DARU Journal of Pharmaceutical Sciences (2019) 27:755–780
https://doi.org/10.1007/s40199-019-00284-1

REVIEW ARTICLE

Natural polyphenols for the prevention of irritable bowel syndrome: molecular mechanisms and targets; a comprehensive review

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Received: 30 March 2019 / Accepted: 14 June 2019 / Published online: 4 July 2019

Abstract

Irritable bowel syndrome (IBS) is a well diagnosed disease, thoroughly attributed to series of symptoms criteria that embrace a broad range of abdominal complainers. Such criteria help to diagnosis the disease and can guide controlled clinical trials to seek new therapeutic agents. Accordingly, a verity of mechanisms and pathophysiological conditions including inflammation, oxidative stress, lipid peroxidation and different life styles are involved in IBS. Predictably, diverse therapeutic approaches are available and prescribed by clinicians due to major manifestations (i.e., diarrhea-predominance, constipation-predominance, abdominal pain and visceral hypersensitivity), psychological disturbances, and patient preferences between herbal treatments versus pharmacological therapies, dietary or microbiological approaches. Herein, we gathered the latest scientific data between 1973 and 2019 from databases such as PubMed, Google Scholar, Scopus and Cochrane library on relevant studies concerning beneficial effects of herbal treatments for IBS, in particular polyphenols. This is concluded that polyphenols might be applicable for preventing IBS and improving the IBS symptoms, mainly through suppressing the inflammatory signaling pathways, which nowadays are known as novel platform for the IBS management.

Keywords Gastroenterology · Irritable bowel syndrome · Mechanism · Inflammation and oxidative stress · Herbal therapy · Polyphenols

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Introduction

Irritable bowel syndrome (IBS)

Pathophysiology & etiology

IBS is a common chronic functional disorder, related to the gastrointestinal system that being categorized as IBS-D with predominantly diarrhea, IBS-C with constipation, or IBS-M that includes both. The most distressing symptoms of the disease include fibromyalgia, chronic pelvic pain, and the interstitial cystitis [1, 2], abdominal pain, straining, myalgias, flatulence, frequency, borborygmi, stool form, mucus, urgency, bloating and feelings of serious illness and incomplete evacuation [3, 4], In addition, the IBS symptoms may transit to other complexes of the gastrointestinal symptoms, such as functional dyspepsia [2].

Since no definitive biomarkers have been found, IBS is often diagnosed clinically. Concerning IBS diagnosis and to reduce the risk of unnecessary surgeries, "Manning" established the first set of formal standardized criteria, needless to exclude other diagnoses. Later, these criteria were improved by expert consensus to create the "Rome criteria" [5]. Most studies utilize either the "Rome II" or "Rome III" criteria, although it has been demonstrated that the "Rome criteria" are only appropriate for clinical trials and not for clinical practices. Other clinical findings such as bloating and psychological stress are regularly used by clinicians in diagnosing IBS [6, 7]. The maximum achievable sensitivity from these criteria (positive diagnosis) ranges from 0.4 to 0.9 [8], with warning signs such as anemia, weight loss, and rectal bleeding [9].

Epidemiology of IBS

IBS is more prevalent in Europe, North and south America; with an average prevalence between 10 and 25% [10]. Data from meta-analysis showed a pooled estimation of international IBS prevalence of 11.2%, with variation by geographic region. The lowest presentation was recorded in South Asia (7.0%), while the highest incidence was found in South America (21%) [11, 12]. By another mean," stigma" is a significant method for diagnosing the IBS symptoms [13, 14]. Obviously, greater stigma causes lower prevalence. Those communities in which a higher stress is perceived or the quality of life (QOL) is lower, a potential of higher prevalence is presumed [15–18].

Current treatments of IBS & their adverse effects

Although there's no definite cure for IBS yet, many medications coexist and have been proven favorable to improve symptoms in all IBS subtypes including; Alosetron (5-HT3–receptor antagonist/5-hydroxytryptamine (Serotonin) receptor antagonist [2] and loperamide, to improve overall symptoms such as abdominal pain, urgency, borborgymi, frequency and stool form [4, 19, 20]. Viberzi (eluxadoline); as a controlling drug, affecting the opioid receptors in digestive system that helps to mitigate the symptoms of abdominal pain and diarrhea in IBS patients [21]. Another group includes Prokinetics, which used for constipation improvement, such as Tegaserod (5-hydroxytryptamine4 (5-HT4)– receptor agonist) [21]. Fiber supplements such as polyethylene glycol 3350, Lactulose [4], Ispaghula husk [22], psyllium and bran [23] are also used for IBS improvement. Tricyclic antidepressants (TCAs) effect on neurotransmitter acetylcholine and are more beneficial for IBS-D, while both selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) are the best choices for controlling the IBS-C symptoms [24, 25].

The antispasmodic drugs (smooth muscles relaxants) such as Dicyclomine and Hyoscamine are medications profitable to relieve the abdominal pain in IBS patients via relaxing the gut smooth muscle [26], however, they can cause constipation. The antibiotic Rifaximin manages the non-constipation IBS by improving bloating and diarrhea [27]. The anticonvulsants Gabapentin and Pregabalin are also applicable for chronic neuphropatic pain. Pregabalin showed clinical efficacy in reducing pain in IBS condition and Fibromyalgia [28–30]. Though, the adverse effects are rare in case of IBS medications, but there are some reports indicating nausea, diarrhea, headache, abdominal pain, discomfort, cardiovascular ischemia (rare), constipation, ischemic colitis (rare), dry mouth and bad taste, dizziness, weight gain, sexual dysfunction, sedation, insomnia, sweating, withdrawal symptoms and somnolence [31–35]. The best available herbal treatments for IBS include natural polyphenolic products extracted from *Perilla frutescens*, *Aloe vera*, *Mentha piperita*, *Cynara scolymus*, *Acacia catechu*, *Camellia sinensis* and polyphenol compounds such as isoflavones baicalin, anthocyanins and quercetin. Such natural polyphenolic products possess numerous anti-inflammatory and anti-oxidant effects, which help to improve the IBS symptoms and the QOL scores in the IBS patients [26, 36–45].

Aim and objectives

The present study investigated the effects of plant-derived dietary polyphenols (i.e. anthocyanins, flavonoids, stilbenes, lignans, phenolic acids), able to downregulate the cellular inflammatory signaling pathways and cytokines. In addition, it is well documented that as antioxidants, polyphenols could protect the cell constituents against oxidative damage, therefore, are capable of limiting the risk of various degenerative diseases associated with oxidative stress [46] and can improve the IBS symptoms.

Method

All relevant clinical, in vitro and in vivo papers, in English, with keywords such as 'IBS' or 'Irritable bowel syndrome' or 'Colon inflammation' or 'oxidative stress' or 'Gastroentric disorders' 'polyphenols' and 'phenolic compounds' were collected between 1973–May 2019 from PubMed, Google Scholar, Scopus and Cochrane library.

Polyphenols and human diseases

Polyphenol compounds are secondary metabolites of plants, found in a different fruits, vegetables, beverages, and cereals. Polyphenols are primarily existed in conjugated form with one or more saccharide group/s (monosaccharides or polysaccharides), often bound to the hydroxyl groups or sometimes directly are linked to an aromatic carbon. The compounds are frequently linked with other compounds, like carboxylic and organic acids, amines, lipids and with other phenols [4].

Polyphenols may be categorized into different subgroups, based on the number of phenol rings in their structures and the intermediates that link these rings together. The main subclasses of polyphenols are consisted of phenolic acids, flavonoids (flavonols, flavones, flavanones, anthocyanins, isoflavones, stilbenes, lignans), and tannins (hydrolyzable and condensed tannins) [47]. Phenolic acids are widely found in foodstuffs and classified as compounds derived from either benzoic acid (hydrolyzable tannins such as gallotannins) or cinamic acid (*p*-coumaric, caffeic, ferulic and sinapic acids, chlorogenic acid). Flavonoids represent the most studied group of polyphenols, with a variety of about 4000 compounds. Flavonoids share a common basic structure with two aromatic rings linked by three carbon atoms; creating an oxygenated heterocycle. Considering the variation of heterocycle involved, flavonoids are characterized as six subsets. Individual differences within each group, arise from the variation in the number and arrangement of the hydroxyl groups. The extent of alkylation and/or glycosylation indicates the individual differences within each group [48]. Consumption of antioxidants has been associated with reduced levels of oxidative damage to lymphocytic DNA. Similar observations have been made with polyphenol-rich food and beverages, indicating the protective effects of polyphenols [49–51]. There are increasing evidence that as antioxidants, polyphenols may protect cell constituents against oxidative damage and, therefore, are able to limit the risk of various degenerative diseases associated with oxidative stress [50–54]. Overall, polyphenols could act as cardioprotective, anticancer, antidiabetic, antiaging, and neuro-protective agents, also may be propitious for the gastrointestinal disorders such as IBS [50].

IBS inflammatory and oxidative mechanism

In IBS state, the serum concentrations of pro-inflammatory cytokines (i.e. tumor necrosis factor alpha (TNF-α) and interleukin-17 (IL-17)) increases, while the serum level of anti-inflammatory cytokines (i.e. IL-10) drops drastically. It was shown that IL-17 is a key factor in the pathogenesis of gut inflammation, through the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), mitogen-activated protein kinase MAP kinase (MAPK) and toll like receptors (TLRs) in the intestinal subepithelial myofibroblasts. Innate TLR-mediated immune system may be activated in patients with IBS. Due to the stimulation of lipopolysaccharides (LPS) via TLR4, they are widely used as ligands, indicating the TLRs consequential roles in IBS. It also increases the pro-inflammatory cytokines such as IL-1β, IL-6, IL-8 and TNF-α in IBS patients, especially in IBS-D and post-infectious IBS (PI-IBS) patients. In vitro studies also showed that the anti-inflammatory cytokine IL-10 decreases in IBS patients. TLRs were found to be activated in animal models with stress exposure, also stress may induce the systemic and intestinal TLR activation, yet its functions in the pathogenesis of IBS remains questionable [52, 53].

