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Clinical outcomes of flavonoids for immunomodulation in inflammatory bowel disease: a narrative review

Scarlet Louis-Jean

Anne Arundel Medical Center, Annapolis

Abstract

Inflammatory bowel disease is a debilitating condition that undergoes a relapsing and remitting course. The pathogenesis of how this disease manifests remains to be elucidated; however, there is growing evidence that a synergism of familial predisposition and epigenetic alterations influenced by environmental factors all contribute to the development of the disease. The role of nutrition in improving the outcomes of the condition has garnered increasing interest, given the greater risks of neoplastic conversion and concerns about inappropriate remission with available pharmacotherapeutic treatments alone. Available reports, often anecdotal, have documented patient relief with employment of various dietary strategies. These have led to curiosity about nutritional assessments and nutrition therapies to ameliorate the morbidity and all-cause mortality of the disease. One group of such nutrition therapies, supported by a compendium of available articles, is flavonoids—although the greater abundance of *in vitro* experiments with relatively few clinical trials has limited their clinical use. Nonetheless, flavonoids have been shown to be functional foods with immunomodulatory capabilities. This article will thus delve into the role of flavonoids in altering the course of the immune response in inflammatory bowel disease, while assessing their clinical outcomes in human trials.

Keywords Inflammatory bowel disease, Crohn's disease, ulcerative colitis, flavonoids, immunomodulation

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Introduction

Inflammatory bowel disease (IBD) is a superordinate term that represents a spectrum of heterogeneous gastrointestinal conditions that include 2 main subtypes: Crohn's disease (CD) and ulcerative colitis (UC). The diseases share common presenting signs and symptoms, such as fatigue, anorexia, abdominal pain, diarrhea and bloody stools, although the latter is more common in UC [1-3]. These conditions are often characterized by an exacerbating and remitting course, whereby individuals can experience both symptom-free periods and disease flares. They are known to be a consequence of multifactorial processes related to polygenic alterations in immune function and response, intestinal dysbiosis, and western-based dietary consumption [1-3]. While treatment regimens often involve the use of immunomodulators, anti-inflammatory agents, and stool modifiers, dietary modification also plays a role in mitigating the overall morbidity and mortality of the disease.

Dietary deficiency, along with the consumption of processed and refined foods, has been implicated in the development and exacerbation of the condition. Many studies have delved into the relative benefits of specific dietary components in ameliorating the inflammatory processes of the disease, focusing on fiber, minerals (e.g., zinc and selenium), unsaturated fatty acids (e.g., mono- and poly-), and flavonoids. This review aims to provide the available data on the immunomodulatory role of flavonoids in mitigating the disease burden of IBD in human trials.

Department of Internal Medicine, Anne Arundel Medical Center, Annapolis, MD, USA

Conflict of Interest: None

Correspondence to: Scarlet Louis-Jean, MD, MBA, Internal Medicine, Anne Arundel Medical Center, Wayson Pavilion Ste 350, 21401, Annapolis, MD, USA, e-mail: ScarletL@auamed.net

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IBD

IBD is defined as a chronic, relapsing, debilitating and incurable disease that leads to the disruption of various

gastrointestinal processes. IBD is characterized by a set of diseases that were recognized, but not fully understood in the antiquities of westernized countries during the advent of the industrial revolution [1-3]. While both conditions, UC and CD, are classified under IBD, they have distinguishable features notwithstanding mucosal inflammation. The first identified subtype of IBD was UC, which is a continuous mucosal inflammatory disease restricted to the colon, extending from the rectum to, frequently, the periappendiceal region (Fig. 1) [1,2]. It is often associated with bloody diarrhea and tenesmus [1,2]. CD is a transmural inflammation involving all layers of the wall of the gastrointestinal tract, with segmental inflammatory lesions that can extend from the oral cavity to the anus, and is often a cause of terminal ileitis, strictures, and fistulas (Fig. 1) [1].

The exact pathophysiology of the disease remains to be fully understood. One risk factor for the predisposition to the disease is familial [2,3]. It often occurs in genetically susceptible individuals, with an incidence that peaks in early adulthood, although presentation can occur at all ages. Genome-wide association studies have identified variants of nucleotide-binding oligomerization domain protein 2 (NOD2) DNA among hundreds of genes that increase individual susceptibility to the pathogenesis of CD, although the concordance rate in monozygotic twins is 10-15% in UC and 30-35% in CD, suggesting a greater likelihood of non-inheritable contributors to the development of IBD [2,3].

