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The Gut-Brain Axis in Irritable Bowel Syndrome: Implementing the Role of Microbiota and Neuroimmune Interaction in Personalized Prevention—A Narrative Review

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ABSTRACT

Background and Purpose: Irritable bowel syndrome (IBS) is a disorder characterized by microbiota-neuroimmune interaction resulting in disturbance to the gut-brain axis (GBA). The purpose of this review is to garner an overview of the different pathophysiological mechanisms indicated in the development of IBS and the associated sequalae on gut microbiota alongside its role in the GBA. Moreover, we aim to provide an insight into the possibility of utilizing personalized medicine when managing said affected populations.

Methods: A comprehensive review was performed of the relevant literature pertaining to the current state of GBA alteration implicated in IBS, comprising microbiota-neuroimmune interaction alongside disturbance and activation, respectively. Different search databases were utilized, including PubMed/MEDLINE and ScienceDirect.

Results: The review demonstrated the most evident etiologies of IBS being the imbalance of microbiota and the alteration to the GBA. Furthermore, the interrelation between microbiota and neuroimmunity was discussed. Promising avenues for IBS prevention and management are offered through emerging research on the pathophysiological mechanisms indicated in IBS-associated GBA alteration. This entails a role for the involved interactions between microbiota modification and neuroimmunity activation.

Conclusion: Promising prospects for symptom prevention and management are signaled by the possibility of personalized therapy specifically designed to address the GBA dysfunction indicated in IBS. Policymakers and developers should encourage further study and allocate available resources to aid researchers in the implementation and identification of novel preventive therapeutics. Furthermore, physicians should advocate and integrate the use of personalized medical approaches of IBS to help ensure a better quality of life.

Abbreviations: 5-HT3, 5-Hydroxytryptamine receptor 3; 5-HT4, 5-Hydroxytryptamine receptor 4; ANS, autonomic nervous system; BOLD, blood oxygen level dependent; CNS, central nervous system; CRH, corticotropin-releasing hormone; ENS, enteric nervous system; FGID, functional gastrointestinal disease; fMRI, functional magnetic resonance imaging; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; GABA, gamma-aminobutyric acid; GALT, gut-associated lymphoid tissue; GBA, gut–brain axis; GI, gastrointestinal; GIT, gastrointestinal tract; HPA, hypothalamic-pituitary-axis; IBD, inflammatory bowel diseases; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, mixed-stool IBS; IL-10, interleukin 10; IL-6, interleukin 6; IL-8, interleukin 8; SCFA, short-chain fatty acids; TNF- alpha, tumor necrosis factor alpha; WHO, World Health Organization.

1 | Introduction

Irritable bowel syndrome (IBS), a prevalent functional gastrointestinal disease (FGID), is recognized for its extended duration of abdominal discomfort in addition to bowel habit changes altering one's quality of life [1]. It is a bowel disorder that is well described in being either hyperactive or hypoactive, sometimes exhibited in the same individual [2]. This may precipitate a plethora of symptoms, of which some are relieved by defecation and others exacerbated by it [2]. Thus, we may distinguish four major clinical presentations of IBS, whereby the following classification has been introduced: IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), mixed-stool IBS (IBS-M), and IBS un-subtyped [2]. The complexity of the diagnosis as it is one of exclusion requires the elimination of a wide range of differentials presenting with similar symptoms [2]. Moreover, the diagnostic criteria proposed by the global gastroenterology community is that of the Rome IV criteria introduced in 2016 [3]. This consists of a combination of the following: recurrent abdominal pain for the past 3 months with disease on an average of 1 day per week, associated with two or more of the following; pain related to defecation, or associated with change of either frequency or form of the stool [3].

Few patients suffer severe complications from the disease itself, but overall productivity, work as well as academic productivity, along many aspects is markedly decreasing [4–6]. New studies have shown that approximately 13.8 productive hours of the 40-h working week, or approximately 30%, are lost in patients with IBS [5, 6]. This may be attributed to frequent visits to respective doctor's clinics, having diagnostic testing routinely performed, and general lethargy related to IBS [7]. In addition, this relation can be bidirectional where decreased work productivity can cause elevated stress and thus exacerbation of symptoms. For instance, the level of anxiety and academic stress was significantly worse in IBS patient in a study done on medical and nursing students in Italy to assess the prevalence of IBS [4]. Furthermore, these factors may be more intense with individuals suffering from anxiety-related disorders concurrently alongside other psychological issues [8]. However, the mental health element of IBS seems to be neglected by clinicians, as most gastroenterologists rarely perform a mental health check-up in their field [7]. It seems that they disregard the mental instability IBS leads to: a well-documented cause of mental health declination as well as an effect on psychiatric illness simultaneously [8]. Actually, a previous meta-analysis details that the prevalence of depression and anxiety among IBS patients is 29% and 39%, respectively [9]. Evidence has shown that individuals with no baseline anxiety or depressive disorders at the beginning of their IBS diagnosis do indeed develop symptoms attributable to a mental health disorder with time. On the contrary, those with the latter disorders and no baseline underlying IBS disorder do report gastrointestinal complains with time pertaining to IBS [10, 11]. Furthermore, a cause–effect relationship was established via a cohort study exhibiting an increased incidence of psychological distress correlating with greater prevalence of gastrointestinal symptoms relating to IBS, thereby instigating an evidence-based causal link between psychological symptoms and IBS [12]. This relationship may be explained by the dysfunction or dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, altering the local immune interactions and microbiota implicated in disease pathophysiology in addition to several proposed mechanisms [12].