It was reported that in various tissues, IL-17 mediates the inflammatory responses and induces a number of genes associated with inflammation such as IL-8 and IL-6 [4, 23, 55, 56]. Clinical trials also demonstrated that the plasma levels of TNFα, IL-1β, IL-6 and IL-8 were higher in IBS patients than in controls [49], while the serum level of IL-10 was significantly lower [54]. Inflammation and the immune activation play undeniable roles in IBS pathogenesis, which initiate the onset of gastrointestinal (GI) symptoms [57]. Generally, the IBS symptoms are associated with gut dysfunction, visceral hypersensitivity and, in some cases with epithelial dysfunction [58]. In between, visceral hypersensitivity is the main cause of chronic pain and discomfort in IBS patients [57, 59]. There is a significant correlation between the serum levels of cytokines (i.e. TNF-α, IL-17 and IL-10), and the intensity of clinical symptoms such as abdominal pain, dissatisfaction with bowel habits, overall GI symptoms, and the IBS Severity Scoring System (IBS-SSS). In addition, the serum levels of TNF-α and IL-1β were significantly correlated with self-reported symptoms of pain frequency and intensity in IBS patients [60]. Taking together, there is a significant correlation between the inflammatory cytokines and the QOL in IBS patients. Low levels of TNFα and IL-17 in serum showed a positive correlation with higher QOL, whereas the low level of IL-10 significantly associated with lower IBS-QOL [45, 61, 62]. QOL is an important factor for IBS patients, which requisites specific treatment and monitoring. Moreover, in IBS patients, the serum level of malondialdehyde (MDA) increases, while the amount of total antioxidant capacity (TAC) drops. It is well accepted that the oxidative stress and

inflammation are inevitably linked, forming a two-way circuit. The immune cells activation and infiltration, can generate reactive oxygen species (ROS) [45, 50, 57, 63], which enhance the expression of inflammatory cytokines such as IL-1β and TNFα [64]. In a trial with 36 IBS patients, the plasma levels of MDA and nitric oxide (NO), and the plasma activities of oxidants such as xanthine oxidase and adenosine deaminase elevated, whereas the levels of antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase (GPx) alleviated [64]. This can clearly indicate the significant associations between the inflammatory cytokines, the intensity of symptoms, and the QOL [45].

Evidence on effectiveness of plants enriched by polyphenol compounds on IBS

Aloe vera

Aloe vera (Asphodelaceae) is a herb used for a variety of diagnosis in traditional medicine [65, 66] (Tables 1 and 2, Fig. 1). The latex and gel are extracted from the leaf of *A. vera* and are rich in polyphenolic compounds such as aloin, aloe-emodin, aloesin, 2'-O-feruloylaloesin, aloeresin A, barbaloin, isobarbaloin, aloenin, aloe-emodin, 8-C-glucosyl-7-O-methyl-(S)-aloesol, isoaloeresin D and aloeresin E. The gel is mostly used for treatment of IBS [57, 73, 76]. The plant is remarkably credited for its hepato-protective, anti-inflammatory [77, 78], and anti-ulcerative [57, 79] effects. In addition, *A. vera* reduces cardiovascular risk factors [80, 81] and diabetes [82], besides is reported to be beneficial in areas of dermatology [76, 83, 84]. The anti-inflammatory effects of *A. vera* could be favorable on symptoms of IBS by reducing the gut hypersensitivity [85]. *A. vera* is commonly used as a strong laxative and improves the gastrointestinal motility [86].

Table 1 Plants enriched by polyphenol compounds to manage IBS

Polyphenol name	Plant/ Part
Aloe vera extracts	Latex and gel extracts
Peppermint extracts	*Mentha piperita*
Olive extracts	*Olea europaea*
asca-feoilquinic acid and flavonoids	*Cynara scolymus (Artichoke)*
luteolin	*Perilla frutescens*
Catechins/ EGCG	*Camelia sinesis*
Catechins/ EGCG	*Acacia catechu*
Trans-Resveratrol	*red grapes/red berries*
Turmeric(Curcuminoids)	*Curcuma longa*
Isoflavones	*Glycine max*
Baicalin	*Scutellaria baicalensis Georgi*
Anthocyanins	Plants flavonoids
Quercetin	Plants flavonol metabolite

Data from clinical trials highlighted remarkable alterations in the IBS symptom scores, prior and post treatment with *A. vera* polyphenolic extracts [65, 87, 88]. Meta-analysis of randomized clinical trials showed that there is a significant difference in *A. vera* treated group compared with the placebo in terms of improving the IBS symptoms, and the QOL scores, however, no sign of heterogeneity was observed [65, 82, 87, 88]. It was shown that in short-term treatment for 1 month, *A. vera* caused a meaningful improvement of the IBS symptoms, and the QOL scores, nevertheless, the long-term treatment over 3 months was not effective. Another meta-analysis reported a high response rate in *A. vera* group in comparison with the placebo group, there was no heterogeneity and adverse events between studies [65, 84, 87, 88]. Following 1-months treatment, the differences in nausea and vomiting groups were not meaningful, similar to the other examinations, the IBS score of QOL was improved in treated groups. Following 3-months treatment, there were significant changes in recovery of pain score, proportion of days with pain, proportion with distension in the past weeks, bowel habit satisfaction and interference with the QOL scores; although, the treatment was ineffective in subjects diagnosed with constipation. In patients with diarrhea or constipation, significant improvement of the IBS scores such as the proportion of days with pain and bowel habit satisfaction, was monitored. Following a month, 43% of patients in the *A. vera* treated group responded to the treatment, although, by 3 months, this number increased to 45%. Of note, there was a continued amelioration of the IBS and pain scores [76, 85].

A great number of active constituents have been isolated from *A. vera*, of which the majority shown precious therapeutic implications towards the prevention and treatment of diseases through manipulation of various biological and genetic activities [65, 86–90]. The *A. vera* polyphenols also act as antioxidants, through scavenging free– and superoxide- radicals, also via their anti-inflammatory properties by inhibiting the prostaglandin E2 (PGE2) production, downregulating the various transcription factors, and suppressing the activities of lipoxygenase (LOX) and cyclooxygenase (COX) enzymes, leading to the IBS symptoms management [89, 90]. Moreover, *A. vera* has shown positive antimicrobial activity, mainly by rupturing bacterial cell walls [87–90].

Antimicrobial activity

The polyphenolic components of *A. vera* shown to have relevant antibacterial and antifungal activities [87, 88, 91]. At high concentrations (1/10), *A. vera* inhibited the growth of *Staphylococcus aureus*, while at moderate concentrations the growth of *Escherichia coli*, *Pseudomonas aeruginosa*, and *Salmonella typhi* were inhibited [76, 92]. It was also demonstrated that *A. vera* is active against both gram- positive and -negative bacteria [89, 90, 93]. In contrast, it was reported that

Table 2 Clinical studies on beneficial effects of polyphenols for the prevention and treatment of IBS

Preparations/Routes of administration treatment & control groups	Study design (clinical trials)	Disease (Model of IBS)	No. of Patients	Treatment duration	Results	Adverse effects	References
2 colpermin capsules 3 times a day consisted of 187 mg of peppermint oil in a pH-dependent, enteric-coated, hard gelatin capsule manufactured by Tillotts of Switzerland dosage 0.2 mL or 0.1 mL 3 times daily and placebo (arachis oil)	Clinical trial	Manning or Rome criteria of IBS	One-tablet group = 102 Two-tablets group = 105	2 weeks	1-abdominal pain ↓ 2-Peppermint oil blocks Ca2+ channels and reduces colonic spasms and associated pain 3- severity of symptom↓ 4-Improvements of symptom ↑		[67]
2 capsules of the study drug (Peppermint oil SST 180 mg, and identical placebo) between 30 and 90 min before breakfast, lunch, and dinner	Clinical trial	IBS was made using the Rome II criteria	45 patients in each group intervention Analyzed group: $n = 33$ placebo Analyzed group: $n = 27$	8 weeks	1-abdominal pain ↓ 2-intensity of abdominal pain or discomfort↓ 3-quality of life on visual analogue scale (VAS) ↑.	1-heartburn (4 in the Colpermin group, 5 in controls), 2-headache (6 in Colpermin, 3 in controls), 3- dizziness (3 in Colpermin, 5 in controls). Other less frequent events included belching, dry mouth, and increased appetite seen in less than 10% of subjects	[67]
One tablet (72 mg) or two tablets (144 mg) of a standardized turmeric extract daily	Clinical trial	Rome II criteria of IBS	One-tablet group = 102 Two-tablets group = 105	8 weeks	1-IBS prevalence at baseline ↓ 2- IBS prevalence ↓ 3-improvement of IBS↑ 4-bowel pattern ↑	In one-tablet group: 1-diagnosis of hyperthyroidism ($N = 1$) 2-ceased treatment for hospital examination ($N = 1$)	
3-antibiotics for respiratory infection ($N = 1$) In two-tablets group: 1-bowel operation ($N = 1$) 2-bowel bleeding ($N = 1$) 3-hospital admission ($N = 1$) 4-fell pregnant ($N = 1$) 5-new medication inferring with IBS ($N = 1$)	[68]						
225 mg twice daily peppermint oil	Clinical trial	Rome II and investigations IBS	peppermint oil group: $n = 52$ placebo group: $n = 127$	4 weeks	≥50% improvement Irritable bowel syndrome symptoms		[69]
peripheral blood mononuclear cells (PBMCs) with various concentration of baicalin (5 μmol/L,	Clinical trial	IBS-D based on the Rome III diagnostic criteria	Each group: $n = 30$		1-the proliferation of cells treated ↓ 2- the percentage of CD4 + CD29+ cells ↓ 3-GATA-3 ↑ but FOXP3, T-bet and RORC↓		[59]

Table 2 (continued)

Preparations/Routes of administration treatment & control groups	Study design (clinical trials)	Disease (Model of IBS)	No. of Patients	Treatment duration	Results	Adverse effects	References
10 μmol/L, 20 μmol/L and 40 μmol/L), and DMSO was the negative control					4- TGF-b, IL-10, IL-4 ↓ but IFN-γ, IL-6, IL-5 ↑ 5- the expression of the pSTAT6/STAT6 ratio ↓ while p-NK-κβ/NK-κβ and p-STAT4/STAT4 ↑		
Colpermin (one enteric-coated capsule containing 187 mg peppermint oil in a thixo-tropic gel to ensure adequate dispersal in the bowel) three to four times daily 15-30 min before meals or placebo (one identical cap-sule containing an inert oil)	Clinical trial		Intervention group: $n = 52$ Placebo group: $n = 49$		1-abdominal pain ↓ 2-abdominal distension↓ 3-stool frequency↓ 4-borborygmi ↓ 5- flatulence↓ 6- Symptom improvements after Colpermin were significantly better than after placebo		[37]
Treatment group = IQP-CL-101 softgel contains 330 mg proprietary mixture of curcuminoids and essential oils from C.longa and C.xanthorrhiza, 70 mg fish oil, 15 mg peppermint oil and 8 mg caraway oil as well as 263 μg thiamine, 39 μg folic acid and 625 μg vitamin D3control group = placebo	Caucasian men and women aged 18–70 years old	ROMEIII criteria for IBS	IQP-CL-101 group = 43 placebo group = 47	8 weeks	1-IBS-SSS↓ 2- Improvement Score of Irritable Bowel Syndrome ↑ 3-IBS-QOL (total score) ↑ 4- abdominal pain ↓ 5- abdominal discomfort ↓		[70]
fermentable oligosaccharides, disaccharides and monosaccharides and polyols (FODMAP)	Clinical trial	Rome III criteria IBS with diarrhea (IBS-D), mixed type IBS (IBS-M) or subtyped IBS (IBS-U)	patients with IBS randomised to a low ($n = 20$) or high ($n = 20$) FODMAP diet	3 weeks	1- IBS-SSS in abdominal pain scores ↓ 2- abdominal distention ↓ in low FODMAP group 3- H2 production ↓ In low FODMAP group 3-Actinobacteria richness and diversity↑ in Low FODMAP 4- Analyzing only the samples of patients with IBS-M and IBS-D (excluding two IBS-C and one IBS-U to create a more uniform group, all with some diar-rhea) we observed higher bacterial richness in the low		[71]

