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REVIEW

Therapeutic Potential of Flavonoids and Flavonoid-Rich Compounds in Irritable Bowel Syndrome

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Abstract: Irritable bowel syndrome (IBS) is a group of functional gastrointestinal disorders, characterized by impaired brain-gut axis (BGA) interactions, leading to symptoms such as abdominal pain, bloating, and discomfort, which significantly affect patients' quality of life. Although individuals with IBS are commonly treated with medications and lifestyle modifications, the side effects of various treatments and their inconsistent efficacy often leads to a recurrence that poses a significant burden for patients. Flavonoids, flavonoid-rich compounds extensively found in plants and known for their low toxicity, have been identified as potentially beneficial for various digestive disorders in recent years; however, clinical trials have not been widely conducted. It was suggested that flavonoids and flavonoid-rich compounds may positively influence IBS symptoms through regulation of low-grade inflammation, oxidative stress in the gut, visceral hypersensitivity (VH), intestinal motility dysfunction, dysbiosis of gut microbiome, and BGA. This article reviews the potential role of flavonoids and their compounds in the therapy of IBS, along with the associated mechanisms. Additionally, we highlight key issues that warrant further investigation and discuss the prospects and challenges of using flavonoids for managing IBS.

Keywords: irritable bowel syndrome, flavonoids, flavonoid-rich compounds, mechanisms

Introduction

Irritable bowel syndrome (IBS) is classified as a group of functional gastrointestinal disorders, with the Rome IV criteria indicating that its pathogenesis is associated with interactions within the brain-gut axis (BGA).[1] This axis refers to the bidirectional relationship between the nervous system and the gut, encompassing the central nervous system (CNS), the enteric nervous system (ENS), the neuroendocrine and immune systems, and the gut microbiota.[2] The primary manifestations of IBS include recurrent abdominal pain, as well as changes in bowel habits and stool characteristics.[3] Based on the primary symptoms and defecation patterns, according to the Bristol Stool Scale, IBS can be classified into four distinct subtypes:[4] IBS with predominant diarrhea (IBS-D), IBS with predominant constipation (IBS-C), IBS with mixed bowel habits (IBS-M), and unclassified IBS (IBS-U), with IBS-D accounting for approximately 30–40% of patients. Additionally, IBS may present following an infectious disease; this condition is defined as "post-infectious IBS" (IBS-PI).[5] The pathophysiological mechanisms of IBS have not been clearly defined. However, disturbances in intestinal motility, visceral hypersensitivity (VH), imbalances in gut microbiota homeostasis, aberrant regulation of intestinal endocrine cells and serotonin, activation of immune cells, and neuropsychiatric factors (including depression and chronic stress) are considered central manifestations and influencing factors.[6–9] Notably, dysregulation of the BGA has a multifaceted and integrative effect on intestinal sensory, motility, and secretory functions, which is believed to be directly related to the development of IBS.[10]

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The current treatment of IBS worldwide remains primarily focused on alleviating individual symptoms, including analgesics, laxatives, antispasmodics, and antidepressants.[11] Medications are prescribed to address various IBS symptoms. However, the side effects of these medications, along with issues such as recurrent IBS after treatment and adverse reactions following discontinuation, should not be overlooked. For instance, an overdose of loperamide may result in serious cardiovascular complications.[12] Rifaximin, a commonly prescribed medication for IBS-D, may be associated with side effects including headache, upper respiratory tract infections, and nausea.[13] Other treatments, including Traditional Chinese Medicine (TCM), microbial therapy, fecal microbiota transplantation, and non-pharmacological approaches (such as psychotherapy), are still under investigation.[14] Although several therapeutic options exist for IBS, traditional medications have notable drawbacks, and the issues of safety and efficacy throughout the treatment process must be thoroughly considered. Therefore, the search for new drug treatments remains an urgent priority.

Flavonoids, as natural polyphenolic compounds, are widely found in plants, fruits, vegetables, and other natural substances. They represent a significant component of various health products and TCM.[15] Flavonoids are categorized into seven subclasses: flavonols, flavones, flavanones, flavanols, isoflavones, anthocyanidins, and chalcones.[16] These compounds exhibit a wide range of antioxidant, anti-inflammatory, antiviral, anti-tumor effects, as well as the ability to reduce insulin resistance.[17,18] Flavonoids and flavonoid-rich compounds have been widely utilized with notable efficacy in therapeutic studies of cardiovascular diseases, urolithiasis, colorectal tumors, and other conditions.[19,20] The therapeutic potential of flavonoids and flavonoid-rich compounds in IBS has also been investigated to varying degrees in both preclinical and clinical research, focusing mainly on the modulation of VH, intestinal motility, barrier function, immune response, gut microbiota, and the BGA. Therefore, this review systematically explores the beneficial effects of flavonoids and flavonoid-rich compounds on IBS, summarizes their potential mechanisms of action, and aims to provide robust evidence and references for future clinical studies. The mechanisms of action of flavonoids and flavonoid-rich compounds in IBS are shown in Tables 1 and 2.

Table 1 The Mechanisms of Action of Flavonoids in IBS

Classification	Chemical Class	Subjects	Effective Dosage	Mechanisms	Reference
Flavonols	Quercetin	Mice	50, 100, and 200 mg/kg	Reduction oxidative stress (CAT and SOD levels). Alleviation intestinal inflammation (IL-17A and IL-22). Improvement intestinal epithelial barrier function (ZO-1 and occludin expression). Gut microbiota modulation (Bacteroides, Odoribacter, Streptococcus, Lactobacillus, and Roseburia).	[21]
	Quercetin	IPEC-1 cells	5 μM	Activation Nrf2 signaling pathway. Reduction oxidative stress (GSH). Improvement intestinal epithelial barrier function (ZO-1, ZO-2, ZO-3, occludin, and claudin-4). Reduction oxidative stress and apoptotic activity (ROS and caspase-3).	[22]
	Myricetin	Rats	25 and 50 mg/kg	Reduction oxidative stress (GPx, SOD, MPO, MDA and nitrite). Alleviation intestinal inflammation (IL-6 and TNF-α). Inhibition COX-2 activity. Inhibition NF-κB activity. Activation Nrf2 activity.	[23]
	Quercetin	Rats	5, 10, and 20 mg/kg	Alleviation VH.Upregulation 5-HT levels. Inhibition EC cell hyperplasia.	[24]
	Glycicumarin and isoliquiritigenin	Colon muscle strips of rats	0.1, 0.25, 0.5, 1.0, 2.0 mg/mL	Reduction colonic motility frequency. Inhibition colon muscle contraction in a concentration-dependent manner.	[25]
	Quercitrin	Mice	100 mg/kg	Modulation gut microbiota β-diversity. Gut microbiota modulation (Akkermansia and Lactococcus). Increase SCFA production (propanoate, isovalerate, hexanoate).	[26]
	Alpha-glycosyl isoquercitrin	Rats	0.05% or 0.5%	Improvement intestinal epithelial barrier function (ZO-1, occludin). Upregulation 5-HT levels Reduction LPS level. Gut microbiota modulation (Bacteroidetes, Butyricicoccus, Allobaculum, Sutterella). Enhancement butyrate levels.	[27]

(*Continued*)

Table 1 (Continued).