Several culprits have been established through scientific study in comprehending the disease causality of IBS, from visceral hypersensitivity to genetics factors, where more recently, low-grade inflammation of the bowel has been explored (Figure 1)

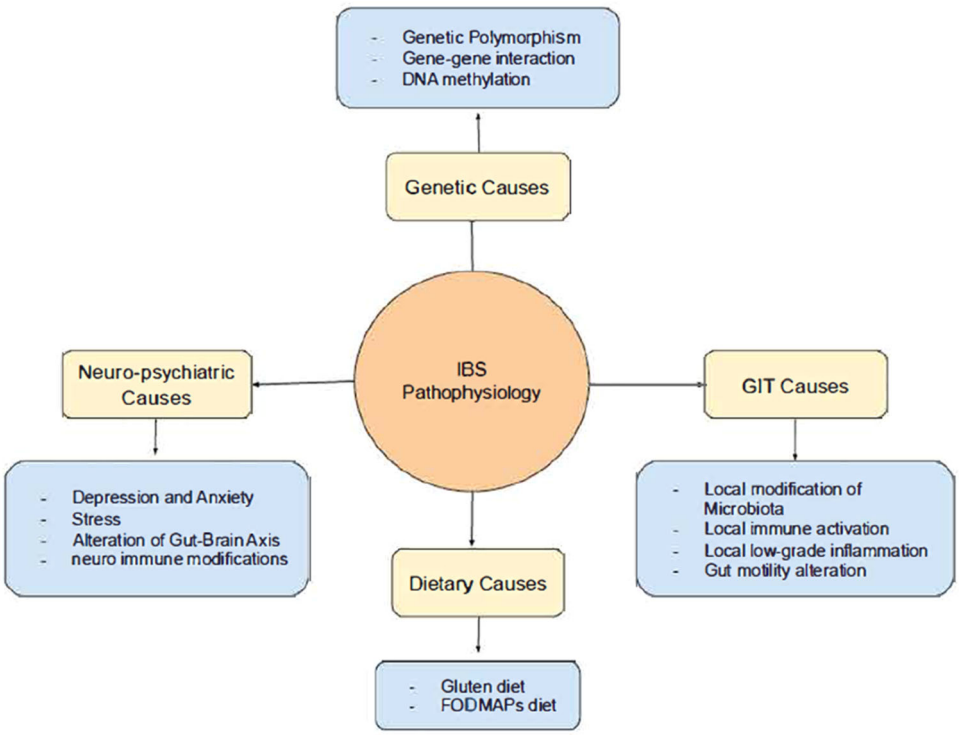

FIGURE 1 | Pathophysiological causes of IBS [17]. Figure created by Fatima Soufan [17, 18].

[13]. However, it is highly unlikely that an IBS patient suffers from one of the proposed etiologies alone, and a cumulative multifactorial proposition is increasingly probable [14]. Conventional insights into IBS suggest an etiology related to the spectrum of "gut-brain disorders", whereas novel concepts suggest the significant role of alterations to gut microbiota and the development of micro-inflammation in the maintenance of the gut–brain axis (GBA) [15, 16]. However, the combination of the altered intestinal microbiota amongst modification circumventing the GBA theorem have been increasingly accepted by the global medical community [13].