Table 2 (continued)

Preparations/Routes of administration treatment & control groups	Study design (clinical trials)	Disease (Model of IBS)	No. of Patients	Treatment duration	Results	Adverse effects	References
					FODMAP group compared with the high FODMAP group Specifically, Firmicutes, Clostridiales and Actinobacteria richness was higher and Actinobacteria bacterial diversity↑		
2 capsules of 20 mg soy isoflavones (contained 10 mg of diadzein, 8.5 mg of genstein and 1.5 mg of glycetin)per day, and one pearl of vitamin D (consisted of 50′000 cholecalciferol IU) bi weekly	100 Women with IBS with age range of 18 to 75 years old and body mass index (BMI) of 18–25	ROME III criteria was used for diagnosis of IBS	*N* = 25 For each group placebo of vitamin D and placebo of soy isoflavones (P + P), or placebo of vitamin D and soy isoflavones (P + S), or vitamin D and placebo of soy isoflavones (D + P), or vitamin D and soy isoflavones (D + S)	6 weeks	1-The IBS- SSS ↓ 2- total score of QOL↑ 3-isoflavones and vitamin D synergistic effect suppress abdominal pain		[72]
patients were treated with either AV using the NLP formulation(this AV formulation came as a pink syrup flavoured with mango) or matching placebo (with the same color and flavour) at a dose of 50 ml taken four times a day	Clinical trial (aged 18–65,and had previously tried but failed conventional management with antispasmodics, bulking agents and dietary intervention)	Rome II criteria for IBS	At 1 months, Placebo (n ¼ 23) Active (n ¼ 26). At 3 months, Placebo (n ¼ 18) Active (n ¼ 24).	3 months (1 month and followed up for a further 2 months)		AV using the NLP formulation was generally well tolerated, with distension as the only apparent side effect. Six patients did withdraw from the study with nausea and/or vomiting. However, a majority of these came from the placebo group and so was not considered to be a significant side effect.	[73]
two capsules of either CU-FEO (Curcumin 42 mg and Fennel essential oil 25 mg,-each capsule)	Clinical trial	Rome III diagnosis of IBS (IBS-D subjects 62%, IBS-C subjects 38%)	A total of 121 consecutive patients (Male = 44 Female =77) CU-FEO group = 60 Placebo group = 61	30 days	1-Abdominal pain severity ↓ 2- IBS-QOL total score↑ 3- improvement of each domain of the IBS-QOL such as Individual domains of dysphoria, body image, food avoidance ↑ 4- ↓TNF-α ↓interferon-γ ↓interleukins 5- nitric oxide synthase ↓, as well as NF-κβ	Nausea (3.4% in placebo group), headache (1.7% in CU-FEO group)	[74]
one capsule of Colpermin (Tillotts Pharma, Ziefen, Switzerland) containing 187 mg or 0.2 ml peppermint oil, three times daily 30 min before each	Clinical trial (The patients mean age was 40.7 years (standard deviation ±11.23 years; range	Rome III criteria for IBS-M or IBS-D with an average daily IBS-related abdominal pain rating of C4 on a 0–10 scale and a Total IBS Symptom	72 patients were randomized to PO (*n* = 35) or placebo (*n* = 37). In the PO group, 16 patients had IBS-M and 19 patients had IBS-D. In the placebo group,18 patients	4 weeks	1-TISS↓ 2- abdominal pain or discomfort ↓ 3- intensity of BM urgency ↓ 4-IBS severe↓ 5-unbearable symptoms.	Treatment-related adverse events were reported by 3 subjects (PO group: 1; placebo group: 2) and consisted of flatulence, dyspepsia, and	[75]

Table 2 (continued)

Preparations/Routes of administration treatment & control groups	Study design (clinical trials)	Disease (Model of IBS)	No. of Patients	Treatment duration	Results	Adverse effects	References
meal. The placebo group received an identical looking placebo	18–60 years), 75% were female, and 77.8% were Caucasian)	Score (TISS) of C2 on a 0–4 scale	had IBS-M and 19 patients had IBS-D (P C 0.35 for all comparisons			gastroesophageal reflux, respectively. All adverse events were mild in intensity with the exception of moderate gastroesophageal reflux reported by 1 patient in the placebo group.	
patients were treated with either AV using the NLP formulation(this AV formulation came as a pink syrup flavoured with mango) or matching placebo (with the same color and flavour) at a dose of 50 ml taken four times a day	Clinical trial	diarrhea predominant and mixed patients	At 1 month, Placebo (n ¼ 14) Active (n ¼ 23). At 3 months, Placebo (n ¼ 11) Active (n ¼ 21).	3 months (1 month and followed up for a further 2 months)	1-At 1 months: improvement in IBS score in active group↑ 2-At 3 months: → In improvement in the IBS score and pain score ↑	AV using the NLP formulation was generally well tolerated, with distension as the only apparent side effect. Six patients did withdraw from the study with nausea and/or vomiting. However, a majority of these came from the placebo group and so was not considered to be a significant side effect.	[73]
Two capsules of peppermint oil or placebo twice a day (prepared in enteric-coated, gastro-protected capsules which do not dissolve during their passage through the stomach and which only dissolve when there is intestinal pH of 7.0 or higher. Each capsule was filled with 225 mg of peppermint oil and 45 mg of Natrasorb, a particular starch that absorbs oils in solid powder (Mintoil ® Cadigroup, Rom e, Italy), while the placebo contained 225 mg of maltodextrin with mint flavour (Cadigroup, Rome, Italy)	Clinical trial	Patients with irritable bowel syndrome according to the Rome II criteria were investigated (all patients had a negative lactose breath test for lactose intolerance(a positive test require an increase in breath hydrogen >20 ppm within 90 or 180 min after an oral ingestion of <20 g lactose powder diluted in 150 ml tap water) and a lactose breath test for bacterial overgrowth (a positive test require two distinct peaks >20 ppm of breath hydrogen within 90 min after 6 g lactose diluted in 150 ml tap water).	50 patients: 24 patients in peppermint oil group (18 women, 6 men; mean age 42, range 22–58) and 26 patients (20 women and 6 men; mean age 40, range 20–60) in the placebo group	4 weeks	1-In PO group→ improvement in total IBS symptoms score ↓ 2-In the PO group →all the symptoms ↓improvement in diarrhoea, pain and bloating	One patient in the peppermint oil group refused to continue the study due to prolonged heartburn and a minty taste in his mouth (may be due to the incorrect assumption of the capsule (patient chewing the capsule) or due to the capsule dissolving too early into the stomach, causing oesophageal reflux of gastric juice mixed with menthol)	[36]

the antibacterial activity of *A. vera* juice was only limited to gram-negative bacteria; *A. hydrophilia* and *E. coli* [89, 90, 94].

Antioxidant activity

The abnormalities between ROS generation and their neutralization lead to overwhelming the body's ability to regulate the ROS production and oxidative stress, playing crucial roles in the pathogenesis of various diseases such as IBS [93, 95]. However, the antioxidat system of the human body is generally able to control and inhibit the free radicals production [96]. This protective system is composed of enzymatic agents (intracellular antioxidant enzymes), as well as antioxidant compounds from foods, which form an integrated system, effective in blocking the oxidative effects of ROS and nitrogen species (NOS) [94] (Table 2, Fig. 1).

A. vera is a great choice for diseases management, mainly through its radical-scavenging asset [97]. Phytochemical investigations showed that the majority of the *A. vera* polyphenolic compounds belong to the non-flavonoid polyphenols. The leaf gel extract is composed of phenolic acids/polyphenols, indoles, and alkaloids; possessing antioxidant properties confirmed by Oxygen Radical Absorbance Capacity (ORAC) and Ferric Reducing Antioxidant Power (FRAP) analyses that help to improve IBS [98, 99].