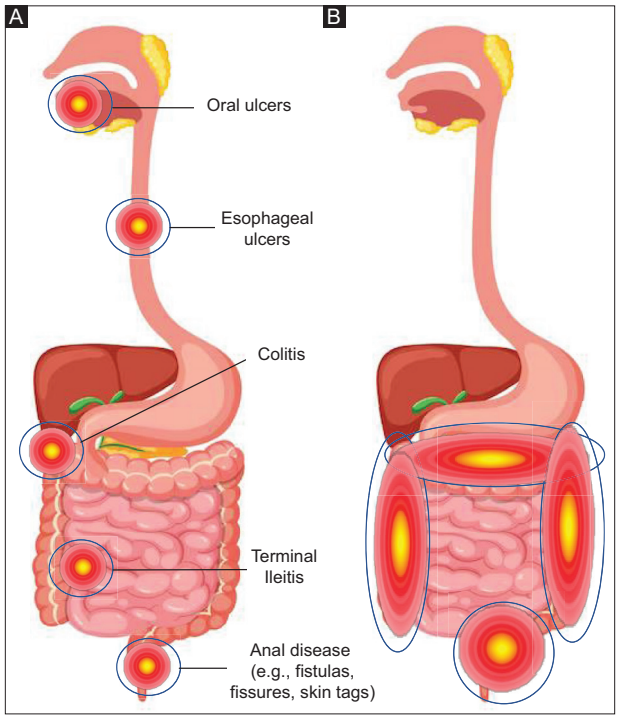


Figure 1 Demonstration of mucosal involvement in inflammatory bowel disease. Crohn's disease (A) is shown to demonstrate inflammation that is transmural, extending from the mouth to the anus in discontinuity (e.g., skip lesions), whereas ulcerative colitis is a continuous inflammation that can extend from the ascending colon to the rectum (B)

T-cell migration, and its interdependent association with increased amounts of intestinal tumor necrosis factor (TNF)-α, have been shown to play a role in the chronicity of intestinal inflammation, owing to its involvement in weakening epithelial barrier function [4,5]. This process is mediated by environmental factors such as diet, smoking and antibiotic use, as they can affect the function of the epithelial barrier via dysregulation of the immune response and overreaction to autophagy [6]. Consequently, this leads to an inappropriate immune-mediated inflammatory response to commensal gut microbes, causing a greater abundance of entero-invasive strains and other potentially pathogenic species of preexisting gut microbes; however, specific organisms have not been identified as causal agents of IBD (Fig. 2) [6].

The role of environmental factors has been substantiated by an observed increase in incidence among first-generation immigrants from countries with low IBD prevalence to ones with higher proportions of affected individuals [7,8]. There has also been a positive correlational shift in the rates of affected individuals in countries that are progressively becoming more industrialized [3]. The role of diet has been supported by reports that it in fact plays an integral part in the modification of IBD progression, via either perpetuation or improvement of the disease [9]. However, nutritional assessments, guidelines for nutritional therapy and dietary recommendations are scarce in the clinical setting, as focus is often placed on the elimination of certain foods, with limited regard to the implementation of diet-based therapies for the amelioration of IBD [10].

The role of nutrition in IBD

Nutrition is regarded as playing an important role during IBD, as it can modulate its pathogenesis via alterations of the intestinal microbiota, immune system, and barrier function of the colonic epithelium [11]. Westernized diets, which tend to be high in fat and refined carbohydrates, are believed to induce epigenetic changes, such as altered expression of microRNAs (miRNAs), DNA methylation and histone modification in the development of IBD [8]. Due to inflammation, accelerated rates of DNA methylation secondary to increased cellular recycling have been observed in colonic epithelial cells in comparison to unafflicted cohorts, whereas variable activity of miRNAs has been identified in the dysregulation of autophagy and intracellular bacterial processing [8,12]. Thus, dietary intake is purported to have a strong association with the disruption of the host's cellular machinery and defense system.

Diet low in soluble fiber has resulted in a similar dysregulation, as it can lead to an increase in mucolytic bacteria known to degrade the colonic mucus layer, which can render the host epithelium vulnerable to enteric pathogens (Fig. 2) [11]. Similarly, diets high in fat and refined sugars lead both to decreased levels of butyrate (a favorable short-chain fatty acid) and increased expression of TNF-α and interferon-γ (Fig. 2). These alterations consequently decrease the overall abundance of anti-inflammatory cytokines and protective T-regulatory cells in the *lamina propria* of colonocytes [11]. In view of such disruptions of the gut mucosal