The GBA is that of a "two-way axis", where each individual entity is affected by another [19]. The central (CNS) and enteric nervous systems (ENS) are highly connected, respectively. Thus, when a sensory stimulus is perceived, the brain—aided by previous memories and higher executive cognition—alters it to fluctuations in mood [20]. This affects the CNS and, in a similar manner, the ENS, which causes changes in immunomodulator secretion, immunity, and motility [20]. This has been well-established in historical studies, where increased descending colon distention has occurred in relation to nociception and emotion phenotype [21]. In another study, corticotropin-releasing hormone (CRH) administration increased gut motility [22], whereby CRH antagonists showed a decreased response [23]. A third study using functional MRI (fMRI) in rectal distention studies illustrated increased blood oxygen level-dependent (BOLD) signals in areas associated with one's emotional state, including the anterior cingulate cortex, midcingulate cortex, insula, prefrontal cortex, and the amygdala [24]. The increase in BOLD activity is critical in elevated neuronal activity, thus the aforementioned areas are more sensitive in IBS populations compared to their counterparts [24].

A personalized approach to preventive therapy against IBS employing that of the GBA hypothesis may be encroached by comprehending the roles of neuroimmune interaction and microbiota alteration. Nonetheless, there remains a dearth in our understanding regarding this correlation, particularly the pathophysiological mechanisms that underpin treatment and prevention. Hence, this review aims to provide an updated insight to the GBA in IBS and the importance of microbiota alteration as well as neuro-immunological interaction in mediating personalized prevention strategies.

2 | The Gut–Brain Axis: A Complex Communication Network

Playing as a bidirectional network of communication, the gut–brain axis constitutes an integration system of both central and enteric nervous systems with each of the gut microbiota and neuroimmune interactions [25]. This communication system is influenced by metabolites secreted by microbes, including short-chain fatty acids and tryptophan, that can primarily affect neuronal signaling and modulate immune responses [26, 27]. In the first direction, from the gut to the brain, the message travels either through the central or enteric and vagal afferent from the microbes in the tract to the brain [25]. This in turn creates a specific response interacting with the autonomic and HPA activities. On the other hand, the core of the gut–brain axis, the interoception, is the ability of the brain to handle the internal physiologic state of an individual and control the appropriate hemostatic reactions to the cognitive and emotional and actions [28]. Failure to fulfill this duty altering this signaling pathway, as in the cases of barrier destruction and microbial dysbiosis, can manifest as disorders of the gut brain axis like IBS [29, 30]. It is important to acknowledge that understanding the gut–brain axis is essential foundation for novel therapeutic directions targeting microbiota and neuroimmunity in IBS.

3 | Microbiota and Its Role in IBS

The surfaces entailing the human body are all lined with many a variety of different microorganism species that constitute the human microbiome [18]. Of these, the gut microbiome in particular is composed of trillions of microorganisms, from fungi and viruses to bacteria, all of which inhabit the human gastrointestinal tract and live in symbiosis with the host [18, 31]. These contribute to the overall maintenance of human health by fostering a profound role in nutrition and immune development as well as host defense (Table 1) [31]. In adults, the gut microbiome is primarily composed of bacteria belonging to the following phyla: *Firmicutes, Bacteroidetes, Enterococci,* and *Propionibacterium*, as the beneficial bacteria, and several opportunistic bacteria including *Bacilli, Clostridia,* and *Staphylococci* groups, among others [18].

Dysbiosis, pertaining to any disruption in the balance of gut microbiota, is found to be associated with several gastrointestinal disorders, including IBS [18, 34]. It has been proposed that an imbalance in intestinal flora is a likely cause of IBS [35]. Several studies have shown that there is a difference in the gut microbiome composition when comparing between healthy controls and IBS patients that may occur due to different mechanisms (Figure 2) [34, 36]. Although the difference is not found to be congruous, which may be due to several factors that affect microorganism composition, one change has been reported by several studies—that of an increase in the ratio between the phyla *Firmicutes* and *Bacteroidetes* with a relative increase in the *Bacilli* and *Clostridia* classes [34]. This may be attributed to the changes in epithelial permeability and low-grade colonic inflammation, which is among suggested mechanisms proposed for IBS pathophysiology [34].

The brain–gut–microbiome axis is a bidirectional pathway of communication [36]. Communication from the gut microbes to the CNS is performed via three channels interacting congruously; nervous, endocrine, and immune pathways [36]. The brain, through the autonomic nervous system (ANS), affects the structure of the gut microbiome through changes in gut motility, intestinal permeability, and hormone/colonic secretions [36]. These changes in physiology play a role in altering the constitution and activity of the gut microbiome [36]. Furthermore, the neuroendocrine system in itself can communicate directly with the gut microbiome via the release of several neurotransmitters, the process of which is regulated by the CNS [36, 37]. In turn, a bottom-up modulation of the CNS by the gut microbiome is conducted mainly through neuroimmune and neuroendocrine mechanisms [36, 37]. Any divergence in this pathway has been shown to play a role in the pathophysiology of

TABLE 1 | Micriobiota classification and role in the gut.