Anti-inflammatory activity

A. vera is one of the best-reputed natural remedies that can control swelling/redness. It was shown the polyphenols of

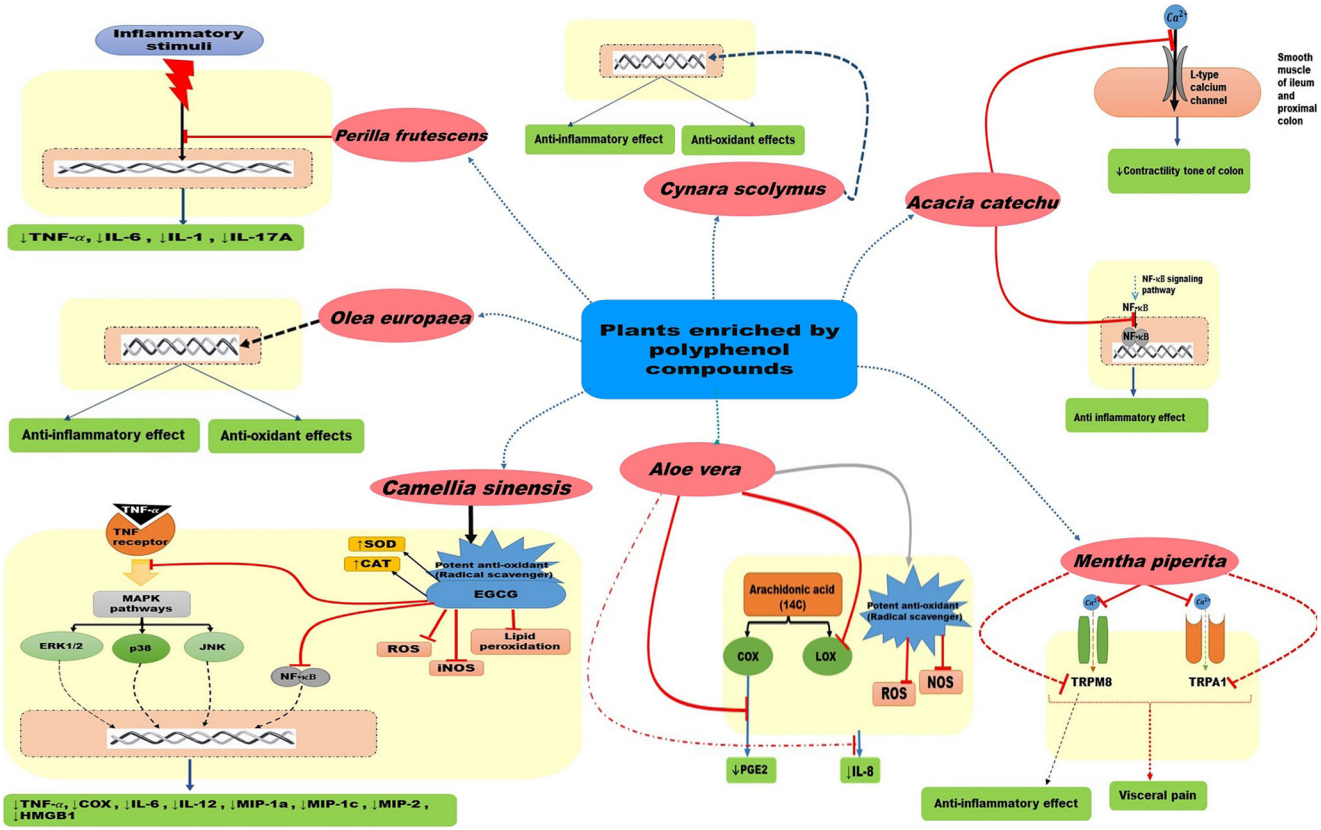

Fig. 1 Plants enriched by polyphenol compounds, prevention and treatment of IBS. cAMP: Adenosine diphosphate, TRPA1: Transient receptor potential ankyrin 1, p38MAPK: p38 mitogen-activated protein kinases, JNK: Jun N-terminal kinase, LOX: Lipoxygenase, COX-1,2: Cyclooxygenase-1,2, IL-8: Interleukin-8, PGE2: Prostaglandin E2, Bcl-2: B-cell lymphoma 2, Bcl-xL; B-cell lymphoma-extra-large, IL-1β: Interleukin-1beta, IL-6: Interleukin-6, MCP-1: Monocyte chemoattractant protein-1, MIP-1α: Macrophage inflammatory protein-1alpha, iNOS: Inducible nitric oxide synthase, TNF-α: Tumor necrosis factor alpha, IFNγ: Interferon gamma, NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells, TLR: Toll like receptor,TLR4: Toll like receptor, TRIF: Tir-domain-containing adapter-inducing interferon-β, TRAF6: Tumor necrosis factor receptor associated factor 6, IKKβ: Inhibitor of kappa beta kinase, MyD88: Myeloid differentiation primary response 88, Akt: Protein kinase B (PKB), mTOR: Mammalian target of rapamycin, IGF-1R: Insulin-like growth factor 1 receptor, IRAK1: Interleukin-1 receptor-associated kinase 1, IRAK4: Interleukin-1 receptor-associated kinase 4, TAK1: Transforming growth factor-beta-activated kinase 1, TIRAP: TIR domain containing adaptor protein, TRAM: Translocating Chain-Associated Membrane Protein, RIP: Receptor-Interacting Protein, IKK : Inhibitor of kappa alpha kinase, IKK : Inhibitor of kappa gama kinase, PI3K: Phosphatidylinositol-3 kinase, IGF-1: Insulin-like growth factor 1. pCREB:phosphorylated cAMP response element binding protein, CREB: CAMP responsive element binding protein ↓: decrease, ↑: increase

Table 3 In vitro studies on beneficial effects of polyphenols for the prevention and treatment of IBS

Preparations/Routes of administration Treatment & control groups	Study design (in vivo)	Disease (Model of IBS)	No. of animals	Treatment Duration	Results	Adverse effects	References
oral administration of curcumin (10, 20 and 40 mg/kg, p.o.) that dissolved in 0.5% sodium carboxymethyl-cellulose and diluted to the desired concentration on the day of testing	Male Sprague–Dawley (SD) rats weighing between 200 and 220 g	Chronic acute combined stress (CAS) model		3 weeks	1-immobility ↓ by curcumin 2- AWR response of chronic acute combined stress rats ↓ The AWR scores ↓ 3–5-HT turn over ↑ 4- BDNF expression in the hippocampus and in colonic ↑ 5- up-regulation of pCREB in the hippocampus and in colonic ↑		[107]
Trans-Resveratrol was prepared to suspension with 0.5% sodium carboxymethyl cellulose and administrated in the volume of 0.01 ml/g daily (2.5, 5, and 10 mg/kg, i.g.) 30 min before CACS. Vehicle (0.5% sodium carboxymethyl cellulose, i.g.)	ICR male mice weighing about 30 g	IBS induced by chronic-acute combined stress (CACS)	Total 96 male ICR mice	3 weeks	1-AWR scores↓ at 0.35 ml so that CACS-induced visceral hypersensitivity↓		[108]
Chang-Kang-Fang formula (CKF) composed of Flavonoids such as hyperoside, quercetin, astragalin, kaempferol, isorhamnetin and wogonin	Male Sprague–Dawley rats obtained as preweanling neonates (younger than 8 days)	colorectal distention IBS	model group ($n = 10$; received same volume of water as vehicle), low-dose CKF-treated group ($n = 10$; treated with 1.3 g/kg/d CKF), middle-dose CKF-treated group ($n = 10$; treated with 2.5 g/kg/d CKF), high-dose CKF-treated group ($n = 10$; treated with 5.0 g/kg/d CKF), and TM treated group ($n = 10$; treated with 17.0 mg/kg/d trimebutine maleate (TM)).	21 days	1-Abdominal withdrawal reflex (AWR) ↓ 2- calcitonin gene-related peptide (CGRP) ↑ 3-CKF significantly reversed the vasoactive intestinal polypeptide (VIP) 4–5-hydroxytryptamine (5-HT) ↑ 5- expression of substance P (SP)↓ 6- CKF at different dosages, reversed destroyed epithelium and inflammatory cells were decreased dose-dependently. 7- the acetic-acid-induced writhing at three dosage levels ↓. 8-intestinal propulsion ↓		[109]
Acacia catechu Willd.	Guinea pigs of either sex (200–400 g)	Diarrhea (IBS-D) by diagnostic criteria Rome III and IV	50 patients: 24 patients in peppermint oil group (18 women, 6 men; mean age 42, range 22–58) and 26 patients (20 women and 6 men; mean age 40, range 20–60) in the placebo group	4 weeks	1-relaxation in ileum and colon contractility ↑ 2-the tone↓ at the low- and high-frequency waves in the colon 3-the concentration-dependent spasmolytic activity↑, both in the ileum and colon 4-the maximum response to carbachol in a concentration-dependent manner with an IC50 value of 0.98 mg/mL (c.l. 0.73–1.14) ↓and behaved as a noncompetitive antagonist since it caused a decrease of the maximum response to agonist 5-Acacia catechu produces noncompetitive reversible antagonism similar to that shown in the ileum. On the proximal colon, the		[110]

Table 3 (continued)

Preparations/Routes of administration Treatment & control groups	Study design (in vivo)	Disease (Model of IBS)	No. of animals	Treatment Duration	Results	Adverse effects	References
					potency is similar than that shown in the ileum 6- inflammatory properties and several signaling pathways involved in inflammation such as Nf-κβand transcription factors with a synergic effect on diarrhea ↓		
The PB was composed of galactooligosaccharide (GOS) plus fructo-oligosaccharide (FOS), inulin and anthocyanins in the form of freeze-dried powder. The powder was suspended in saline before treatment	Four-weeks-old female specific pathogen-free (SPF) C57BL/6 mice	PI-IBS	model 60 mice were randomly divided into 4 experimental groups (15 mice per group in 3 cages), among which 3 groups were given a gavage of saline (MOCK group), PB (1.26 mg/g body weight, PB group), PB and probiotics (1.26 mg/g body weight PB plus 3.0107 CFU/mouse of both Lactobacillus acidophilus NCFM and Bifidobacterium lactis HN019, PB/ProBio group), respectively.	8 weeks	1- IL-1β IL-1β, IL-8 and TNF-α↓ 2- the AWR score ↓ by PB or PB/ProBio treatment so the visceral hypersensitivity↓ 3- the expression of Occludin (OCLN) ↑both in PB andPB/ProBio groups 4- expression of PPAR↓ in the MOCK group 5- expression of PPAR ↑ in the PB group and the PB/ProBio group 6- Linear discriminant analysis (LDA) showed that the abundance of the bacteria genera of Vampirovibrio and Akkermansia in MOCK group↓, while in the PB/ProBio groups ↑. 7-The relative abundance of the genera ClostridiumXIVa, Clostridium sensu stricto, Prevotella, Butyricicoccus, Ochrobactrum, Barnesiella, Gemmiger, Mucispirillum, Intestinimonas, and Mucispitillum in PB group or PB/ProBio group in compared with the MOCK group ↑.		[111]

A. vera reduced edema by inhibiting the PGE2 production from [14C] arachidonic acid [77, 100], besides, *A. vera* gel inhibited the production PGE2 and secretion of IL-8 [101, 102]. According to Hong et al. 2018, *A. vera* showed anti-inflammatory effects on various conditions. Its oral administration was helpful in ameliorating the gastric ulcer and repressing the inflammatory mediators in damaged tissues and increased the QOL scores. It is suggested that the anti-inflammatory properties of *A. vera* is probably the main related mechanism of action for IBS treatment with this plant species [65] (Table 2, Fig. 1).

Mentha piperita

Peppermint oil isolated from *Mentha piperita* (Lamiaceae), contains a mixture of terpenes and has been shown to possess various therapeutic effects such as reducing colonic spasm during barium examination [103, 104], relieving non-ulcer dyspepsia [105], and alleviating tension-type headaches [106] (Tables 2 and 3, Fig. 1). The oil shown significant antiviral activity against Herpes simplex viruses (HSV)-1 and HSV-2 [61], either alone or in combination with other herbals or medications. L-menthol is the principal component of the oil, accounting for 35–50% of the compounds. Peppermint is being used for centuries as a digestive aid, and specifically has been evaluated as a potential IBS therapy for several decades [112, 113].

Peppermint oil and L-menthol, are known to be serotonergic (5HT3) antagonism [114], smooth muscle calcium channel antagonism [112] and can reduce the calcium influx [113], also accounted as kappa opioid agonism [115], carminative [116], anti-infective [117], and anti-inflammatory agents [118]. Clinical studies introduced the oil as an attractive pharmacotherapy candidate for IBS, even better than antispasmodics; tricyclic antidepressants, and fiber [119].