Classification	Chemical Class	Subjects	Effective Dosage	Mechanisms	Reference
Flavones	Luteolin	Rats; NCM 460 cells	80 mg/kg/d (rats); 1, 5, and 25 μM (cell)	Reduction oxidative stress (ROS). Inhibition intestinal motility. Activation Nrf2/HO-1 pathway.	[28]
	7,8-Dihydroxyflavone	Colon muscle strips of rats	1 mg/kg	Activation colonic motility. Activation TrkB/Akt/M3 pathway.	[29]
	Luteolin	Colon muscle strips of mice	10, 20 and 30 mm	Inhibition colonic smooth muscle motility. Inhibition L-type calcium channel activity.	[30]
	Luteolin	Mice	80 mg/kg	Improvement colonic function and inhibition intestinal dysmotility. Activation intestinal motility-related biomarkers (ACh). Activation ICC. Inhibition AQP-3, AQP-4, and AQP-8 expression	[31]
	Apigenin	Rats	20 mg/kg	Alleviation VH and intestinal motility. Inhibition mast cell and microglial activation. Improvement intestinal epithelial barrier function (ZO-1, Occludin). Gut microbiota modulation (Limosilactobacillus, Escherichia-Shigella, Enterococcus, Bifidobacterium, Streptococcus). Inhibition TLR4/MyD88/NF-κB pathway.	[32]
Flavanones	Kurarinone	Rats	100 mg/kg	Alleviation VH and intestinal motility. Alleviation intestinal inflammation (IL-6, TNF-α and IL-1β). Improvement intestinal epithelial barrier function. Activation AhR activity.	[33]
	Puerarin	Rats	6, 12 and 24 mg/kg	Alleviation intestinal inflammation (IL-1β, TNF-α and IL-6). Improvement colonic mucus barrier (occludin). Downregulation mast cell numbers. Gut microbiota modulation (Muribaculaceae, Lactobacillaceae, Ruminococcaceae, Peptostreptococcaceae). Inhibition CRF1 expression via HPA axis regulation. Activation colonic epithelial cell proliferation (p-ERK/ERK pathway).	[34]
	Naringenin	Mice	50 mg/kg	Alleviation VH. Reduction oxidative stress (GSH, MPO). Alleviation intestinal inflammation (IL-33, TNF-α and IL-1β). Inhibition NF-κB activity. Inhibition mechanical hyperalgesia and neutrophil recruitment. Activation NO–cGMP–PKG–K^+ channel signaling pathway.	[35]
	Eriodictyol 7-O-rutinoside	Mice	30 mg/kg	Alleviation VH. Suppression sensory injury via opioid and γ-aminobutyric acid receptor type A	[36]
	6-prenylnaringenin	Mice	200–400 mg/kg	Alleviation VH. Inhibition ERK activity (ERK-positive cell number). Inhibition Cav3.2 T-type Ca^{2+} channels.	[37]
	Hesperidin	Rats	50, 100, and 200 mg/kg	Activation intestinal motility. Upregulation 5-HT levels. Activation intracellular-free Ca^{2+}. Activation cAMP/PKA pathway.	[38]
Isoflavones	Soy isoflavones and cholecalciferol	Human	Soy isoflavones (40 mg/day), cholecalciferol (50,000 IU/15 days)	Alleviation intestinal inflammation (TNF-α). Inhibition NF-κB activity.	[39]
Anthocyanins	Cyanidin-3-O-glucoside	HepG2 cells	100 μg/mL	Inhibition oxidative stress (SOD, CAT and GPx). Gut microbiota modulation (Escherichia–Shigella, Lactobacillus, Bacteroides, Butyricimonas, Akkermansia). Activation Nrf2/HO-1 pathway.	[40]
Chalcone	Xanthohumol	Rats	10 mg/kg	Regulation HPA axis. Gut microbiota modulation (Asteroplasma, Lachnospiraceae, and Coprococcus). Activation SCFAs level.	[41]

Abbreviations: 5-HT, 5-hydroxytryptamine; Ach, acetylcholine; Akt, protein kinase B; CAT, catalase; CRF1, corticotropin-releasing hormone receptor 1; ERK, extracellular signal-regulated kinases; GSH, glutathione; HO-1, Heme Oxygenase-1; IL, interleukin; LPS, lipopolysaccharide; MDA, malondialdehyde; MPO, myeloperoxidase; MyD88, myeloid differentiation primary response gene 88; NF-κB, nuclear factor kappa B; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; PKG, protein kinase G; ROS, reactive oxygen species; SCFA, short-chain fatty acids; SOD, superoxide dismutase; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-α; TrkB, tyrosine kinase receptor B; VH, visceral hypersensitivity; ZO-1, zonula occludens-1; cGMP, cyclic guanosine monophosphate.