Microbiota	Beneficial	*Lactobacillus* *Bifidobacterium* *Enterococci* *Propionobacteria*	Role of microbiota in the gut	Nutrition	Synthesis of Vitamin K and B by *Bifidobacterium*
	Opportunistic	*Bacteriodes* *Bacilli* *Clostridia* *Enterobacteria* *Actinobacteria* *Peptococci* *Staphylococci* *Streptococci*		Immune development and host defense	Production of short chain fatty acid that have anti-inflammatory and immunomodulating characteristics
References			[18]		[32, 33]

Note: Table created by Fatima Soufan [18, 32].

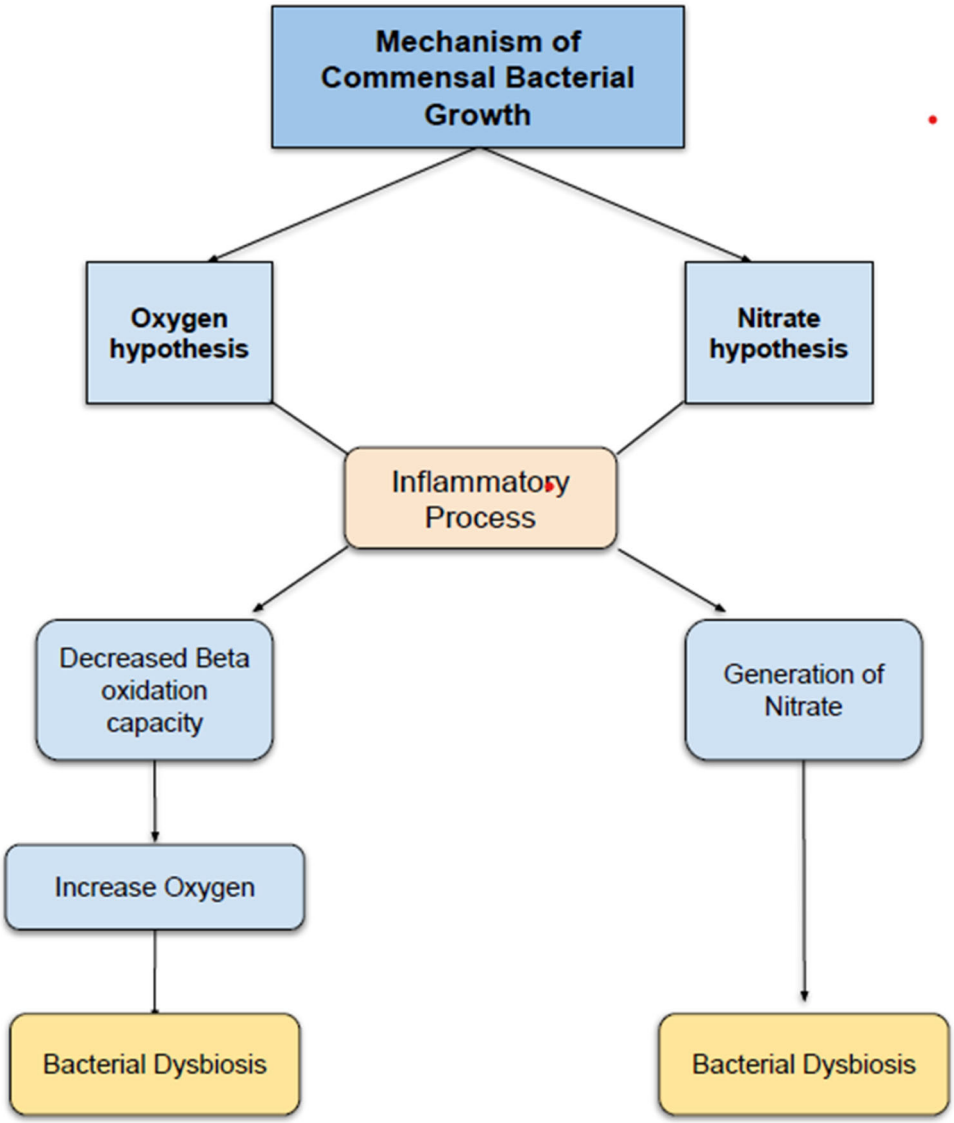

FIGURE 2 | Mechanisms of commensal bacterial growth resulting in dysbiosis [18]. Figure created by Fatima Soufan [17, 18].

several functional GI disorders, including that of IBS [34, 36, 37]. Studies have also demonstrated that the gut microbiota contribute to intestinal inflammation and immune dysfunction via the GBA [35].