Following oral administration at a dose of 187 mg (three to four capsules daily), the oil positively affected the abdominal pain, distension, stool frequency and consistency, borborygmi, and flatulence, in about 78% of patients, significantly more effective than the placebo. It was rapidly absorbed from the proximal gut, and frequently showed unwanted effects such as heartburn. Stool consistency improved from watery to soft or normal, corresponding to the decrease in stool frequency. However, it had no effect on upper digestive tract symptoms, such as nausea, acid regurgitation, belching, heartburn and skin rush [36, 37, 67, 69]. Patients treated with this oil experienced reduction in abdominal pain or discomfort, and the mean intensity of bowel movement (BM). Similarly, the oil caused a decrease in Total IBS Symptom Score (TISS), significantly greater than the placebo group at 24 h [120]. Subjects receiving peppermint oil experienced a significant decrease in the number of severe and unbearable symptoms at 28 days compared with those receiving the placebo. The reduction from baseline in the number of severe and unbearable symptoms was also more pronounced for the peppermint oil group compared with the placebo at 24 h, but did not reach statistical significance [69, 120].

In individuals diagnosed with either abdominal pain or discomfort, colpermin (peppermint-oil formulation) increased the number of patients free from abdominal pain or discomfort and the IBS score of QOL, also reduced the intensity of abdominal pain or discomfort significantly. Adverse events were mild, transient, and well tolerated. The most frequently observed adverse events were heartburn, headache, and dizziness. Other less frequent events included belching, dry mouth, and increased appetite, which were reported in less than 10% of subjects [75].

Effects on GI tract neuromotor function

Peppermint oil reverses the acetylcholine-induced contraction and antagonises the serotonin-induced contraction through calcium channel block [113, 121]. It was observed that menthol induced circular smooth muscle relaxation in human colon, by directly inhibiting the contractility via blocking the Ca^{2+} influx through sarcolemma L-type Ca^{2+} channels [113, 121].

The oil may also directly affect the enteric nervous system. Using cultured murine small intestine interstitial cells of Cajal, it was shown that menthol acts via the transient receptor potential cation channel, subfamily A, member 1 (TRPA1) receptor to induce the membrane potential depolarization in a concentration dependent manner. G protein stimulation as well as the external Ca^{2+} and Ca^{2+} release from the intracellular stores also were involved [122]. In addition, it was evidenced that prostaglandin production was also implicated in stimulating the effects of menthol on the interstitial cells. The peppermint oil (via menthol) can decrease the visceral pain when administered orally or intraperitoneally in IBS patient [123], by reducing the TRPM8 and/or TRPA1 receptors of the transient receptor potential cation channel (TRP channels) superfamily located in the gut [124].

Effects on inflammation

It has been evinced that the oil (menthol) possesses impressive anti-inflammatory activities, thus it could improve the IBS scores. The peppermint oil prevents both xylene-induced gut inflammation in mice and acetic acid-induced colitis in rats [123, 125] (Tables 1 and 2, Fig. 1). Menthol was shown to suppress the production of inflammatory mediators from human monocytes [118]. It is known that immune cells contain TRP channels. It is believed that the anti-inflammatory effects of the peppermint oil may be mediated, at least in part, via TRPM8, since its activation downregulates chemically-induced colitis in mouse models [126, 127].

Cynara scolymus (artichoke)

Artichoke species is described as a medicinal plant used in gastric conditions due to its anti-dyspeptic action, which is promoted by its choleretic properties (Alves and Botsaris, 2007) (Table 1, Fig. . 1). Treatment with artichoke leaf extract, rich in phenolic compounds such asca-feoilquinic acid and flavonoids, contributed to a significant increase of the bile flow and cholesterol reduction in rats [128]. Artichoke displays a significant antispasmodic potential, due to the presence of sesquiterpene cinaropicrin. In another study, the phenolic metabolites such as flavonoids and caffeine derivatives were introduced responsible for treatment of digestive disorders, relieving loss of appetite, nausea and abdominal pain [95].

Many investigations have shown the benefits of artichoke polyphenols in IBS patients. The extract of *C. scolymus* was able to affect the intestinal microbiota and displayed significant antispasmodic effects [129] (Table 1). According to a clinical study involving 244 participants with dyspepsia, the volunteers which received 320 mg of the artichoke extract twice daily for 6 weeks, the symptoms of diarrhea/constipation were improved [77]. In another investigation with 208 IBS patients, the incidence of the disease was dropped significantly (26.8%), after the use of the artichoke leaf extract [101]. In agreement with these studies, it has been shown that following the administration of artichoke, the IBS symptoms and the QOL score were relieved in 96% of the IBS patients [130]. A 40% reduction in dyspepsia symptoms was recorded in individuals that received *C. scolymus* extract containing phenolic metabolites such as flavonoids and caffeine-like acids [131, 132]. Such findings confirm the articular use of the artichoke in gastrointestinal problems.

Perilla frutescens

Perilla frutescens is a plant species with leaves enriched with polyphenols. It has known anti-allergic, respiratory, and digestive treating effects (Table 1, Fig. . 1). The plant contains various phenolic compounds such as phenolic acids, cinnamic acid derivatives, flavonoids, and lignans. Gallic acid, hydroxytyrosol (3,4-DHPEA), cinnamic acid derivatives (coumaroyl tartaric acid, caffeic acid and rosmarinic acid), flavonoids, scutellarein 7-O-diglucuronide, luteolin 7-O-diglucuronide, apigenin 7-O-diglucuronide, luteolin 7-O-glucuronide, and scutellarein 7-O-glucuronide), and anthocyanins (mainly cis-shisonin, shisonin, malonylshisonin and cyanidin 3-O-(E)-caffeoylglucoside-5-O-malonylglucoside) [133]. In a double-blind, randomized, placebo-controlled parallel trial, 50 participants with gastrointestinal discomfort were treated with *P. frutescens* extract, receiving 150 mg of the extract twice daily during 4 weeks. It was reported that all the gastrointestinal symptoms including bloating, passage of gas, GI rumbling, feeling of fullness, and abdominal discomfort were significantly attenuated [134] (Table 1, Fig. . 1).

Preclinical investigations suggested that *P. frutescens* stimulated the motility of the intestinal tract. In another study, *perilla* extract and the isolated vicenin 2 reduced the acetylcholine- or Ba(2+)-induced-contraction of rat ileum, representative of an antispasmodic effect [135]. *P. frutescens* is able to ameliorate Dextran sulfate sodium (DSS)–induced colitis via downregulating the pro-inflammatory and inducing the anti-inflammatory cytokines. In this study, *P. frutescens* significantly suppressed the mRNA expressions of TNF-α, and IL-17A in distal colon. Among the isolated phenolic compounds, luteolin repressed the production of TNF-α-, IL-1, IL-6, and IL-17A. Apigenin reduced the IL-17A secretion and increased the anti-inflammatory cytokine IL-10. These reports suggest that *P. frutescens* polyphenols are potential therapeutical phyto-medications to manage IBS and increasing the QOL scores [136–138].

Acacia catechu - polyphenol (catechins)

In animal model of IBS, *A. catechu* (Fabaceae) caused relaxation in the ileum and colon contractility [110] (Table 3, Fig. . 1). Qualitative analysis of the ileum showed that *A. catechu* extract containing polyphenols i.e. catechins, reduced the tone of colon contractility, in particular, at high-frequency waves. All the frequency ranges significantly decreased from the spontaneous values and enhanced the QOL score in IBS [110, 139, 140].

The functional activity of *A. catechu* extract against L-type calcium channels was assessed in the ileum and the proximal colon smooth muscles. *A. catechu* induced a concentration-dependent spasmolytic activity, both in the ileum and colon. *A. catechu* produced noncompetitive reversible antagonism, similar to that shown in the ileum. On the proximal colon, the potency was similar to that shown in the ileum [68, 110, 139, 141].

A. catechu polyphenols displayed weak antimicrobial activity against gram-bacteria such as *C. jejuni, E. coli*, and *Salmonella spp*. *A. catechu* did not affect neither gram positive tested species. Actually, its main polyphenolic compounds, catechins, were reported to possess anti-inflammatory properties, by inhibiting several signaling pathways such as Nf-$k\beta$ and other transcription factors with a synergic effect on diarrhea in IBS [110, 139].

Camellia sinensis- polyphenol (catechins)

Polyphenols of tea (*Camellia sinensis,* Theaceae), commonly known as catechins, proven to be potent scavengers [142] of free radicals [39] (Table 3, Fig.. 1). Epigallocatechin gallate (EGCG) is the strongest antioxidant compound in tea catechins [38, 40, 139, 143]. Due to its antioxidant properties, EGCG found helpful to decrease the potential effect of some neurotoxin in neurodegenerative disorders, attenuated the toxic effect of ROS and

hampered the caspase-3 activity in neuronal cultures [139, 144]. Besides, EGCG shown to inhibit the lipid peroxidation promoted by iron ascorbate in homogenates of the brain mitochondrial membranes [110, 139, 145]. Furthermore, EGCG is reported to inhibit the transition of metal-catalyzed free radicals formation and chelate metal ions. EGCG treatment inhibited the activity of the enzyme inducible nitric oxide synthase (iNOS) [40, 146] in activated macrophages, while the compound promoted the activity of the antioxidant enzymes; superoxide dismutase (SOD) and catalase (CAT), that could be useful to control the inflammation process [147].

EGCG also inhibited the NF-$\kappa\beta$ activation induced by many pro-inflammatory stimuli such as ultra-violate (UV), LPS, TNF-α and IL-1 [139, 143, 148, 149], resulting in a decline in the expressions of the inflammatory gene products including lipoxygenase, COX, NOS, and TNF-α in IBS [144, 150, 151]. It has been demonstrated that the suppression of the kinase activity of I$\kappa\beta$ in macrophages and the intestinal epithelial cell line 6 (IEC-6), can downregulate the activation of NF-κB [139, 147]. It was reported that EGCG blocked the TNF-α-induced phosphorylation of MAPKs family, such as extracellular signal-regulated kinase 1/2 (ERK1/2), p38 and JNK in synovial fibroblasts [152–154], while other studies pointed out that EGCG inhibited the LPS-induced activation of p38, but enhanced the phosphorylation of ERK1/2 in J774.1 macrophage cells [147, 152]. The green tea polyphenols inhibited p44/42 MAP kinase expression and reduced the viability of smooth muscle cells in a p53- and NF-$\kappa\beta$ -dependent manner [139, 149, 155]. Experimental data suggested that EGCG selectively inhibited LPS-induced release of high mobility group box 1 (HMGB1), TNF-α, IL-6, IL-12, and chemokines, including macrophage inflammatory protein (MIP)-1a, MIP-1c, MIP-2, normal T cell expressed and secreted RANTES (CCL5), monocyte chemoattractant protein-1 MCP1, keratinocytes chemoattractant and chemokine (C-X-C motif) ligand 16 CXCL16 in IBS. EGCG increased the QOL scores such as abdominal pain, nausea, vomiting, diarrhea and constipation [40, 156–159].

