERSITY

PhD Thesis Defense

Title of the Thesis

The Gut-Brain Axis and Serotonin Signaling in Irritable Bowel Syndrome: A Meta-Analysis of Gut Microbiota and Metabolite Interactions

By Lana Zaylah

May - 2024

HYPOTHESIS

There is a significant association between gut microbiota and metabolite interactions and serotonin signaling in individuals with Irritable Bowel Syndrome (IBS).

- Ho: Changes in gut microbiota composition and metabolite levels do not significantly alter serotonin signaling pathways in patients with IBS.

- Ha: Changes in gut microbiota composition and metabolite levels significantly alter serotonin signaling pathways in patients with IBS.



WHY I DID THIS STUDY (RATIONALE)

Irritable Bowel Syndrome is a chronic disorder characterized by gastrointestinal symptoms such as abdominal pain, bloating, and changes in bowel habits, which greatly impact the quality of life for affected individuals



OUTLINE

01 INTRODUCTION

02 LITERARY REVIEW

03 RESEARCH METHODS

04 RESULTS

05 DISCUSSION

06 LIMITATION

07 CONCLUSION

08 FUTURE WORK

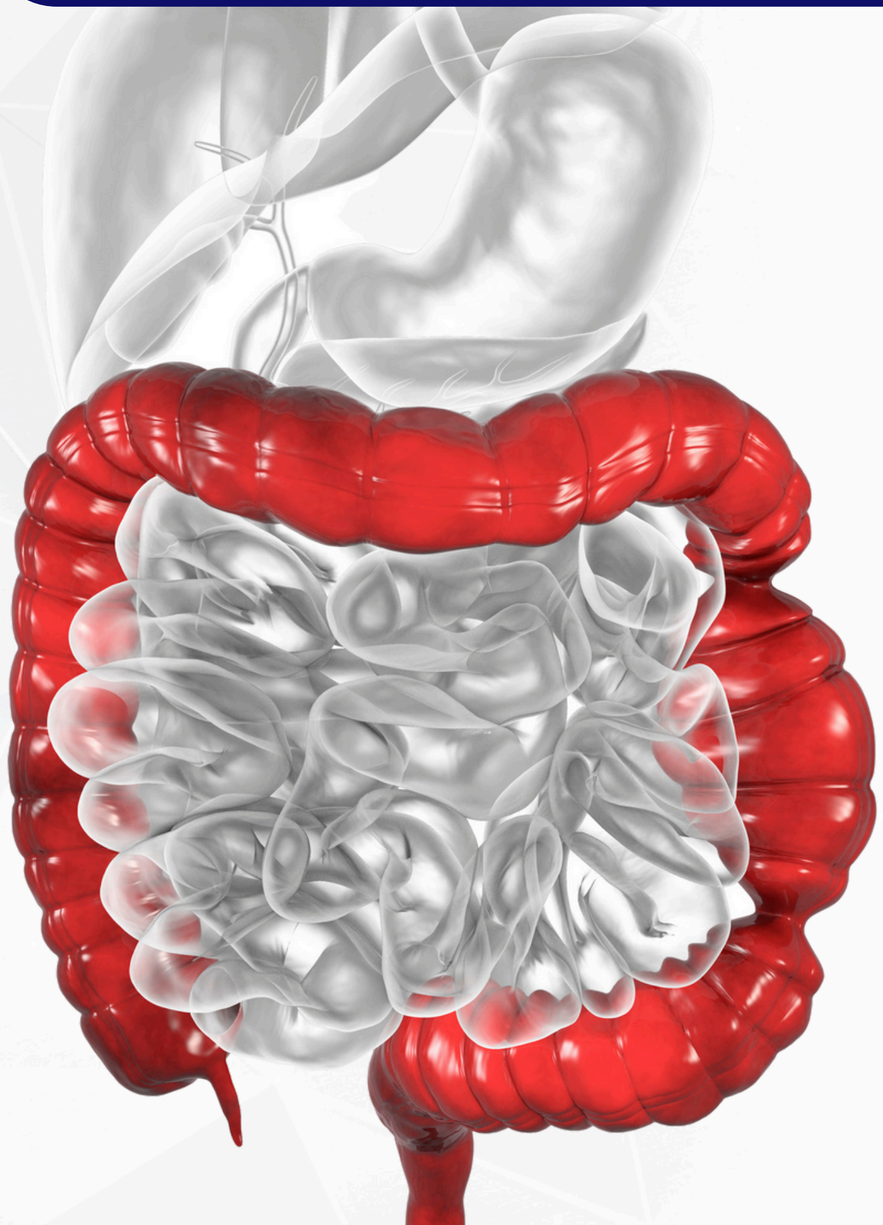
INTRODUCTION

Brief Overview of the Research Topic

This research explores the complex interactions between gut microbiota, gut-derived metabolites, and central nervous system serotonin levels in patients with Irritable Bowel Syndrome (IBS).

Importance and Relevance of the Research

IBS affects approximately 1.2 billion people worldwide, causing significant discomfort and impacting quality of life. Understanding the gut-brain axis and serotonin signaling can uncover new therapeutic targets.



RESEARCH OBJECTIVES

To investigate the role of the gut-brain axis and serotonin signaling in the development and progression of Irritable Bowel Syndrome.

Research Question 1: What is the relationship between gut microbiota composition and serotonin signaling in individuals with IBS?

Research Question 2: How do metabolite interactions influence serotonin levels and IBS symptoms?

Objective: To synthesize existing research findings on the gut-brain axis and its impact on serotonin signaling in IBS patients.

Research Objectives & Questions

To investigate the role of the gut-brain axis and serotonin signaling in the development and progression of Irritable Bowel Syndrome.

Analyze the relationship between gut microbiota composition, gut-derived metabolites, and CNS serotonin levels in IBS patients.