Table 2 The Mechanisms of Action of Flavonoid-Rich Compounds in IBS

Name	Main Ingredients of flavonoids	Subjects	Effective dosage	Mechanism of action	Reference
Serpylli herba extract	Kaempferol, quercetin and luteolin	Rats	100 mg/kg	Alleviation intestinal inflammation (IL-1β). Inhibition COX-2 expression.	[42]
Grape seed extract	Proanthocyanidin	Caco-2 cells	12.5 μg/mL	Reduction oxidative stress (ROS, SOD1, SOD2, GPx). Alleviation intestinal inflammation (IL-8, TNF-α and IL-6) Restoration mitochondrial function. Inhibition and mitochondrial superoxide production. Improvement intestinal epithelial barrier function (ZO-1, occludin, claudin-1).	[43]
Crataegus azarolus berries	Quercetin	Rats	100, 200, and 400 mg/kg	Reduction oxidative stress (SOD, CAT, GPx). Alleviation intestinal inflammation (C-reactive protein and alkaline phosphatase)	[44]
Camelina sativa	Quercetin-2″-O-apiosyl-3-O-rutinoside and rutin	Mice	5 g/kg	Reduction oxidative stress (MDA, SOD, GPx).	[45]
Chang-Kang-Fang	Epicatechin and hyperoside	Rats	0.54, 1.08, 2.15 g/kg	Alleviation intestinal inflammation (IL-1β, TNF-α and IL-6). Inhibition mast cell infiltration. Improvement intestinal epithelial barrier function (occludin). Inhibition TLR4/NF-κB/NLRP3 signaling pathway.	[46]
Mao Jian Green Tea	Apigenin, eriodictyol, luteolin, and naringenin	Rats	17 mg/mL	Alleviation VH and colonic motility. Upregulation 5-HT expression. Activation HTR4 expression.	[47]
SiNiSan	Isorhamnetin, quercetin, naringin, and kaempferol	Rats	10 g/kg	Alleviation intestinal dysfunction and VH. Alleviation intestinal inflammation (IL-1β, PKC). Activation NGF and HTR2A expression.	[48]
Tilia tomentosa Moench	Quercetin and kaempferol	Colon muscle strips of rats	0.5–36 μg/mL	Inhibition colonic motility. Involvement NO and tachykininergic pathways.	[49]
SiNiSan	Isorhamnetin, quercetin, naringin and kaempferol	Mice	6.24 g/kg	Alleviation VH. Alleviation intestinal inflammation (TNF-α, IL-1β, and IL-6) Improvement intestinal barrier function (ZO-1, occludin). Regulation TLR4/MyD88/NF-κB signaling pathway.	[50]

(*Continued*)

Table 2 (Continued).

Name	Main Ingredients of flavonoids	Subjects	Effective dosage	Mechanism of action	Reference
WeiChang'An Pill	Quercetin and catechin	Rats	21.60, 43.20, 64.80, 86.40, 108.00 mg/mL	Alleviation VH. Inhibition NF-κB expression. Regulation cAMP pathway.	[51]
Pugionium cornutum (L). Gaertn	Quercetin	Colon muscle strips of rats	0, 20, 40, 60, 80 or 100 mg/mL	Inhibition colonic motility Activation intracellular calcium influx. Involvement COX and NO/PKC signaling pathways.	[52]
Cucumis melo L. seeds	Rutin, naringenin, and quercetin	Mice	50, 100, 150, 200, and 300 mg/kg	Inhibition colonic motility. Regulation calcium-mediated smooth contraction	[53]
Rosmarinus officinalis L.	Diosmetin, rutin, and apigenin	Mice	25, 50 and 75 mg/kg	Bidirectional regulation of intestinal motility (low dose: laxative; high dose: antidiarrheal). Activation K^+ channels. Modulation of cholinergic and histaminergic receptors.	[54]
Cirsium palustre extracts	Apigenin, luteolin and apigenin 7-O-glucuronide	Colon muscle strips of pigs	0.001–100 μM	Bidirectional regulation of intestinal motility.	[55]
Cynanchum thesioides	Quercetin and tamarixetin	Rats	0.27 g/kg	Alleviation VH. Gut microbiota modulation (Pseudomonas, Fusobacterium and Bacteroides). Upregulation lysine biosynthesis.	[56]
Persimmon fiber-rich ingredients	Gallic, protocatechuic acids, delphinidin and cyanidin	Caco-2 cell	100, 250, and 500 μg/mL	Alleviation intestinal inflammation (TNF-α, IL-1β, and IL-6). Gut microbiota modulation (Firmicutes). Upregulation butyric acid level.	[57]
Amomum tsaoko	(+)-epicatechin, (-)-catechin, L-epicatechin, and isoquercitrin	Mice	250, 375 and 500 mg/kg	Activation colonic motility Upregulation 5-HT, phospholipase A2, and COX-2 expression. Gut microbiota modulation (Lactobacillus, Bacillus; Lachnospiraceae).	[58]

Abbreviations: 5-HT, 5-hydroxytryptamine; CAT, catalase; COX, cyclooxygenase; COX-2, cyclooxygenase-2; cAMP, cyclic adenosine monophosphate; GPx, glutathione peroxidase; HTR, 5-hydroxytryptamine receptor; IL, interleukin; MDA, malondialdehyde; MyD88, myeloid differentiation primary response gene 88; NF-κB, nuclear factor kappa B; NGF, nerve growth factor; NO, nitric oxide; PKC, protein kinase C; ROS, reactive oxygen species; SOD, superoxide dismutase; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-α; VH, visceral hypersensitivity; ZO-1, zonula occludens-1.

Flavonoids: Structure, Sources, and Biochemical Properties

Flavonoids are a class of polyphenolic compounds widely distributed in the plant kingdom, primarily located in the leaves, flowers, roots, stems, and fruits of plants. Flavonoid molecules possess a C6-C3-C6 carbon backbone (primary structure) comprising a benzo-γ-pyranone and a benzene ring.[17] The benzene and phenyl rings are designated as the A and B rings, while the oxygenated γ-pyranone ring is referred to as the C ring. Flavonoids can be classified into various subclasses based on the position of the B ring attached to the C ring, the oxidation state of the heterocyclic ring, and the degree of saturation. Isoflavones represent a distinct subclass of flavonoids, characterized by the B ring being attached to

the third position on the C ring. In contrast, the other subclasses—including flavones, flavonols, flavanones, flavanols, anthocyanidins, and chalcones—exhibit the B ring attached to the second position on the C ring. Based on the degree of saturation of the central heterocyclic ring, flavonoids can be categorized into two major classes: saturated and unsaturated. The unsaturated class includes flavones, flavonols, and isoflavones, whereas anthocyanidins and flavanones belong to the saturated class.[59]

Quercetin, rutin, kaempferol, isorhamnetin, myricetin, and tamarixetin represent the flavonols subclass prevalent in green leaves, fruits, and grains.[60] Flavones are one of the most prominent subclasses of flavonoids, abundant in foods such as chamomile, celery, carrots, and mint, where they are primarily found in glycoside form, characterized by compounds like apigenin, luteolin, 7,8-dihydroxyflavone, and tangerine.[61] Flavanols, including catechin, epigallocatechin, and epicatechin, are primarily present in tea plants, tea leaves, and certain fruits.[62] Flavanones serve as both direct precursors and terminal products of other flavonoid compounds, predominantly present in citrus fruits. These compounds are optically active and commonly occur as naringin, naringenin, and eriodictyol.[63] Isoflavones, including puerarin, genistein, and daidzein, are mainly derived from soybeans and other legumes[64] and are widely used in nutraceutical preparations due to their high bioavailability. Anthocyanidins, including delphinidin, cyanidin, and petunidin are less stable and often exist in glycosylated forms, making them difficult to absorb and metabolize. They are primarily found in angiosperms and many blue, purple, and red fruits.[65] Chalcones, which serve as precursors for flavonoids and isoflavonoids, are widely distributed in the Fabaceae, Moraceae, Zingiberaceae, and Cannabaceae families, with xanthohumol and isobavachalcone being notable derivatives known for their significant biological and pharmacological activities.[16] Sources, structures, and classifications of flavonoids are shown in Figure 1.