3.1 | Neuroimmune Interactions in IBS

The nervous and immune systems work in tandem in host defense [38]. This combined neuroimmune system acts to protect healthy human tissue [38]. Communication entails G-protein and tyrosine kinase receptors. Although this interaction is crucial for host protection, it has potential for unrestrained amplification, which in turn may facilitate pathology development [38].

In the human body, the gut is considered as the largest organ for immunity when considering its T-cell heavy content owing a surface area of almost 400 m^2 [31]. The innate and adaptive immune systems are found in the scattered, connective, and organized gut-associated lymphoid tissue (GALT) [31]. This comprises lymphoid-dense Peyer's patches, isolated lymphoid follicles, and the appendix [31].

One proposed mechanism for IBS pathophysiology is abnormal neural pathways with changes in both immune and endocrine systems [35]. Intestinal flora play a role in both the immune and nervous system of the intestinal mucosa, though the mechanism of which is not fully understood [35]. The intestinal mast cells release inflammatory mediators, which in turn act on the endocrine and nerve cells, to release neurotransmitters. These affect intestinal motility and sensation, leading to hypersensitivity within intestinal nerves, precipitating IBS symptoms [35]. This clinical presentation is attributed to abnormal colonic motility alongside visceral and central sensory abnormalities [35]. In other words, intestinal inflammation changes the nature of gut microbes which in turn alter the neurotransmitters in the brain [39]. For instance, microbes of the gastrointestinal tract release short-chain fatty acids (SCFAs) that reinstate blood–brain barrier and rehabilitate microglia which is highly critical for the neuroimmune regulation [40, 41]. This will in turn regulate the immune system cells and fine-tune the epithelial cells of the gut supporting the neuroimmune functions, and by that emphasizing on the essential role of a healthy gut on the neuroimmune stability. Therefore, alterations in gut microbes are connected to neurotransmitter expression abnormalities, and so would affect the intestinal neuronal pathway [35]. For instance, this will affect the production of gut hormones as glucagon-like peptides (GLP-1, GLP-2) as well as peptide YY (PYY) that are essential for the intestinal micro-motility and mucosal integrity [42]. This microbial dysbiosis is directly associated with activation of systemic immunity as well as the dysfunction of the autonomic nervous system, particularly with the imbalance between sympathetic and parasympathetic signals leading to exacerbation of IBS symptoms specifically with bowel movements [43]. Actually, a previous study showed that this imbalance is present in patients with IBS when compared to controls [44]. In addition, another study done on females with IBS showed decreased vagal activity associated with marked constipation [44].

3.2 | Microbiota and Neuroimmunity: Understanding the Interaction

The GBA has long been described to simplify the study of the effect of stress on the human gastrointestinal system [45]. This has been studied across many different papers for more than 70 years and has shown that almost all gastrointestinal illnesses may be exacerbated by stress [45]. New studies have demonstrated that IBS has a particular sensitivity to stressors unlike other disorders [45]. The mechanism in which the GBA affects an IBS patient may be due to increased sensation of abdominal movement and contraction from hypersensitivity, or from increased uncontrolled motor contraction of the gastrointestinal smooth muscle [20]. This mechanism is also affected by peripheral modulators, as soothing memories and hypnosis provide relief and increasing stressors and unpleasant conditions tense the patient more [20].

Previous authors have described the enormous effect microbiota has on the GBA by introducing the term psychobiotics, which refers to microorganisms capable of affecting the GBA through release of psychoactive modulators [46]. The need for the existence of this term becomes apparent when the positive response of patients with gastrointestinal disturbances, also suffering from mood disorders, have been reported after the use of psychobiotics [47, 48]. On the contrary, novel studies have elucidated that some intestinal microbiota may affect the HPA axis and in turn increasing the level of stress hormone in the blood exacerbating the symptoms of IBS [49]. Other mechanisms in which gut microbiome influences the GBA are via cytokines, neuronal effect on the vagus nerve, and metabolic effects [50]. This may explain the fact that more than half of the patients suffering from IBS experience psychiatric illnesses that are not limited to depressive episodes, panic attacks, and anxiety [51, 52].

The microbiome–gut–brain effect is more apparent when studying the commonly used treatments that may help IBS patients, most notably IBS-M patients, include the low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet [7]. Ingestion of these poorly absorbed elements generally do not pose a problem on the healthy population [53], whereas IBS patients report great improvement of their symptoms after relying on the low FODMAP diet [7]. The gut microbiome of the positive responders appears to differ from the healthy microbiota, which postulates the effect of bacterial dysbiosis in a disturbed GBA as in IBS [54]. On the other hand, Melanocortin peptides, exerting their effect through MC1–MC5 melanocortin receptors, are considered of high immunomodulatory effect and strong anti-inflammatory influence [55], which in light of inflammatory reactions, can help reduce the symptoms of IBS. Thereby, the activation of this system can alter key mechanisms in IBS exhibiting a neuroprotective potential highlighting the association between microbiological dysbiosis and neuroimmune dysfunction.