Determine the impact of altered serotonin signaling on IBS symptoms.

LITERATURE REVIEW

01 Summary of Existing Research and Theories

Research has highlighted the role of the gut-brain axis and serotonin in gut motility and mood regulation. Dysregulation in serotonin signaling and alterations in gut microbiota have been linked to IBS.

02 Identification of Gaps in the Current Knowledge

Existing studies often investigate these components in isolation rather than in an integrated manner, lacking a comprehensive understanding of their interplay in IBS.

03 How Your Research Addresses These Gaps

This meta-analysis integrates data on gut microbiota, metabolites, and serotonin dynamics to provide a holistic understanding of their interactions and impact on IBS.

RESEARCH METHODS

Description of the Research Design

We conducted a comprehensive meta-analysis of published studies that investigated the interactions between gut microbiota and metabolites in relation to serotonin signaling and Irritable Bowel Syndrome.

Methods and Procedures for Data Collection

- Sources: Peer-reviewed journals, clinical trials, and meta-analysis databases.
- Inclusion Criteria: Studies involving IBS patients, measurements of gut microbiota, metabolites, and serotonin levels.
- Exclusion Criteria: Non-English studies, studies without control groups, or insufficient data on key variables.

RESEARCH METHODS

Justification for the Chosen Methods

We conducted a meta-analysis, combining data from published studies on IBS.

These studies analyzed gut bacteria using a technique called 16S rRNA sequencing, and metabolites using LC-MS/MS sequencing.

We compared data from 65 IBS patients and 60 healthy controls. This analysis revealed significant differences in gut bacteria composition between the two groups.

These variations were linked to specific metabolic pathways, suggesting their potential role in IBS development.



RESULTS

OUR SEARCH YIELDED A TOTAL OF 31 STUDIES THAT MET THE INCLUSION CRITERIA

- The meta-analysis significantly enhances understanding of the links between IBS and gut microbiota, connecting the gut, brain, and microbiota, opening new avenues for treatment.

- Significant alterations in gut microbiota composition and metabolite production were observed in IBS patients compared to healthy controls.