Most flavonoids exhibit low bioavailability, whereas isoflavones possess the highest bioavailability among all flavonoid types. Furthermore, the metabolites resulting from the degradation of flavonoids in the body positively affect human health. Glycosylated flavonoids form β-glycosides, which are metabolized by gut microorganisms into phenolic

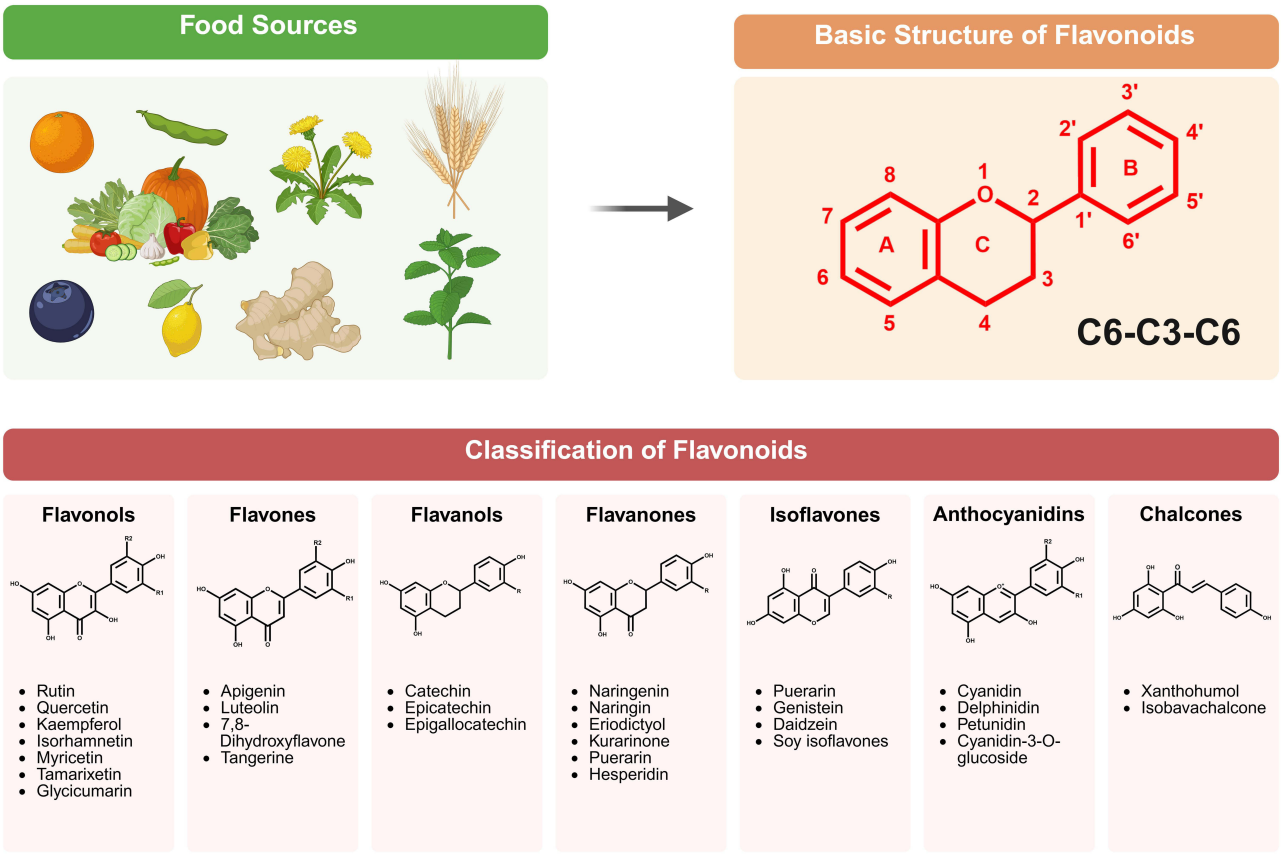

Figure 1 Sources, structures, and classifications of flavonoids. Created in BioRender. xia, y. (2025) https://BioRender.com/9tyh1he.

acids, thereby enhancing absorption.[66] These metabolites play a beneficial role in managing local inflammatory states. They can also act indirectly as prebiotics, promoting the growth of probiotics and thereby improving intestinal health. Quercetin and chlorogenic acid are metabolized in the colon to produce various low molecular weight phenolic acids, which exhibit antiproliferative activity on colon cells.[67] Flavonoids undergo modifications in the gastrointestinal tract, including glycosylation, methylation, and glucuronidation, resulting in various flavonoid conjugates with distinct biological activities.[68] Flavonoids are recognized for their diverse biological and pharmacological activities, including antioxidant, anti-inflammatory, anti-allergic, antibacterial, antidiarrheal, and anticancer properties. Flavonoids can regulate blood glucose levels and enhance cardiovascular function.[69–72] Due to their structural characteristics, flavonoids hold significant potential for health promotion and disease prevention. They are crucial in pharmaceutical research and natural drug development, and are widely utilized in the formulation of nutraceuticals and pharmaceutical preparations.

Pathophysiology of IBS

Accumulating evidence underscores the multifactorial nature of IBS, encompassing low-grade inflammation and immune dysregulation, VH, gut motility disturbances, and microbiota alterations. Low-grade inflammation and immune activation serve as central mediators linking environmental stressors to gut-brain interactions and mucosal barrier dysfunction. Potential factors influencing the manifestation of IBS are shown in Figure 2.