Olea europaea

Olive polyphenols (i.e. gallic, p-hydroxybenzoic, protocatechuic, vanillic, syringic, caffeic, ferulic, p-coumaric, and sinapic acids, and flavonol glycosides such as luteolin-7-glucoside and rutin as well as anthocyanins, cyanidin 3-O-glucoside, and cyanidin 3-O-rutinoside) [160], have direct contact with the gastric and intestinal mucosa, allowing a direct cellular exposure, while avoiding the first-pass hepatic metabolism. Several studies shown that the olive polyphenols and/or derivatives can passively diffuse into enterocytes quite readily [42, 161]. Olive oil polyphenols can also directly impact digestive health by promoting the intestinal microbiome that supports the intestinal immune homeostasis, which expands the potential benefits to a broad spectrum of diseases known to be tied into this system such as IBS [161] (Table 1, Fig. 1).

Topical application of olive polyphenols can improve wound healing processes, somehow relevant to digestive health, as the oral administration of these polyphenols can serve as a topical treatment to the gastric and intestinal mucosa [161, 162], due to their utility in restoring damaged and inflamed mucosa. The combination of systemic effects paired with direct topical effects on mucosa, modulation of microbiome, and the immune modulatory effect; all contribute to the observed benefits of olive polyphenols in a wide variety of digestive issues including IBS [163].

Evidence on effectiveness of polyphenol compounds on IBS

Trans-resveratrol

The natural occurring metabolite 3,5,4′-trihydroxy-trans-stilbene is a polyphenol compound extracted from many plant species, particularly from the skin of red grapes and red berries. Resveratrol has a great history of pharmacological activities with a well-documented inhibitory effect on diverse cellular events associated with tumor initiation and development [164]. Literature review showed that resveratrol possesses anti-oxidant, anti-inflammatory [165, 166], and cardioprotective properties [166, 167] (Table 3, Fig. 2). The compound has also shown neuroprotective activities, by targeting various molecules such as brain-derived neurotrophic factor (BDNF) and phosphodiesterases (PDEs) [41, 168]. It is suggested that this compound could have antidepressant and anxiolytic-like effects in various animal models [166, 169–171] by increasing the BDNF protein levels in the hippocampus [172]. It was evidenced that resveratrol protects the intestinal barrier function against oxidative stress [173], by binary effects on central nervous and peripheral disorders. For instance, resveratrol improves the psychiatric and intestinal dysfunction through inhibition of the cAMP degrading phosphodiesterases (PDEs), the enzyme responsible for BDNF regulation [41, 168, 174].

The high expression of PDE4 in the brain-gut axis has particular role in the IBS pathology [175, 176]. PDE4 inhibitors alleviate the intestinal dysfunction by reducing defecation [166, 177], therefore, resveratrol may block the PDE4 subtypes and the downstream signaling, improving the IBS-like symptoms and the score of QOL [166]. Among 4 subtypes of PDE4 (PDE4A-D), PDE4A signaling shown protective effects against IBS insults, reversed the IBS-related depression- and anxiety-like behaviors, as well as the intestinal dysfunction, by regulating the brain-gut axis. It has been shown that resveratrol ameliorated the chronic-acute combined stress (CACS)-induced intestinal dysfunctions like IBS. Pre-treatment of resveratrol for 3 weeks, significantly

reduced the CACS-induced abnormality of the intestinal motility by increasing the migration distance to total intestinal length. In addition, resveratrol caused CACS-induced visceral hypersensitivity by diminishing abdominal withdrawal reflex (AWR) scores, demonstrating that resveratrol has anti-IBS-like effects in rodent model of IBS and increases the score of QOL [178]. Chronic treatment of trans-resveratrol diminished histological scores in the inflammatory damaged ileum dose-dependently. However, it could not completely reverse the CACS-induced ileal and colonic damages, signifying that trans-resveratrol possessed anti-inflammatory effects on CACS-induced IBS model [174].

Trans-resveratrol normalized PDE4A, pCREB, and BDNF protein levels in the ileum and colon

It is evidenced that CACS significantly augmented the PDE4A, phosphorylated cAMP response element binding protein/CAMP responsive element binding protein 1 (pCREB/CREB), and the BDNF protein levels, in comparison with the control groups in vivo (Table 3). In the colon and ileum, resveratrol treatment reduced the expressions of these proteins by decreasing PDE4A, pCREB/CREB, and the expression and protein levels of BDNF, suggesting that resveratrol is useful in CACS condition, induced abnormalities of PDE4A expression and the CREB-BDNF signaling in the ileum and colon [166, 174, 179].

Antioxidative and anti-inflammatory properties

Resveratrol also shown to inhibit the lipid peroxides production and can modulate the lipoprotein metabolism [176, 180] (Table 3, Fig. 2). Its anti-oxidative and anti-inflammatory effects [181, 182] was correlated with disruption of arachidonic acid metabolism and inhibition of COX-1 and COX-1 hydroxyperoxidase [164]. The stilbene can reduce the LPS- and/or phorbol 12-myristate- induced COX-2 levels, also modulated the overexpression of COX-2 [183–185].

Villegas et al. 2004 showed that the expression of COX-2 was diminished in apical epithelial cells of the inflamed colon in resveratrol-treated rats. The authors concluded that decreased apoptosis in colonic mucosa was due to increased DNA fragmentation in trinitrobenzene sulphonic acid (TNBS)-treated rats [186].

Besides inhibiting COX-2, resveratrol suppressed the iNOS expression and subsequent NO production in cultured cells [183, 187, 188]. It was seen that the activation of immune cells, such as neutrophils, macrophages, and cytotoxic T cells leads to the intestinal barrier destruction through physical contact. This process may also occur by releasing of reactive oxygen and nitrogen radicals, cytotoxic proteins, lytic enzymes, or cytokines such as TNF-α and IL-1β [189–191].

The inhibition of the key-pro-inflammatory mediators is important to control the inflammatory responses. IL-1β is considered as the primary stimulator of diarrhea (the major symptom of the intestinal inflammation) [192]. It was shown that resveratrol contributes to decrease the PGD2 in the colon tissue. PGD2 is the main PG produced by mucosal mast cells and is crucial for restraining the colon inflammation [192–196].

Resveratrol participates in increasing the anti-inflammatory immune-regulatory cytokine IL-10 [197]. In animal model of LPS-induced airway inflammation, resveratrol inhibited the MPO activity (an indicator of the infiltration of the colon with polymorphonuclear leukocytes) and cytokine-induced neutrophil chemoattractant-1 (CINC-1) level in the lung tissue [178]. In a human study, resveratrol reduced the release of IL-8 and granulocyte-macrophage colony stimulating factor from alveolar macrophages in chronic obstructive pulmonary disease [198]. In another study, the activities of T- and B-cells were ameliorated by resveratrol, leading to decreased PGE2 and various cytokines such as TNF-α, IL-1β, IL-6, interferon gamma (IFNγ) and IL-12 secretions [192, 199].

Resveratrol is a well-recognized compound able to inhibit a wide strata of the inflammatory agents-induced the NF-κB activation. A number of molecular targets of resveratrol are recognized in TLR-mediated signaling pathways. It has been demonstrated that resveratrol inhibition of IκB (Inhibitor of kappa B) kinase, led to the inhibition of LPS-induced IκB degradation, resulting in prevention of NF-κB translocation and transactivation [196, 200]. TLR4-TRIF pathway-induced IκB degradation is assumed to be mediated via the interaction between TRIF and tumor necrosis factor receptor associated factor 6 (TRAF6) in association with the N-terminal part of tir-domain-containing adapter-inducing IF-β (TRIF) [197, 201]. Resveratrol was also shown to inhibit myeloid differentiation primary response 88 (MyD88)- independent signaling pathways and the expression of their target molecules [178, 199]. It was evident that COX-2 is a rate-limiting enzyme in the process of the inflammatory mediator's production, with NF-κB being the upstream regulator of COX-2. Of note, the anti-inflammatory activity of resveratrol is mostly attributed to the inhibition of COX activity [198, 202, 203]. Resveratrol interferes the pro-inflammatory signaling of thrombin, which in turn, reduces the secretion of adenosine nucleotide from activated platelets and decreases neutrophil functions, by inhibiting the PAP and purinergic 2 receptor (P2-receptor) signaling through MAPK, cJun, and JNK pathways [192–195].

Curcumin Curcumin, is the major ingredient of turmeric, extracted from the rhizomes of *Curcuma longa* (Zingiberaceae), and traditionally used as a herbal medicine for its anti-inflammatory, choleretic, antimicrobial, anticancer, and hepatoprotective properties [204]. Curcumin shown to exert antioxidant, neuroprotective, and carminative actions through inhibiting the expression of both COX-2 and iNOS, which would be

beneficial in disturbed gastrointestinal tract function such as IBS [182, 205] (Table 3, Fig. 2). Curcumin promoted a symptomatic improvement (i.e. more formed stools, less frequent bowel movements, and less abdominal pain and cramping) [206], and decreased the IBS prevalence and scores, besides improved the IBS symptoms and the QOL scores (Table 2) [68, 70, 206]. Curcumin significantly up-regulated 5- HT 1A release and reuptake in IBS patients, also increased the BDNF protein level in the hippocampus [74, 107]. Administration of curcumin (20 and 40 mg/kg) decreased the immobility and augmented fecal output comparing with the non-stressed vehicle group. Curcumin (40 mg/kg) inhibited the chronic acute combined stress in rats' fecal output and decreased the AWR responses significantly.. Chronic administration of curcumin (20 and 40 mg/kg) elevated the 5-HT levels dose dependently, when compared with the stressed rats (Table 2). In this study, curcumin decreased 5-HT turnover, as represented by the ratio of 5-hydroxyindoleacetic acid main metabolite of serotonin (5-HIAA/5-HT). Curcumin at 40 mg/kg enhanced the BDNF level and up regulated pCREB in chronic acute combined stressed rats. However, low doses of curcumin (10 and 20 mg/kg) did not change the ratio of pCREB/CREB; while at a higher dose (40 mg/kg), curcumin was found effective [107, 109].