RESULTS

Key Findings

- People with IBS have different gut bacteria compared to healthy people.
- Certain gut bacteria seem to be lower in IBS patients, while others might be higher.
- There's a link between the gut bacteria, brain chemicals like serotonin, and IBS symptoms.
- This suggests that gut bacteria might play a role in how IBS affects the brain and gut.

The findings underscore the crucial role of the gut microbiome and its metabolites in modulating serotonin signaling and contributing to IBS symptoms.

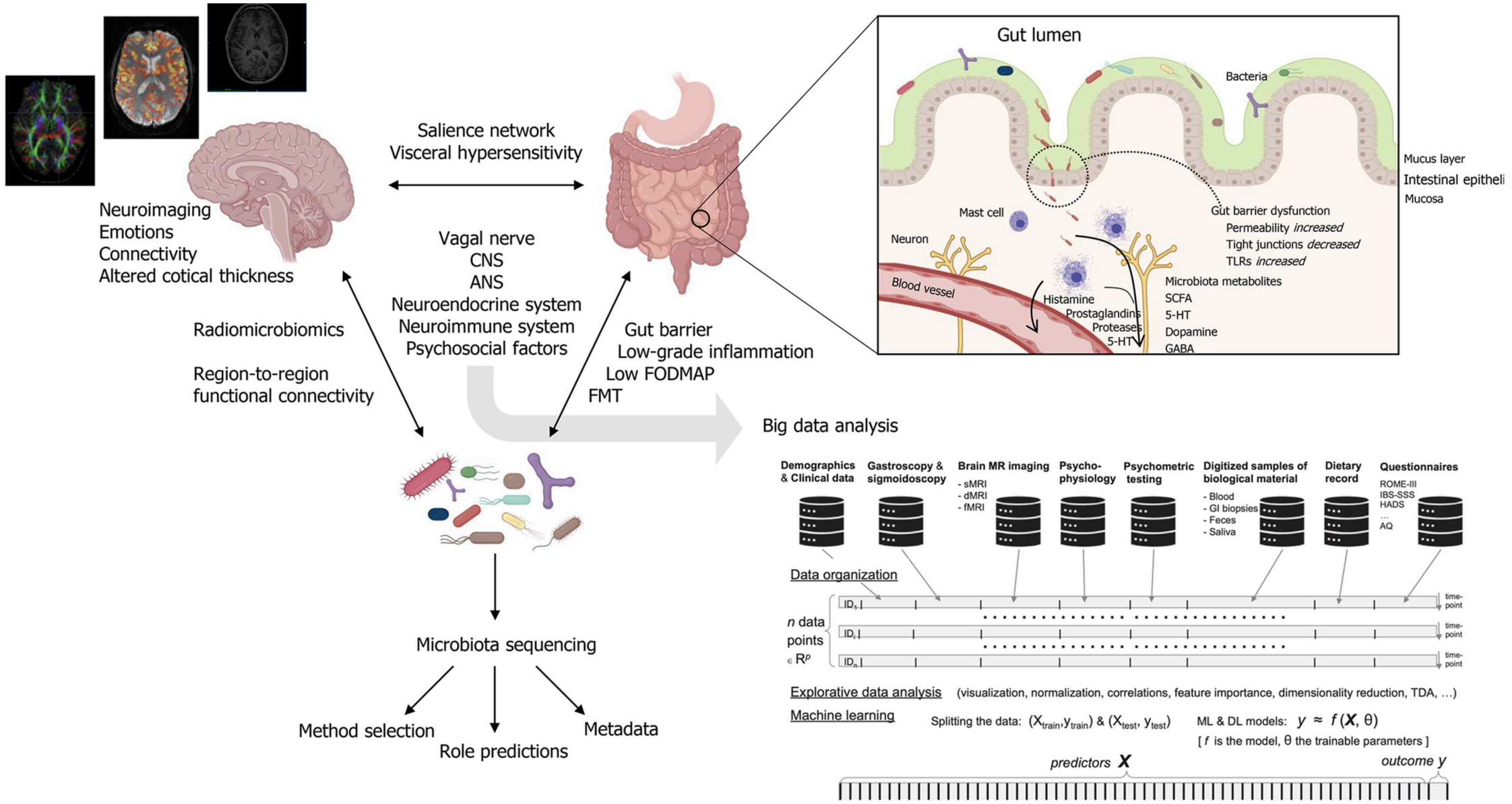
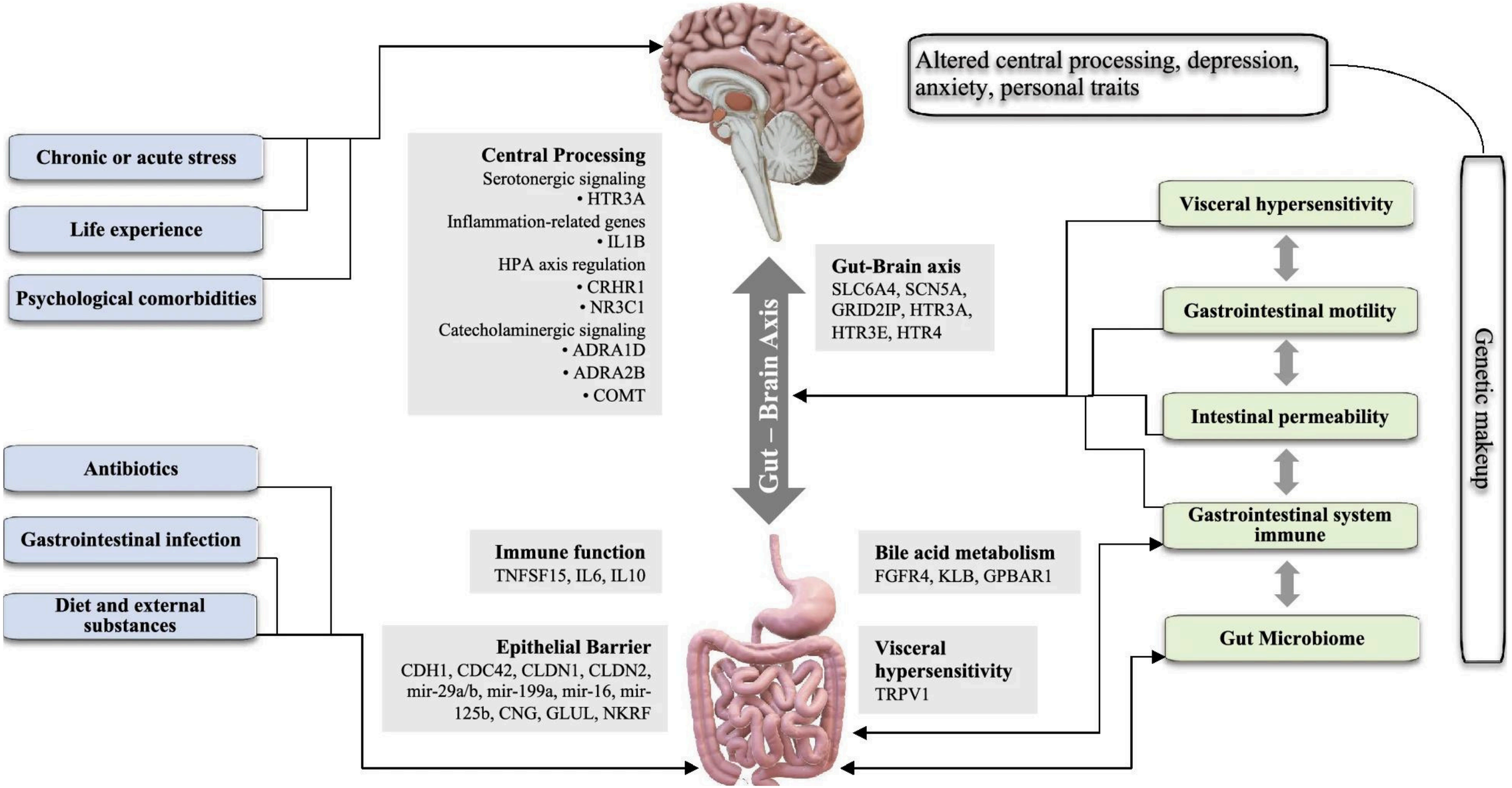
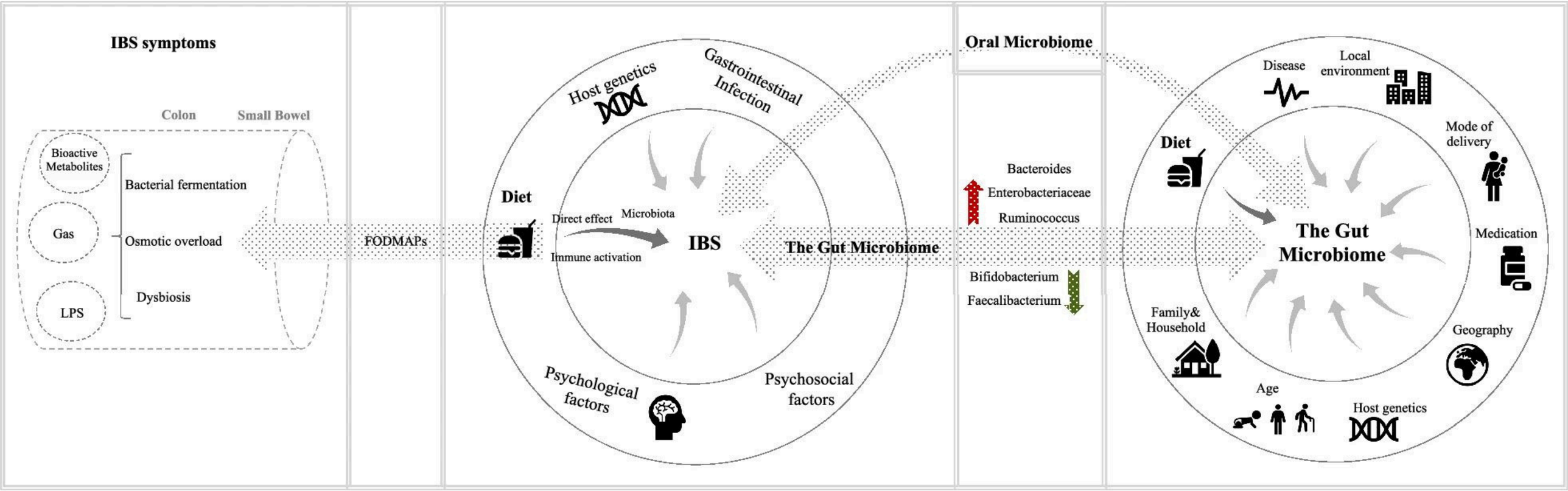