Low-grade inflammation is increasingly recognized as a contributing factor in IBS pathogenesis. Clinical investigations demonstrate that patients with IBS exhibit a higher systemic immune-inflammatory index, characterized by increased platelet and neutrophil counts and reduced lymphocyte levels.[73] The activation of mucosal immune cells is significantly elevated, with increased numbers of T cells and mast cells.[74] The gastrointestinal tract, highly sensitive to stress and external insults, experiences oxidative stress and excessive reactive oxygen species (ROS) accumulation, potentially leading to localized mucosal injury, ulceration, inflammation amplification, and barrier disruption. The interaction between lipopolysaccharide (LPS) and the Toll-like receptor 4 (TLR4) / cluster of differentiation 14 (CD14) receptor complex may trigger an inflammatory cascade, compromising the integrity of the intestinal barrier. Nuclear factor kappa B (NF-κB), the terminal effector transcription factor in the TLR4 signaling pathway, plays a key role in the transcription and translation of inflammatory mediators.[75] Mild inflammation also activates nearby enteric neurons, inducing neuropeptide release that subsequently stimulates immune cells to produce immunomodulators, thereby influencing gut-brain communication.[76]

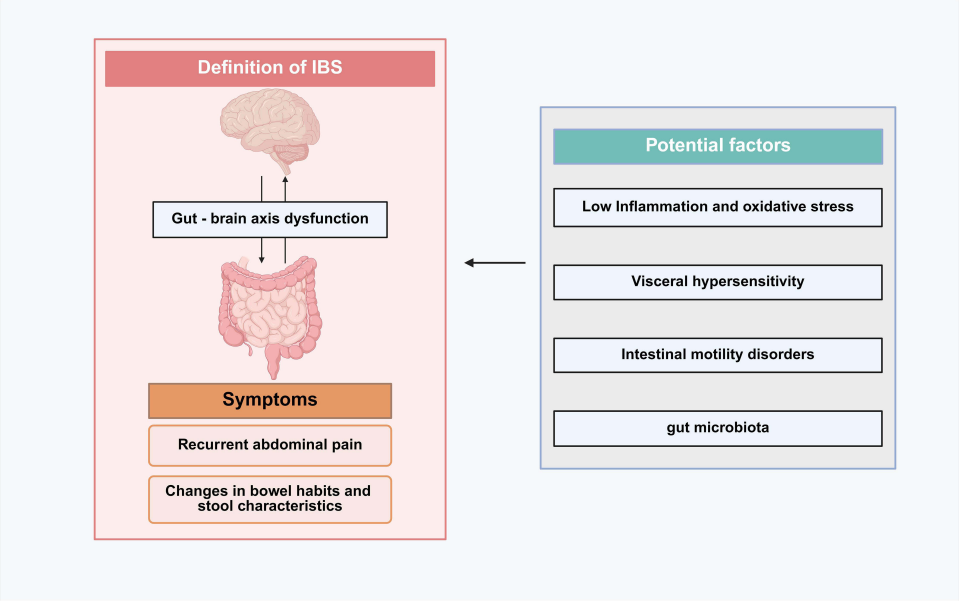

Figure 2 Potential factors influencing the manifestation of IBS. Created in BioRender. xia, y. (2025) https://BioRender.com/s47x062.

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VH is a hallmark of IBS, characterized by nociceptive amplification and altered pain processing. Low-grade mucosal inflammation triggers immune activation, cytokine release, and immune cell infiltration, sensitizing visceral afferents and leading to abdominal pain.[77] Notably, mast cells, protease activity, and transient receptor potential vanilloid subfamily 1 (TRPV1) receptors are particularly implicated,[78] alongside other nociceptive receptors such as acid-sensing ion channels, purinergic, histaminergic, and protease-activated receptors 2 (PAR2).[74] Immune activation, characterized by the presence of mast cells and macrophages, significantly contributes to the mechanisms underlying VH. Increased mast cell populations can compromise the epithelial barrier[74,79] and provoke neuroimmune responses through the release of tryptase, histamine, and nerve growth factor (NGF), which activate PAR2 and TRPV1 receptors, thereby signaling to the CNS and contributing to hypersensitivity.[80]

Gastrointestinal motility plays a crucial role in digestion, absorption, and waste elimination. Colonic motility results from the interaction of enteric neurons, smooth muscle cells, and interstitial cells of Cajal (ICC), and is modulated by hormones and inflammatory mediators.[81] The colon exhibits rhythmic myogenic contractions for mixing and neurally mediated contractions, such as giant migratory contractions, for propulsion. Neural control involves both the ENS and CNS. Therefore, regulating intestinal motility positively impacts the treatment of patients with IBS.[82]

Alterations in gut microbiota play a pivotal role in IBS. While the complete microbiome composition is not fully characterized, dominant phyla include Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria.[83] Patients with IBS often exhibit reduced microbial diversity and significant shifts in microbial abundance,[84] with increased levels of Enterobacteriaceae, Lactobacillaceae, and Bacteroides.[85] This change is reflected at the phylum level by an increase in the Firmicutes phylum and a decrease in the Bacteroidetes phylum,[86] along with a reduction in beneficial genera such as Bifidobacterium and Lactobacillus.[87] These alterations may enhance intestinal permeability and promote bacterial translocation, triggering immune activation[88] and chronic low-grade intestinal inflammation.[89] Dysbiosis also disrupts gut-brain signaling, potentially intensifying visceral pain[90] and promoting comorbid anxiety and depression.[91] Moreover, microbial metabolites, including short-chain fatty acids (SCFAs), bile acids, and serotonin, influence gut motility and sensitivity, further contributing to symptomatology. Therefore, targeting microbial composition and metabolism represents a promising avenue for IBS management.[92] Elevated levels of 5-hydroxytryptamine (5-HT) in the colon, along with decreased expression of the serotonin reuptake transporter (SERT), may lead to diarrhea and increased visceral sensitivity. Gut microbiota stimulates mucosal mast cells to release prostaglandin E2 (PGE2), which downregulates SERT, resulting in increased mucosal 5-HT levels. Increasing evidence suggests that the gut microbiota-mediated serotonin pathway plays a significant role in the pathogenesis of IBS-D.[93]

The Role of Flavonoids and Flavonoid-Rich Compounds in the Treatment of IBS

Low-Grade Intestinal Inflammation and Oxidative Stress

Quercetin can effectively alleviate oxidative stress and inflammation, showing protective effects in both in vivo and in vitro models. In vivo, quercetin has been shown to positively influence intestinal health by increasing catalase (CAT) and superoxide dismutase (SOD) activities, reducing interleukin-17A (IL-17A) and IL-22 levels, upregulating tight junction proteins zonula occludens-1 (ZO-1) and occludin, and decreasing the abundance of Bacteroides.[21] In vitro, Quercetin has been shown to protect intestinal epithelial cells from diquat-induced injury by reducing ROS, preventing mitochondrial depolarization, and inhibiting caspase-3-dependent apoptosis, while preserving intestinal mucosal barrier function (ZO-1, ZO-2, ZO-3, occludin, and claudin-4). This protective effect was mediated through activation of nuclear factor erythroid 2-related factor 2 (Nrf2) and modulation of glutathione (GSH)-based redox balance.[22] In another fundamental study, luteolin alleviated colonic ROS and improved barrier function in rats with IBS-D through the Nrf2 / Heme Oxygenase-1 (HO-1) signaling pathway.[28] Myricetin (3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)-4-chromenone) has been shown to restore antioxidant enzyme levels, attenuate lipid peroxidation, and reduce inflammatory markers, including NF-κB, Nrf2, IL-6, and tumor necrosis factor-α (TNF-α), thereby protecting intestinal tissues.[23] Cyanidin-3-O-glucoside exhibits enhanced antioxidant properties after fermentation by intestinal microorganisms, effectively scavenging ROS, increasing SOD, CAT, and glutathione peroxidase (GPx) activities, reducing

malondialdehyde (MDA) levels, and protecting cells from H_2O_2 damage, thereby demonstrating significant anti-inflammatory and antioxidant effects.[40]