The activation of the nuclear factor erythroid 2-related factor 2 (Nrf2)-antioxidant mediator response pathway is an important mechanism involved in intracellular defense against oxidative stress. Nrf2participates in controlling the gene expression of the proteins relevant to the detoxication and elimination of reactive oxidant radicals in the system. A randomized clinical trial revealed that curcumin promoted the translocation of the Nrf2 from the cytoplasm to the nucleus. The glucose oxidase (GO)-induced increase of the expression of the extracellular matrix remodeling (ECM) molecules in human chronic somatomamotropin (HSCs) was also detected. Curcumin-induced the Nrf2 activation, inhibited the expression of ECM molecules in HSC, which was attributed to its antifibrogenic properties. In addition, GO-induced oxidative stress increased the smooth muscle α-actin (α-SMA) expression in HSCs, and the transformation of HSCs to the myofibroblast-like cells. Subsequent to the activation of curcumin-induced Nrf2, the expression of α-SMA and the HSC activation were suppressed, which were also associated with its antifibrotic effects. In addition, pre-treatment with curcumin significantly suppressed the oxidative stress and ROS, in part, due to the Nrf2-induced expression of the endogenous glutathione (GSH) [72]. Further, curcumin stimulated the antioxidant defense by promoting the Nrf2-induced GSH production, induction of glutamate cysteine ligase transcription, and through direct interaction with superoxide anion and hydroxyl radicals [68].

Curcumin (in micro to millimolar ranges) is capable of free radicals scavenging, both in vitro and in vivo [109, 207, 208] (Table 4, Fig. 2). The compound showed inhibitory effect on the lipid peroxidation and can maintain the activity of various antioxidant enzymes and ROS scavengers. It was shown that curcumin inhibited the LPS-induced production of TNF-α and interleukin IL-1β in human monocytic macrophage cell line, Mono Mac 6, and the compound reduced the biological activity of TNF-α [209, 210].

Curcumin decreased the expression of - IL-1β, IL-6, IL-8, MIP-1α and MCP-1 in phorbol 12-myristate 13-acetate (PMA)- or LPS-stimulated human monocytes and alveolar macrophages in a dose- and time- dependent way [211–213]. In vivo, curcumin significantly diminished the inflammation by inhibiting the mRNA induction of IL-6, IL-1β, TNF-α and iNOS [213–217].

Isoflavones Chronic visceral pain, a marked characteristics of IBS, linked with the estrogens activity in women [218], particularly during menstrual period [219] (Table 2, Fig. 2). Reduction of estrogens leads to increased gut hypersensitivity and permeability in IBS women [220]. In the other hand, the estrogen receptor type β (ERβ) is predominantly expressed in the colon, however, the estrogen like compounds such as isoflavones may stimulate the ERβ, and can reduce the gut hypersensitivity [220]. Diadzein, glycetin and genistein are the major compounds of soy (*Glycine max*, Fabaceae) isoflavones, acting as 17- β estradiol with high affinity for ERβ [221]. Administration of soy isoflavones, reduced the IBS-severity scoring QOL system (IBS-SSS) in IBS patients. Isoflavones significantly improved the QOL scores, for example, the abdominal pain severity, duration and distension in patients [72].

Inhibition of NF-κB pathway activation Soy isoflavones were ascertained to inhibit and block the NF-κβ protein activation. NF-κβ is reported to regulate the immune response against a variety of stimuli such as free radicals, stress, toxines, heavy metals, oxidize Low-density lipoprotein LDL, and infection [220, 222, 223] (Table 2, Fig. 2). In vitro, the phosphorylation of IκB and sequestering of NF-κ*B* complexes into the cytoplasm was inhibited by genistein. At lower concentrations, genistein decreased the NF-*B*/p65 nuclear protein level dose-dependently, mainly by inhibiting the phosphorylation of IκB protein. Likewise, genistein hampered the translocation of NF-κ*B* dimers to the nucleus and their binding to DNA, leading to the inhibition of the NF-κB downstream genes transcription, reduced the IBS symptoms and elevated the QOL scores [220, 222, 223]. This compound also inhibited the Notch-1 expression and downregulated the NF-$\kappa\beta$ targeted proteins, cyclin B1, B cell lymphoma 2 (Bcl-2), and B cell lymphoma-extra-large (Bcl-xL) [220, 224]. Thus, genistein could offer a therapeutic possibility in blocking both the NF-$k\beta$ and Notch-1 pathways. Notch1 signaling was shown to determine the specialization and differentiation of various cells during the developmental processes [221, 224].

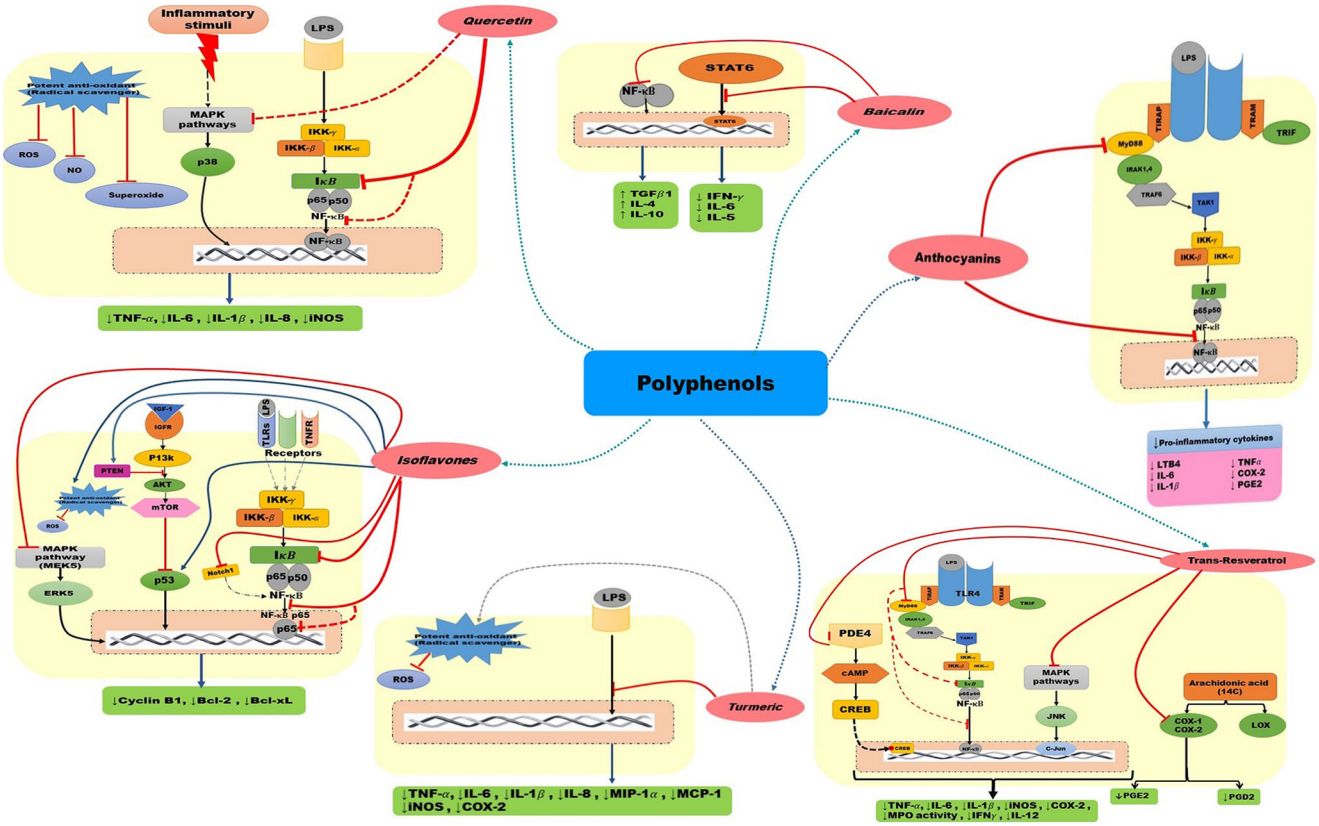

Fig. 2 Phenolic compounds, prevention and treatment of IBS. cAMP: Adenosine diphosphate, TRPA1: Transient receptor potential ankyrin 1, p38MAPK: p38 mitogen-activated protein kinases, JNK: Jun N-terminal kinase, LOX: Lipoxygenase, COX-1,2: Cyclooxygenase-1,2, IL-8: Interleukin-8, PGE2: Prostaglandin E2, Bcl-2: B cell lymphoma 2, Bcl-xL; B cell lymphoma-extra-large, IL-1β: Interleukin-1beta, IL-6: Interleukin-6, MCP-1: Monocyte chemoattractant protein-1, MIP-1α: Macrophage inflammatory protein-1alpha, iNOS: Inducible nitric oxide synthase, TNF-α: Tumor necrosis factor alpha, IFNγ: Interferon gamma, NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells, TLR: Toll like receptor, TLR4: Toll like receptor, TRIF: Tir-domain-containing adapter-inducing interferon-β, TRAF6: Tumor necrosis factor receptor associated factor 6, IKKβ: Inhibitor of kappa beta kinase, MyD88: Myeloid differentiation primary response 88, Akt: Protein kinase B (PKB), mTOR: Mammalian target of rapamycin, IGF-1R: Insulin-like growth factor 1 receptor, IRAK1: Interleukin-1 receptor-associated kinase 1, IRAK4: Interleukin-1 receptor-associated kinase 4, TAK1: Transforming growth factor-beta-activated kinase 1, TIRAP: TIR domain containing adaptor protein, TRAM: Translocating Chain-Associated Membrane Protein, RIP: Receptor-Interacting Protein, IKKα: Inhibitor of kappa alpha kinase, IKKγ: Inhibitor of kappa gama kinase, PI3K: Phosphatidylinositol-3 kinase, IGF-1: Insulin-like growth factor 1. pCREB: phosphorylated cAMP response element binding protein, CREB: CAMP responsive element binding protein. ↓: decrease, ↑: increase, ⊣: inhibit

Effects on PI3K/Akt/mTOR signaling pathway The phosphatidylinositol3-kinase/protein kinase-B/mammalian target of rapamycin (PI3K/Akt/mTOR) intracellular pathway has a great importance in cellular cycle, including survival or protein synthesis. This protein is also linked to the cellular proliferation, cancer and longevity (Table 2, Fig. 2). Hyper-activation of this pathway attributed with tumoral development and resistance to the current anticancer therapies [72, 225]. PI3K/Akt/mTOR is the most frequently activated signaling pathway [226] in estrogen receptor–positive-positive breast cancers. Hence, PI3K/Akt/mTOR inhibition expanded the endocrine therapy benefit, from the first-line setting and beyond [223, 224, 226].

It has been established that the activation of PI3K/Akt pathway is mediated by the insulin-like growth factor 1 receptor (IGF-1R). At high concentrations, genistein inhibited the activation of the IGF-1R/Akt signaling pathway, leading to apoptosis, mainly through downregulation of Bcl-2 and upregulation of Bcl-2 associated X (Bax) [222, 227]. On the other hand, at low doses, genistein exhibited the estrogen stimulatory effects, leading to enhancement of the mRNA expression of the IGF-1R. In PI3K/Akt cascade, genistein induced the expression of phosphatase and tensin homolog (PTEN), the natural inhibitor of PI3K/Akt signaling pathway, and improved the IBS symptoms and the QOL scores. Besides, genistein prompted the PTEN and p53 expressions. Genistein moderates the PI3-K/Akt cascade in several points, either by hindering the IGF-1R or by motivating the inhibitory effects of PTEN, or less often, by reducing the protein expression of total and phosphorylated Akt [228, 229].