The role of intestinal bacteria in IBS as an important mood regulator is still under investigation. This idea has had increasing momentum after many studies in which IBS patients who were administered probiotics for as little as 4 weeks

reported relief and improvement of their mental condition, particularly depression [56]. This influence is reported to be by means of serotonin biosynthesis (*Escherichia*, *Enterococcus*, *Candida*, and *Streptococcus*) [57–59] via the enterochromaffin cells in the microbiota–gut–immune-glia axis [60]. The benefits of a healthy microbiome are not limited to serotonin synthesis only. Indigestible plant derived polysaccharides can be broken down by probiotics to short-chain fatty acids (SCFA) as lactic and acetic acids [56]. Their function as an immuno-modulator in decreasing inflammatory cytokines has also been well described [56]. Neurochemical production of neurotransmitters, including GABA (*Lactobacillus* and *Bifidobacterium*), tryptamine, noradrenaline, dopamine (*Bacillus*), and acetylcholine (*Lactobacillus*) in the gut has been pronounced [56, 61–63].

3.3 | Implementing Personalized Prevention Plans Mediated by the Microbiota—Neuroimmunity Interaction in IBS

3.3.1 | Precision Medicine in Gastroenterology

Precision medicine, a term that was initially denoted in 2011, is a method developed to find an accurate and exact strategy to prevent, detect, and manage certain diseases [64]. It is an approach that targets the illness based on patient's specific biological characteristics [65]. However, personalized medicine, a promising newly emerging terminology, is more broad and able to achieve the goal set by the WHO for health [65]. It tackles health from biological, psychological, and social perspectives [65]. This helps in using patients' genetic factors, environmental background, and behavioral style to categorize them so that they can be targeted precisely when treated for a certain disease [64].

Based on the extensive requisites in an individualized approach, thorough evaluation is needed to assess individual's sociodemographic factors, behavioral determinants, personal and family medical history, and genetic susceptibility [66]. Besides, complex diseases are now comprehensively analyzed; beside primitive investigations usually performed, certain genetic and immunological profiling are added [67]. Additionally, considering multiple factors together tailors risk stratification and thus allows targeting and educating patients with amplified vulnerability [67].

To illustrate precision and personalized medicine applied with different strategies showed a successful approach in different medical disciplines, one of which was the field of gastroenterology [67–69]. In Inflammatory bowel diseases, patient specific features are considered very crucial to target treatment and enhance clinical outcome [67]. For instance, genetic variations, lifestyle factors, and even the severity of the disease all are determinants that tailor treatment of IBD and have an impact on the clinical result [67]. Moreover, prevention and treatment of different gastrointestinal tumors depends on patient's biopsychosocial aspects [68]. To illustrate, concentrating on different behavioral traits, as tobacco and alcohol use, and specific comorbidities, like chronic gastritis and having stomach polyps, and unique genetic mutations and conditions such as familial adenomatous polyposis and lynch syndrome are factors that increase likelihood of developing gastric cancer [70]. Thus, an individualized approach is essential to precisely sort people to avoid and prevent developing gastric cancer [71].

3.3.2 | Personalized Prevention Plans in IBS

Back to our topic, irritable bowel syndrome, being a chronic heterogeneous functional gastrointestinal disease, requires a detailed patient targeted approach to prevent it and ameliorate its symptoms (Figure 3) [69]. It is evident by literature that IBS is altered by any dysregulation at the level of GBA and thus it is affected by modifications of gut microbiota, CNS, ENS, ANS, endocrine, and immune system [67]. Based on the multi-factorial aspect behind the pathogenicity of IBS a wide spectrum of presentations enhances the need for personalized plans to target patients [72].

Individualized assessment of gut microbiota in IBS is of crucial role since researchers failed to find a distinctive gut microbiota profile for patients suffering from IBS [73]. This could be due to the alteration of gut microorganism composition that is influenced by various factors such as age, sex, ethnicity, and diet [74]. It is worthy to note that comprehending the signature gut microbiota in IBS can help clarify the interlink between gut microbiota and the pathophysiology of the disease [74]. Additionally, it is an essential and freshly evolving way to guide targeted interventions aiming to restore gut dysbiosis and lessen symptoms [69]. For that, different targeted therapies such as the use of prebiotics, probiotics, antibiotics, and fecal microbiota transplantation address the imbalance of gut microbiota and play a crucial role in managing patients' symptoms [69].