While individual flavonoids show promising effects, flavonoid-rich compounds have also demonstrated significant therapeutic potential. Serpylli herba extract, enriched with kaempferol, quercetin, and luteolin, alleviated low-grade inflammation in the colon and significantly reduced the expression of IL-1β and cyclooxygenase-2 (COX-2) in a rat model of IBS induced by deoxycholic acid.[42] Proanthocyanidin-rich grape seed extract significantly reduced ROS levels and mitochondrial superoxide production in LPS-induced human Caco-2 colon cells. It increased the expression of SOD1, SOD2, and GPx, restores impaired mitochondrial function, enhances epithelial barrier integrity through upregulation of tight junction proteins ZO1, occludin, and claudin 1, significantly reduces the secretion of IL-8, TNF-α, and IL-6, and alleviates intestinal inflammation.[43] The relatively high content of quercetin in the aqueous extract of Crataegus azarolus berries prevented the depletion of antioxidant enzyme activities, including SOD, CAT, and GPx, and reduced the expression of inflammatory markers (C-reactive protein and alkaline phosphatase) in castor oil-induced diarrhea in rats.[44] Camelina sativa methanolic and ethanolic extracts, enriched with quercetin-2″-O-apiosyl-3-O-rutinoside and rutin, demonstrated beneficial effects on the oxidative stress state of brain and intestinal tissues in a stress-exposed IBS mouse model by decreasing MDA and SOD activity and increasing GPx activity.[45] Chang-Kang-Fang, rich in flavonoids such as epicatechin and hyperoside, alleviated diarrhea symptoms in IBS-D rats by modulating neuroimmune and inflammatory pathways, inhibiting mast cell infiltration and proinflammatory cytokines (IL-1β, TNF-α, IL-6), enhancing barrier integrity via occludin, and suppressing the TLR4/NF-κB/NLR family pyrin domain-containing protein 3 (NLRP3) signaling pathway.[46] In a clinical trial, the combination of soy isoflavones and cholecalciferol significantly improved various biochemical parameters related to inflammation and intestinal permeability in women with IBS, specifically demonstrating a significant reduction in TNF-α levels and lower NF-κB levels. Additionally, compared to the control group, plasma inflammatory markers and fecal protease activity were significantly reduced.[39]

Visceral Hypersensitivity: Visceral Injurious Sensation and Pain

Kurarinone, a flavonoid extracted from saffron acacia, acts through the macrophage-derived aromatic hydrocarbon receptor to significantly attenuate VH in a 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced mouse model of IBS. It also reduces mucosal barrier permeability, enhances IL-10 expression, and inhibits pro-inflammatory responses in macrophages, thereby alleviating intestinal inflammation.[33] Puerarin, a natural isoflavone derived from Pueraria lobata, has demonstrated significant effects in reducing the number of mast cells and inhibiting VH in IBS-D rats subjected to neonatal maternal separation and colonic acetate stimulation. The mechanism may involve modulating the hypothalamic–pituitary–adrenal (HPA) axis through decreased expression of corticotropin-releasing hormone receptor (CRF). Additionally, puerarin enhances colonic epithelial cell proliferation through upregulation of extracellular regulated protein kinases levels (p-ERK/ERK) and repairs the colonic mucus barrier by increasing occludin expression, indicating its potential as a therapeutic agent for IBS-D.[34] Intestinal enterochromaffin (EC) cells and 5-HT play significant roles in developing VH in IBS. Quercetin, the primary polyphenolic flavonoid found in fruits and certain medicinal plants, has been shown to reduce EC cell density and 5-HT levels in a dose-dependent manner in PI-IBS rats, and inhibit VH in IBS-D rats subjected to TNBS stimulation.[24] One of the most widely distributed flavonoids, apigenin, has been shown to inhibit mast cell activation through the TLR4 / myeloid differentiation primary response gene 88 (MyD88) / NF-κB pathway, thereby inhibiting VH and upregulating the expression of ZO-1 and occludin to water avoidance stress in IBS-D rats.[32] Studies have shown that naringenin effectively reduces acute pain behaviors induced by acetic acid, formalin, capsaicin, and PGE2 while decreasing mechanical hypersensitivity. Its mechanism of action includes the inhibition of oxidative stress, the production of inflammatory cytokines (IL-33, TNF-α, IL-1β), NF-κB activation, and the activation of the Nitric Oxide (NO) / Cyclic Guanosine Monophosphate (cGMP) / Protein Kinase G (PKG) sensitive potassium channel signaling pathway.[35] Eriocitrin (eriodictyol 7-O-rutinoside) from lemon fruits effectively reduces acetic acid-induced visceral pain and thermal nociceptive responses caused by hot plates. It exhibits potent anti-injury sensory effects, which may be mediated through opioid and γ-aminobutyric acid receptor type A receptors.[36] 6-Prenylnaringenin, a component of hops, effectively blocks Cav3.2 T-type calcium channels and upregulates ERK activities in mice, significantly reducing neuropathic pain and VH with limited side effects.[37] In a randomized, double-masked trial of soy isoflavones and vitamin D combination therapy, although the treatment did not significantly improve IBS symptom severity scores or disease-

specific quality of life, it did result in a significant improvement in total scores, indicating clinical significance. After 6 weeks, the effects on abdominal pain severity, duration, distension, bowel habit satisfaction, and life disruption were significantly different among the study groups. In conclusion, the interaction between soy isoflavones and vitamin D significantly improved the total IBS score, suggesting a synergistic effect of these nutrients on intestinal hypersensitivity.[94]