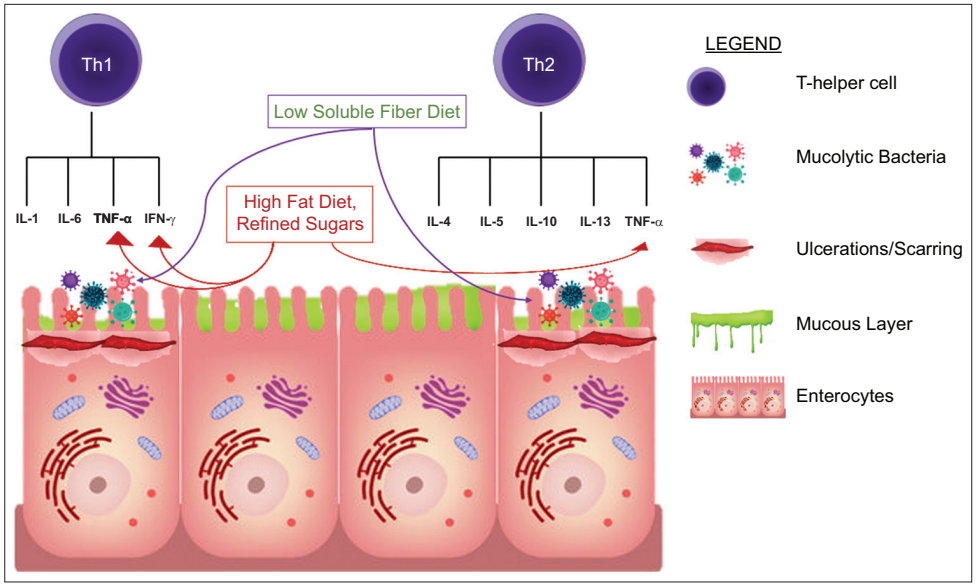


Figure 2 Pictographic representation of the Th-mediated inflammatory pathway in inflammatory bowel disease. On the left-hand side is the Th1 mediated inflammatory process observed in Crohn's disease, whereas the right-hand side depicts the role of Th2 cells in ulcerative colitis. A diet high in fat and refined sugars is seen increasing the production of the proinflammatory cytokines TNF-α and IFN-γ. The mucous layer is reduced on both the flanked epithelial cells, with a consequent increase in the abundance of entero-invasive gut bacteria. This process can be seen as being induced by a low soluble fiber diet. The epithelial cells in the center depict the expected cellular environment of the normal gastrointestinal tract
IFN, interferon; IL, interleukin; Th, T helper; TNF, tumor necrosis factor

homeostasis, it is prudent to suggest avoidance of obesogenic or western-industrialized foods, while encouraging greater consumption of foods rich in specific micronutrients. However, it should be noted that the available data have only demonstrated an association between dietary consumption and disease onset or burden. Considering the heterogeneity of outcomes and unaccounted confounders, possibly owing to biases or ineffective study methods, causal relationships cannot be determined. Nonetheless, given the concerns of limited drug response and the nutritional adequacy of enteral and parenteral nutrition in the management of IBD, there is a greater demand for the employment of nutritional assessments and focus on diet-based therapies [10].

Flavonoids

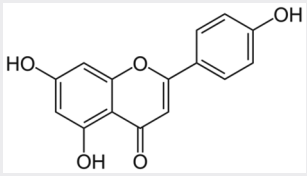
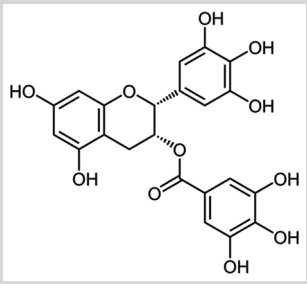
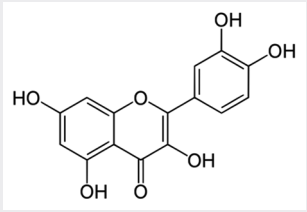
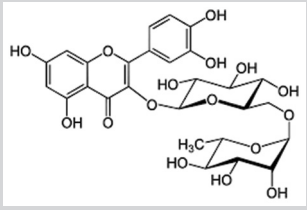
Flavonoids are benzo-γ-pyrone-derived bioactive polyphenolic compounds, synthesized from phenylalanine during plant stress. They are responsible for the admirably rich colors that typify many plants, and have been purported to exert antioxidant, anti-inflammatory, and anti-allergic effects [13-15]. There are more than 5000 types of flavonoids: they have been subdivided into varying classes, based on structural differences in their heterocyclic oxygen ring, and include: 1) anthocyanidins; 2) flavanols; 3) flavanones; 4) flavonols; 5) flavones; 6) isoflavones; 7) neoflavonoids; and 8) proanthocyanidins [16-18]. Their phytochemical properties, which cannot be synthesized by humans, are involved in enzymatic inhibition of pathogenic microbes and regulation of gene expression. They are often found at variable concentrations in food plants, such as flowers, stems, fruits, legumes, cereals, vegetables, seeds, herbs, nuts, tea, wine, and cocoa [16,18].