Furthermore, the increase in gut permeability due to alteration in microbiota in IBS patients allows health care providers to target different biomarkers that are related to enhanced permeability [75]. For instance, Zonulin, a biomarker that reflects gut barrier dysfunction, is increased in both blood and stool samples of IBS patients and is related to severity of symptoms [76]. Thus by estimating the levels of these biomarkers individualized approach could be adopted to help restore normal gut integrity [75].

Besides, the GBA assessment showed that in IBS, psychological stress induces immunological dysregulation through neuronal triggering and triggers mast cells to release different markers such as chemokines, cytokines, serotonin, and histamine [77]. Collectively these markers induce gut inflammation and enhance barrier dysfunction contributing in the development of various IBS symptoms [77]. On the other hand, serotonin by itself can stimulate mast cells and thus amplify the inflammatory cascade in the gut [77]. For that the regulation of the inflammatory cascade at the level of gut mucosa in IBS is attained by targeting serotonin pathway. To illustrate, studies showed that agents targeting serotonin pathway interfere in the inflammatory cascade and cause amelioration in IBS symptoms [78–82]. In particular, serotonin reuptake inhibitors [80], 5-HT3 antagonists [83–85], and 5-HT4 agonists [78, 79] have been enrolled in the symptomatic management of IBS.

Moreover, the increase in pro-inflammatory cytokines (IL-6, IL-8, and TNF-alpha) and the decrease in anti-inflammatory cytokines (IL-10 and transforming growth factor beta) [84–86]

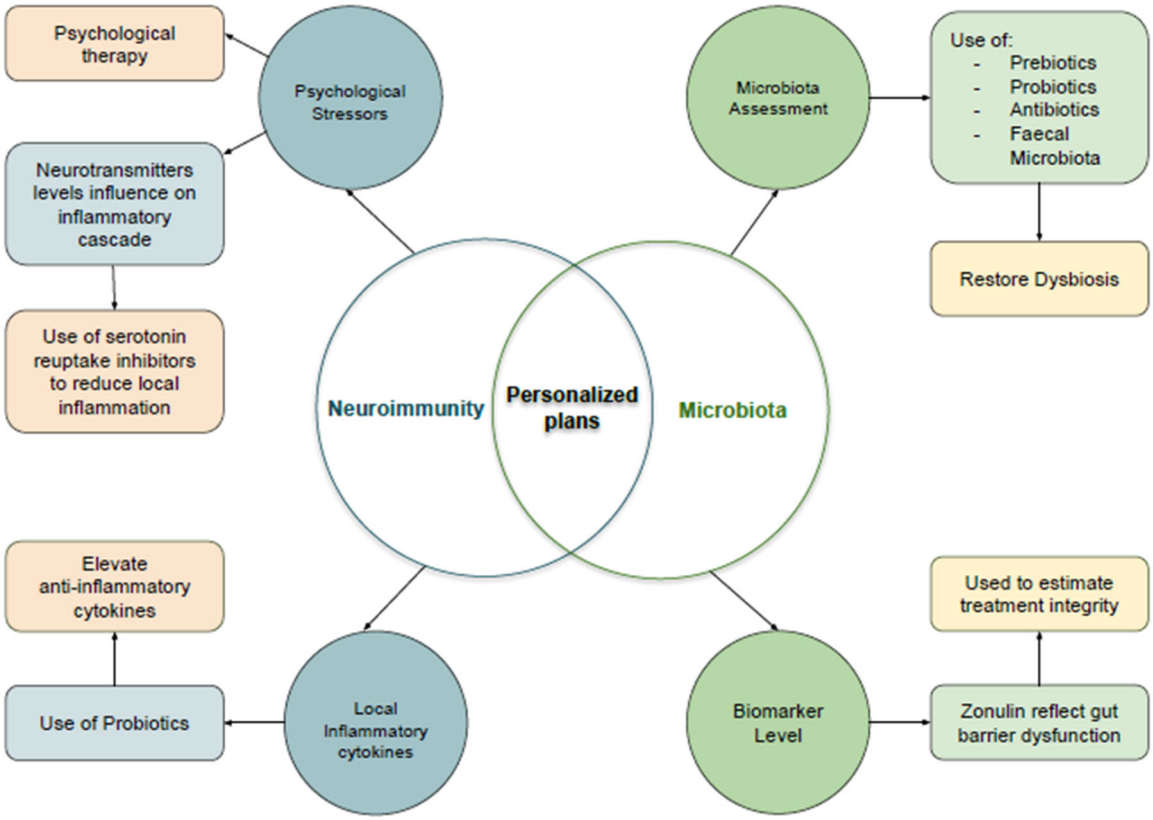

FIGURE 3 | Multifactorial aspects of personalized prevention plans in IBS. Figure created by Fatima Soufan [17, 18].

seen in IBS patients can cause alterations in the gut function through their neuromodulatory effect. Probiotics, for example, can interfere in gut immune response through the elevation of anti-inflammatory cytokines and thus alleviate IBS symptoms [87]. For that understanding the neuroimmunity profile of patients suffering from IBS has a great impact on tailoring the management in an individualized manner [72].