Studies have shown that flavonoid-rich compounds and herbal preparations play a significant role in the treatment of IBS. The ethanolic extract of Mao jian green tea (MJGT), which includes apigenin, eriodictyol, luteolin, and naringenin as its main components, significantly reduced VH in rats. This effect may be attributed to a reduction in the secretion of 5-HT and the upregulation of 5-hydroxytryptamine receptor 4 (HTR4) expression.[47] TCM preparations often incorporate various herbal ingredients, characterized by multiple components and targets of action that synergize to exert therapeutic effects. SiNiSan, which is rich in isorhamnetin, quercetin, naringin, and kaempferol, alleviates intestinal dysfunction and VH in IBS-D mice by regulating the TLR4/MyD88/NF-κB signaling pathway, downregulating inflammatory markers such as TNF-α, IL-1β, IL-6, and PKC, and upregulating NGF and HTR2A. Additionally, it promotes the expression of tight junction proteins like ZO-1 and occludin, suggesting a role in regulating serotonin levels and enhancing intestinal barrier function.[48–50] WeiChang'An Pill (WCAP), which contains quercetin and catechin, significantly enhances levels of cyclic adenosine monophosphate (cAMP), p-PKA, 5-HT, and proteins in the cAMP signaling pathway in IBS-D rat models. In contrast, NF-κB expression decreases due to low-grade inflammation. These changes indicate that WCAP may help reduce diarrhea and visceral sensitivity by regulating the cAMP pathway.[51]

The Role of Intestinal Motility Regulation

Extracts from Pugionium cornutum (L). Gaertn, which are rich in quercetin, promote the relaxation of gastric smooth muscle cells and inhibit contraction in colonic smooth muscle strips in vitro. This relaxation effect is mediated by stimulating intracellular calcium influx and antagonizing acetylcholine. Additionally, the mechanism involves the COX and NO/PKC signaling pathways.[52] The ethanol extract of Cucumis melo L. seeds (Cm.EtOH) is rich in rutin, naringenin, and quercetin. Studies have shown that Cm.EtOH can inhibit smooth muscle contraction in a concentration-dependent manner by antagonizing calcium-mediated repolarization action potential signals, thereby alleviating diarrhea symptoms in rats and exhibiting antispasmodic and antidiarrheal effects.[53] Tilia tomentosa Moench extract is enriched with quercetin and kaempferol derivatives, which have been found to inhibit excessive contraction of gastrointestinal smooth muscle, possibly through NO and tachykininergic pathways.[49] Glycicumarin and isoliquiritigenin have been shown to effectively relieve abdominal pain symptoms; additionally, in vitro, they inhibit the contraction of rat colon muscle strips in a concentration-dependent manner, reducing colonic motility frequency.[25]

Hesperidin significantly improved gastrointestinal transit function in a rat model of loperamide-induced constipation by promoting the expression of 5-HT4 receptors and increasing intracellular free calcium, and enhancing the expression of proteins related to the cAMP/PKA pathway.[38] 7,8-Dihydroxyflavone, known as a tyrosine kinase receptor B (TrkB) agonist, significantly relieved loperamide-induced functional constipation in rats by enhancing cholinergic contraction of colonic smooth muscle and activating the TrkB/PKB signaling pathway.[29] The ethanol extract of MJGT can improve delayed gastric emptying and intestinal transit in IBS-C rats by downregulating the secretion of 5-HT.[47] Bidens tripartita extract and its main flavonoid component, cynaroside, have a significant prokinetic effect on intestinal smooth muscle, enhancing the acetylcholine (ACh) response by over 250%. This effect may benefit functional bowel disorders as IBS-C.[95]

Luteolin has been shown to increase the expression of colonic ICC markers and intestinal motility-related biomarkers, including vasoactive intestinal polypeptide, and ACh, thereby enhancing intestinal motility and gastric emptying in mice with loperamide-induced constipation.[31] However, in another study, luteolin exhibited different effects; it relieved colon hypermotility in IBS-D rats and inhibited colon smooth muscle contraction in vitro in a dose-dependent manner,[28] this effect may be mediated by inhibiting L-type calcium channel currents.[30] The primary active ingredients of Rosmarinus officinalis L. include diosmetin, rutin, and apigenin, which possess dual effects of alleviating diarrhea and promoting bowel movements, in addition to exhibiting anti-anxiety activity. At low doses, rosemary acts as a laxative, whereas at high doses, it exhibits a significant anti-diarrheal effect. The mechanism of action involves the regulation of cholinergic and histaminergic receptors, as well as effects on K^+ channels.[54] Cirsium palustre extracts may regulate colon contraction, with the

flavonoids in the extract playing a significant antispasmodic role (apigenin, luteolin, apigenin 7-O-glucuronide). However, different flavonoid monomers may exhibit varying or opposing effects on intestinal contraction. Among these, apigenin and apigenin 7-O-glucuronide demonstrate stimulating effects on spontaneous and acetylcholine-induced colon motility, whereas luteolin and apigenin suppress the contractility of colonic smooth muscle.[55]

The Modulating Effect of Gut Microbiota and the Gut-Brain Axis

Various natural flavonoids have been shown to play an essential role in regulating intestinal microbial homeostasis. Quercetin intervention has reversed IBS-induced changes in gut microbiota, decreasing levels of Bacteroides while enhancing Odoribacter, Streptococcus, Lactobacillus, and Roseburia.[21] Puerarin has been shown to improve the ecological balance of the gut microbiota and repair the colonic mucosal barrier in IBS-D rats, resulting in a higher abundance of Lactobacillus and a simultaneous inhibition of the number and abundance of Prevotella.[34] Apigenin, abundant in many plants and fruits, has been shown to regulate the abundance of Firmicutes and Bacteroidetes in the gut microbiota. Additionally, apigenin regulates BGA by modulating the gut microbiota and inhibiting mast cell activation.[32] Quercitrin significantly improved the β-diversity of the gut microbiota, increased the abundance of probiotics such as Akkermansia and Lactococcus, and enhanced the content of SCFAs.[26] Water extracts from cynanchum thesioides, rich in quercetin and tamarixetin, can reduce the abnormal abundance of Pseudomonas and Fusobacterium, increase the enrichment of Bacteroides, enhance lysine biosynthesis, and help maintain intestinal microbial balance and inhibit VH in rats with IBS-D.[56] Alpha-glycosyl isoquercitrin has been shown to reduce stress-induced gut microbiota abnormalities (Bacteroidetes, Butyricicoccus, Allobaculum and Sutterella), upregulate hippocampal 5-HT levels, lower serum LPS levels, and reverse the decrease in butyrate levels in cecal contents by increasing the expression of ZO-1 and occludin proteins, thereby enhancing intestinal barrier function.[27] The naturally derived flavonoids xanthohumol and quercetin exert an antidepressant effect by regulating the HPA axis, restoring brain-derived neurotrophic factor levels, modulating BGA (Asteroplasma, Lachnospiraceae, and Coprococcus), and enhancing the level of SCFAs, effectively improving the depressive and anxious behaviors of mice that have been separated from their mothers.[41] A by-product of persimmon processing is a significant source of dietary fiber, rich in gallic acid, protocatechuic acid, delphinidin, and cyanidin. These compounds have been shown in studies to promote the growth of Firmicutes, which are beneficial gut microbiota. Additionally, they can inhibit the action of inflammatory factors such as IL-1β, IL-6, and TNF-α, exert anti-inflammatory effects in vitro, and increase the production of butyric acid and other metabolites from beneficial microorganisms.[57] Cyanidin-3-O-glucoside upregulates beneficial gut microbiota, including Escherichia–Shigella, Lactobacillus, Bacteroides, Butyricimonas, and Akkermansia, while activating the Nrf2/HO-1 signaling pathway.[40]