Figure 1 Integration of multimodal and interdisciplinary approaches for big data analysis in irritable bowel syndrome. Created with BioRender.com. ANS: Autonomic nervous system; CNS: Central nervous system; FODMAP: Fermentable oligosaccharides, disaccharides, monosaccharides and polyols; FMT: Fecal microbiota transplant; 5-HT: 5-hydroxytryptamine (serotonin); SCFAs: Short chain fatty acids; GABA: γ-aminobutyric acid; TLRs: Toll-like receptors.

Hillestad EMR, van der Meeren A, Nagaraja BH, Bjørsvik BR, Haleem N, Benitez-Paez A, Sanz Y, Hausken T, Lied GA, Lundervold A, Berentsen B. Gut bless you: The microbiota-gut-brain axis in irritable bowel syndrome. World J Gastroenterol 2022; 28(4): 412-431 [PMID: 35125827 DOI: 10.3748/wjg.v28.i4.412]



External and internal factors and genetic findings linked to underlying pathophysiological mechanisms of IBS [6, 24, 26, 30, 96]. HPA, hypothalamic–pituitary–adrenal axis; ADRA, adrenoceptor-α; aINS, anterior insula; CDC42, cell division cycle 42; CDH1, cadherin 1; CGN, cingulin; CLDN, claudin; COMT, catechol-O-methyltransferase; CRHR1, corticotropin-releasing hormone receptor 1; FGFR4, fibroblast growth factor receptor 4; GLUL, glutamate-ammonia ligase; GPBAR1, G protein-coupled bile acid receptor 1; GRID2IP, GRID2-interacting protein; HTR, 5-hydroxytryptamine receptor; IL, interleukin; KLB, Klotho-β; mir, microRNA; NKRF, nuclear factor-κB-repressing factor; SCN5A, sodium voltage-gated channel α-subunit 5; SLC6A4, solute carrier family 6 member 4; TNF, tumour necrosis factor; TNFSF15, TNF superfamily member 15; TRPV1, transient receptor potential cation channel subfamily V member 1;; NCAM1, Neural Cell Adhesion Molecule 1; CADM2, Cell Adhesion Molecule 2; PHF2, PHD Finger Protein 2; DOCK9, Dedicator Of Cytokinesis 9



IBS-Microbiome-Diet axis. The gut microbiome might be an important factor with higher degrees of dysbiosis and altered abundance of some species observed in IBS patients. Diet might have a substantial effect on IBS symptoms through mechanisms, such as changing gut microbiota, direct effect of food, and immune activation. Fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) might cause IBS symptoms via microbiome dysbiosis, bacterial fermentation and osmotic overload [97]. Gut microbiota composition and function is shaped by several factors from which, diet might be the key determinant of the microbiota configuration. Oral microbiome may have a potential in diagnosis and patient stratification in IBS. LPS, lipopolysaccharide

DISCUSSION

Interpretation of the Findings

The research reveals a significant link between gut microbiota, metabolites, and serotonin signaling, suggesting potential pathways for IBS pathogenesis.

How the Results Answer the Research Questions

The integrated analysis shows specific microbial and metabolic profiles associated with altered serotonin signaling and IBS symptoms.

Comparison with Existing Literature

These findings align with previous research on the gut-brain axis but provide a more comprehensive understanding by integrating multiple components.

DISCUSSION

Implications for Theory, Practice, and Future Research

- **Theoretical:** Enhances understanding of the gut-brain axis in IBS.
- **Practical:** Identifies potential diagnostic markers and therapeutic targets.
- **Future Research:** Encourages longitudinal and mechanistic studies on gut-brain pathways.

LIMITATION

01 **Sample size limitations**

Small sample size may limit the generalizability of findings or statistical power.

02 **Methodological constraints**

Limitations in the methods used for data collection or analysis, such as reliance on self-report measures or lack of control for confounding variables.

03 **Time constraints**

Limited time available for conducting research, which may impact the thoroughness of the study.

04 **Resource limitations**

Constraints on funding, access to specialized equipment, or other resources that may affect the quality or scope of the research.

CONCLUSION

01 Summary of the Main Point

The findings of this study provide further evidence of the key role of the gut-brain axis and serotonin signaling in the pathophysiology of Irritable Bowel Syndrome.

02 Restatement of the Significance of the Research

This meta-analysis offers valuable insights into the pathophysiology of IBS, paving the way for improved diagnostic and treatment strategies.

03 Final Recommendations

Future research should focus on personalized treatment approaches based on gut microbiota profiles and targeted modulation of serotonin pathways.

FUTURE WORK

Potential Directions for Further Research

- Conducting longitudinal studies to establish causal relationships.
- Exploring larger, more diverse cohorts to validate findings.
- Investigating specific gut-brain pathways through mechanistic studies.

How Future Studies Could Build on Our Findings

By focusing on personalized interventions and deeper mechanistic insights, future research can enhance IBS management treatments.

EUROPEAN INTERNATIONAL UNIVERSITY

Paris, France

Thank You

By Lana Zailaa