3.3.3 | Successful Stories and Future Insights

Successful approaches in personalized medicine among patients with IBS are escalating. Such as an illustration, the assessment of individual microbiome composition tailors the management of IBS by various microbiome targeted therapies such as prebiotics, probiotics, and fecal microbiota transplantation [11]. Moreover, targeting the serotonin pathway by multiple agents such as SSRI and SNRI offer promises in personalized medicine [80].

Further, with advancing technologies, it is important to develop and utilize AI models in the preventive plans. Recommendation systems with AI-based models, utilizing deep learning algorithms, can be developed targeting specific dietary alterations and stress management techniques recommending them with specific instructions based on the pre-known analyzed personal data (genetic profile, microbiota, stress level, and diet). Furthermore, by integrating recurrent neuronal networks, these systems can track changes and adapt to new data from wearable devices thus updating prevention plans as needed. For instance, wearable patches can analyze sweat and skin secretions continuously to detect metabolites. In addition, personalized dietary AI assistant can be advanced and recommended as a real time assistant to improve gut–brain axis health by suggesting modification tailoring meal plans of the patients.

3.4 | Challenges and Limitations

However, many challenges and limitations are met while studying such a complex and heterogeneous disease through a precisely individualized approach. Understanding the complexity of the disease pathophysiology hinders health care providers' ability to find a way to prevent the disease and works more on the amelioration of symptoms. Besides, the variability in patients' biopsychosocial factors affects the degree of response to different treatments and requires targeting large samples to study the influence of targeted therapies. Although some biomarkers are linked to IBS still the shortage of knowledge of these markers cause a great challenge in studying IBS using a personalized and precise plan. Future directions should include the development of advanced techniques able to categorize patients based on their biopsychosocial factors. Also, further research should target large and variable samples to deeply understand the effect of diverse personalized plans in IBS prevention and management. Additionally, it is important to direct further research to explore the bidirectional relation between gut and neuroimmunity to search for more biomarkers that are of great value in individualizing plans for avoidance and treatment of IBS.

4 | Conclusion

Several theories are proposed as a possible pathophysiology of the functional gastrointestinal disorder known as IBS: altered microbiota of the intestine and irregularities in the GBA are two of the more accepted theories. Studies demonstrated that microbiota affects the GBA by releasing psychoactive modulators and the HPA which in turn regulates the level of stress hormones in the blood. The personalized medical approach, which focuses on health from biological, psychological, and social aspects, has shown encouraging outcomes in various medical specialties, including gastroenterology. In IBS, its wide spectrum of presentation and multifactorial etiology strengthens the need for the personalized approach. For instance, it is essential to assess the microbiota and target the alteration by restoring gut dysbiosis. In addition, studies have shown that neurotransmitters and cytokines also play a role in changing the gut function, and so grasping the neuroimmunity profile of IBS patients enhances personalized management.

The effect of microbiota on GBA and dysbiosis and their relation to neuroimmunity in IBS provides a promising basis for further development of tailored personalized management of the illness. Thereby, further investigations should focus on specifying the specific types of microbes, exploring the microbiota–neuroimmune interaction, and identifying specific biomarkers for the diagnosis and risk stratification of patients allowing the development of personalized prevention and management plans. Furthermore, prioritizing interdisciplinary research and investigations by policy makers by allocating available resources and supporting arising researchers. In addition, embracing personalized medicine by physicians and clinicians by education and integration of microbiota investigation and neuroimmune targeting methods in the management plans. In essence, revolutionizing the IBS management and prevention by implementing and advocating the methods of personalized medicine may provide better quality of life for millions.

Author Contributions

Fatima Soufan: writing – original draft, methodology, writing – review and editing, formal analysis, data curation. **Abir Ghosson:** data curation, formal analysis, methodology, writing – original draft. **Rayyan Jaber:** writing – original draft, methodology, formal analysis, data curation. **Adel Ghandour:** data curation, formal analysis, methodology, writing – original draft. **Olivier Uwishema:** conceptualization, writing – original draft, writing – review and editing, project administration, formal analysis, supervision.

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Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

Transparency Statement

The corresponding author Olivier Uwishema affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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