The ethanol extract of MJGT is rich in apigenin, luteolin, and naringenin. Studies have shown that, compared to the IBS-C group, the intestinal microbial composition following MJGT administration has undergone significant changes, including an increase in the Bacteroides/Firmicutes ratio and a decrease in the abundance of the Lachnospiraceae family.[47] The flavonoids in Amomum tsaoko, such as (+)-epicatechin, (-)-catechin, L-epicatechin, and isoquercitrin, not only increase the 5-HT content and the expression of HTR2A, phospholipase A2, and COX-2, all of which are involved in the serotonergic synaptic pathway, but also enhance the expression of transient receptor potential A1, promoting the release of myosin light chain 3, which facilitates smooth muscle motility. Furthermore, these flavonoids have been shown to modulate the gut microbiota by increasing the abundance of Lactobacillus and Bacillus while decreasing the dominance of symbiotic bacteria such as Lachnospiraceae, potentially relieving constipation by regulating the gut microbiota and the serotonergic synaptic pathway.[58]

Challenges and Future Directions

Despite the growing interest in flavonoids as therapeutic agents for IBS, several challenges hinder their clinical application. One major issue is their poor oral bioavailability. Studies have shown that the absorption of flavonoids after ingestion is often less than 10%, with some compounds falling below 5%.[96] For instance, quercetin, known for its anti-inflammatory and anticancer effects, exhibits low solubility and limited systemic availability.[97] To address this issue, advanced delivery systems such as hydrogels, nanoparticles, nanoemulsions, and lipid vesicles are being explored to

improve the bioavailability of flavonoid compounds.[98–100] For example, alginate/chitosan microspheres loaded with puerarin have demonstrated better therapeutic outcomes in IBS-D compared to free puerarin.[101]

Another challenge lies in the inconsistency of the effects of flavonoids. Some compounds, such as luteolin, may exert opposing effects on colon function depending on the experimental context, reflecting variability across IBS subtypes. Further studies are needed to clarify these pathways and to determine how specific flavonoids interact with IBS pathophysiology. In addition, many studies rely on plant extracts or traditional medicinal preparations, where the active flavonoid components are not clearly defined. Future research should focus on purified flavonoids to identify the specific monomers responsible for therapeutic effects. This approach would help standardize treatment and enhance reproducibility. Clinical evidence for flavonoids in IBS remains limited, with most current data derived from preclinical studies. Although flavonoid compounds are primarily extracted from natural sources and have demonstrated high safety in preclinical studies, clinical trials for treating IBS are still in the early stages. Before flavonoids can be widely promoted for the treatment of IBS, more comprehensive clinical studies are needed to determine appropriate dosing, indications, and potential toxicity and side effects. Additionally, combination therapies represent a promising therapeutic strategy. The combination of metamizole and hesperidin has demonstrated synergistic effects, effectively alleviating VH in mice while reducing the risk of adverse effects.[102] Such multi-target approaches may enhance treatment outcomes and warrant further investigation.

Conclusion

Flavonoids, a class of natural polyphenolic compounds, play diverse roles in modulating the pathological mechanisms of IBS. Research indicates their capacity to attenuate oxidative stress, inhibit inflammatory cascades including NF-κB and TLR4 signaling pathways, enhance intestinal barrier function by upregulating tight junction proteins, and regulate gut motility and the GBA. Furthermore, certain flavonoids influence neurotransmitters and their receptors, particularly those involved in the serotonin pathway, thereby modulating VH and neural signaling. These complementary mechanisms collectively underscore the therapeutic potential of flavonoids in addressing the complex pathophysiology of IBS.

This review highlights flavonoids as promising multi-target therapeutic agents for IBS, emphasizing their value as safe, plant-derived alternatives or adjuncts to conventional treatments. By synthesizing evidence from both in vivo and in vitro studies, this article provides a comprehensive overview of how flavonoids modulate key pathological processes in IBS. These insights not only support the development of flavonoid-based therapies but also inform future research aimed at enhancing bioavailability, identifying specific active constituents, validating clinical efficacy, and exploring synergistic effects with other treatment modalities.

Abbreviation

5-HT, 5-hydroxytryptamine; Ach, acetylcholine; BGA, brain-gut axis; CAT, catalase; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; CD14, cluster of differentiation 14; CNS, central nervous system; COX-2, cyclooxygenase-2; CRF, corticotropin-releasing hormone receptor; EC, enterochromaffin; ENS, enteric nervous system; ERK, extracellular signal-regulated kinases; GSH, glutathione; GPx, glutathione peroxidase; HPA axis, hypothalamic-pituitary-adrenal axis; HO-1, Heme Oxygenase-1; HTR, 5-hydroxytryptamine receptor; IBS, Irritable bowel syndrome; IBS-C, IBS with predominant constipation; IBS-D, IBS with predominant diarrhea; IBS-M, IBS with mixed bowel habits; IBS-PI, post-infectious IBS; IBS-U, unclassified IBS; ICC, interstitial cells of Cajal; IL, interleukin; LPS, lipopolysaccharide; MDA, malondialdehyde; MJGT, Maojian green tea; MyD88, myeloid differentiation primary response gene 88; NF-κB, nuclear factor kappa B; NGF, nerve growth factor; NLRP3, nucleotide-binding oligomerization domain-like receptor protein 3; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; PAR, protease-activated receptors; PGE2, prostaglandin E2; PK, protein kinase; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; SERT, serotonin reuptake transporter; SNS, SiNSan; SOD, superoxide dismutase; TCM, Traditional Chinese Medicine; TLR4, Toll-like receptor 4; TNBS, 2,4,6-trinitrobenzene sulfonic acid; TNF-α, tumor necrosis factor-α; TrkB, tyrosine kinase receptor B; TRPV1, transient receptor potential vanilloid subfamily 1; VH, visceral hypersensitivity; ZO-1, zonula occludens-1.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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