Effects on MAPK/ERK signaling pathway Genistein inhibits the MAPK signaling pathway through different mechanisms

Table 4 In vitro studies on beneficial effects of polyphenols for the prevention and treatment of IBS

Preparations/Routes of administration Treatment & control groups	Study design (in vitro)	Results	References
Curcumin	Hepatic stellate HSC-T6 cells	1-Protection against GO-induced oxidative stress 2-Promotion of nuclear translocation of Nrf2 3-GO-induced smooth muscle α-actin (α-SMA) expression & secretion of extracellular matrix (ECM)↓ 4-Abdominal pain & the discomfort score of IBS patients ↓	[208]

(Table 2, Fig. . 2). In MDA-MB-231 cells, genistein suppressed the protein levels of MEK5, total extracellular signal-regulated kinase 5 (ERK5) and phospho-ERK5 in a dose-dependent manner [223]. In human breast adenocarcinoma cell line (MCF-7 cells), high dose of genistein triggered apoptosis by activating the p38 MAPK through Ca2+ release from the estrogen receptor [230]. Genistein can also induce breast cell growth [231]. The stimulatory effects of genistein is attributed to delayed and prolonged phosphorylation of ERK1/2. Co-incubation of MCF-7 cells with an ERK inhibitor abolishes the endoplasmic reticulum transactivation, indicating that the MAPK/ERK signaling pathway is necessary for the endoplasmic reticulum-mediated transcription [231].

The same stimulatory effects were observed in erbB-2-transfected estrogen receptor positive MCF-7 cells treated with low doses of genistein. These effects were due to the enhanced activation of estrogen receptor, MAPK/ERK1/2 and PI3K/Akt signaling pathways, underlying that the close estrogen receptor positive/erbB-2 cross-talk results in reducing apoptosis [232]. Therefore, isoflavones and in particular, genistein, can participate in several pathways involved in cellular apoptosis and survival regulation.

Effects of soy Isoflavones on ROS and DNA damage Plethora data anticipated that ROS can induce epigenetic alterations or stimulate several growth-promoting signaling pathways such as PI3K/Akt, ERK1/2, MAPK/ERK or EGFR, resulting in mitochondrial dysfunction and DNA damage in IBS (Table 2, Fig. 2) [233, 234].

Higher ROS level and greater DNA damage are a result of the estrogen activity, majorly mediated by the estrogen receptor dependent mechanisms [235]. More precisely, the high estrogen receptor/estrogen receptor ratio determines the oxidative status, in response to estrogen. Alike estrogen, genistein modulates oxidative stress according to the estrogen receptor/estrogen receptor ratio [236, 237]. It was stated that genistein modulated the cellular oxidative profile, either by supporting ROS accumulation or by decreasing the antioxidant defense, hence, inducing the cell death. For example, in MCF-7 cells, genistein at high doses decreased the expression of antioxidant enzymes such as CuZnSOD, MnSOD and thioredoxin reductase (TrxR), also upregulated the GPx expression. Consequently, the extent of cellular oxidative stress changes, triggering apoptosis and autophagy induction [238].

Upon ROS accumulation, cells undergo irreversible DNA damage and death [239]. In addition, genistein suppressed the cytochrome enzymes CYP1A1 and CYP1B1, reducing the oxidative DNA damage and cell death in IBS models, also increased the QOL scores [240, 241].

Baicalin

Baicalin is a flavonoid isolated from *Scutellaria baicalensis Georgi*, and is known to have pro-inflammatory and aldose reductase inhibitory activities [59] (Table 2, Fig. 2). It was shown that treatment with baicalin (20 and 40 μmol/L), significantly decreased the percentage of $CD^{4+}CD^{29+}$ cells [59]. This natural compound is suggested as a potential immune inhibitor and could be helpful to control the inflammatory responses and enhanced the QOL scores [240].

Effects of Baicalin on the expression of p-STAT4/STAT4, p-STAT6/STAT6 and p-NK- κβ /NK-κβ

Randomized clinical trial showed that the phosphorylated signal transducer and activator of transcription protein (p-STAT) 4/STAT4 is a great regulator of immune reactions. Baicalin at 40 and 20 μmol/L significantly increased the p- Nk-*kβ*/Nk-*kβ* compared with control in IBS subjects, nonetheless, the p-STAT6/STAT6 were downregulated. The concentrations of IL-6, IFN-γ and IL-5 were significantly lowered, whereas, the concentrations of IL-4, IL-10 and transforming growth factor beta 1 (TGF-β1) were elevated [59] (Table 2, Fig. 2).

Anthocyanins Anthocyanins are secondary metabolite belonging to an important class of flavonoids. These colored flavonoid derivatives are commonly found in plant kingdom. Anthocyanins are classified into six major compounds; cyanidin, delphinidin, malvidin, pelargonidin, peonidin and petunidin, depending on the flavylium B-ring. The antimicrobial, antioxidative, anti-inflammatory, and anti-mutagenic properties of anthocyanins have been reviewed extensively [242] (Table 3, Fig. 2).

It was demonstrated that anthocyanins reduced the COX-2 level in the colon and visceral adipose tissue, also lowered the mRNA level of IL-1β in the visceral adipose tissue and IL-6 in the colon [243].

Anthocyanins mediated inflammatory process via TLR4

TLRs belong to the family of type I transmembrane receptors, a class of pattern recognition receptors (PRRs) presented in various cell types of cells, alike epithelial and immune cells. Both the epithelial and immune cells involve in tolerance to the complex of gut microflora, and mediate the inflammatory responses against invading pathogens [244–246].

TLRs are crucial to distinguish the invader pathogens and to induce the immune responses, mainly through the recognition of a variety of pathogen-associated molecular patterns (PAMPs), among which the LPS, peptidoglycans and lipoproteins are the most important types [246–248].

TLR4, a member of TLRs activated by LPS and non-agonist bacterial compounds such as saturated fatty acids, leading to the activation of NF-κβ and production of pro-inflammatory IL-6, IL-1β and TNF-α [244, 248, 249]. The activation of TLR4 dimerizes itself and triggers the production of pro-inflammatory cytokines and IF- type 1 that could be blocked by anthocyanins and improve IBS symptoms [244, 246, 250] (Table 3, Fig. 2).

Quercetin Quercetin is an abundant flavonol metabolite (primarily as quercetin glycosides), distributed in a wide variety of plant species [251] (Table 3, Fig. 2). Quercetin was shown to inhibit the intestinal motor function of IBS rats with diarrhea [252], also improved the defecation function. In IBS rats, this flavonoid inhibited the enterospasm-induced intestinal hyperactivity by antagonizing the calcium channel competitively and by reducing the colonic motility in a dose-dependent manner [252, 253]. Quercetin relieved the colorectal distension-induced visceral pain by suppressing the extracellular signal regulated protein kinase pathway [252, 253].

In vivo rat model, low, moderate or high concentrations of quercetin significantly decreased the AWR responses. A lower content of calcitonin gene-related peptide (CGRP) was observed in quercetin treated group as compared with the normal group. The CGRP content increased, once treated with 'Chang-Kang-Fang formula' (containing quercetin) (Table 3) [109].

Treatment with quercetin significantly reversed the vasoactive intestinal polypeptide (VIP) value in IBS rats. The amount of 5-HT and substance P were significantly enhanced in middle (1.3 g/kg/d) and high doses (5.0 g/kg/d) quercetin treated groups in the normal group. In damaged mucous epithelium of rats, following quercetin treatment, the inflammatory cells were decreased dose-dependently. The gastric nuclide retention rates and the intestinal propulsion were significantly lower in quercetin treated groups at both middle and high concentrations [109, 254, 255].

Quercetin is an antioxidant agent and one of the most potent scavenger of ROS, superoxide [256, 257], NO [258] and peroxynitrite [259]. Quercetin was shown to inhibit the LPS-induced inflammatory mediators such as TNF-α, and IL-1β cytokines in glial cells [260, 261], and the IL-8 productions in macrophages [262]. It was evident that in the same cell line, pretreatment of quercetin inhibited the iNOS mRNA, iNOS protein, NO production, TNF-α, IL-1β and IL-6 [263].

Quercetin has also been exhibited to inhibit IgE-mediated release of histamine, tryptase and the gene expression/production of known inflammation signaling agents such as TNF-α, IL-1β, IL-6 and IL-8 in PMA in calcium ionophore-stimulated cultured human mast cells [264]. Quercetin inhibited the iNOS mRNA and NO production in LPS/IFN-γ-activated macrophage cells [265, 266].

The administration of quercetin prevented the NF-κB activation through the stabilization of the NF-κB/IκB complex, inhibiting the IκB degradation, and reducing the pro-inflammatory cytokines and NO/iNOS expressions in RAW 264.7 macrophages. In human mast cells, quercetin potently downregulated the NF-κB/DNA binding activity induced by PMA and calcium ionophore, although the binding activity of AP-1 did not changed [150, 256]. In the same model, quercetin attenuated the PMA- and A23187-induced phosphorylation of p38 MAPK, but not JNK or ERK [262, 264]. In contrast, in an LPS-induced macrophage model, quercetin blocked the activation of phosphorylated ERK kinase and p38 MAPK, but not JNK MAPK [264]. As a result, quercetin can be used as an anti-inflammatory and anti-oxidative candidate for treating IBS and the compound can improve the QOL scores.

Conclusion

Clinical trials, in vitro and pre-clinical studies support the effects of polyphenols in IBS improvement from different plant sources, of which several were characterized by acceptable safety and efficacy profiles. Given the clear potential for polyphenols, these bioactive agents can prevent certain disease such as cancer [267], cardiovascular disease, hypertension [268], type 2 diabetes [269], Alzheimer diseases [270] and gastrointestinal disorders [271], also they have shown health promoting qualities. Although plethora evidence proven that natural polyphenols, singly or in combination, are safe to be consumed, there are considerable data indicating that polyphenols at high concentrations can possibly cause adverse effects through their pro-oxidative effects [271]. Taking into account, the anti-inflammation and anti-oxidative mechanisms of such polyphenols could be utilized as adjuvant therapy in patients diagnosed with IBD, either alone or along with

the conventional medicaments, to reduce the incidence of adverse effects or to overcome the drug resistance. Well-designed clinical trials are suggested to confirm the benefits of polyphenols as a part of IBS therapy regimens. Molecular structures of the active polyphenols should also be considered as a skeleton, which could be modified with synthetic manipulations to reach more potent IBS drugs.

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