The phytochemical property of flavonoids was a sought-after component in traditional medicinal preparations, such as propolis honey and royal jelly [19,20]. In recent years, flavonoids have received increased attention, due in part to the compound's antiangiogenic and antiproliferative/anticancer potential [21]. Higher intakes of foods containing such compounds have been linked to a reduction in all-cause mortality in age-adjusted models (odds ratio [OR] 0.81, 95% confidence interval [CI] 0.71-0.93), with the strongest associations observed in wine and tea consumers [22]. Populations with a higher dietary intake of foods and beverages containing flavonoids have shown an inverse correlation in the incidence of cardiovascular disease [23]. Moreover, there is a growing body of data demonstrating the compounds' ability to regulate the intestinal immune system through suppression of immune cells and effector molecules (e.g., chemokines, cytokines, and TNF). These effectors have been shown to all play a role in the inflammatory process of IBD. Specific flavonoids, such as apigenin, epigallocatechin gallate, quercetin and rutin, have been identified as compounds with the ability to exert such properties (Table 1) [15,16,24].

The role of flavonoids in IBD

Fruits and vegetables account for 300 mg/kg of fresh weight content in flavonoids, with the average daily adult consumption approximating 20-1000 mg [25,26]. However, a great deal of the flavonoid concentration is lost in food preparation and

Table 1 Flavonoids that have been shown to exert anti-inflammatory properties, their heterocyclic ring structure, and overall immunomodulatory effects

Flavonoid	Heterocyclic ring structure	Immunomodulatory effects
Apigenin		Suppression of immune cells and effector molecules, such as: Chemokines Cytokines Tumor necrosis factor Enzymatic inhibition of pathogenic microbes. Regulation of gene expression.
Epigallocatechin gallate		
Quercetin		
Rutin		

processing. Additionally, the bioavailability of the compounds is often partial for specific types of flavonoids, as a large proportion remain unabsorbed and are found in greater concentrations in the gastrointestinal lumen [27]. The rate of absorption is seemingly determined by the presence or absence of glycosylation of the compounds, although the validity of this notion has been questioned in light of the variability in absorption among the classes of flavonoids [28]. For example, the predominantly glycosylated form of quercetin is more readily absorbed, while catechin, a non-glycosylated flavonoid, is often absorbed with the same relative efficiency [29,30]. Nonetheless, the reduction in the absorptive capacity of specific flavonoids, leading to greater concentrations in the colon, suggests these compounds have proximal roles in subverting the pathogenesis of IBD.

Immunomodulatory effects of flavonoids

Inflammation is a normal biological process that is activated in response to infection, tissue injury and chemical irritation [31]. It is normally transient with resolution of the inciting event; however, dysregulation and derangement of this process can cause continued inflammation, leading to the onset of many diseases. In the case of IBD, an alteration in the colonic epithelial barrier leads to the recognition of luminal antigens by T helper (Th) cells, which propagates a dramatic cascade of proinflammatory cytokines (e.g., interleukin [IL]-1, IL-4, IL-5, IL-6, IL-10, IL-17A, TNF-α, and interferon-γ) thereby disrupting intestinal homeostasis (Fig. 2) [31,32]. CD is believed to be a Th1-mediated response, with ensuing activation of IL-1, IL-6, TNF-α, and interferon-γ, whereas UC is mediated by Th2 cells and the release of IL-4, IL-5, IL-10, IL-13, and TNF-α (Fig. 2) [31,33-36]. The immunomodulatory role of flavonoids has been exhibited in *in vitro* studies, in which the levels of IL-1β and TNF-α were reduced with administration of quercetin or baicalin; a similar reduction in TNF-α and interferon-γ was also observed with quercetin use [32]. However, given the paucity of clinical trials, it is difficult to confirm whether similar results at the molecular level have been appreciated in human models, though human trials have seen a reduction in inflammatory markers, disease severity scores and indices, and endoscopic changes.

Clinical trials

Epigallocathechin-3-gallate (EGCG)

In a 9-week open pilot trial that enrolled a total of 13 patients with mild-to-moderate UC to receive anthocyanin-rich bilberries, 90.9% of patients exhibited a positive response and 63.4% achieved remission, as determined by a decrease in endoscopic Mayo score (P<0.001), histologic Riley index, and fecal calprotectin (P=0.049) [37,38]. An increase in fecal calprotectin with cessation of bilberry consumption was observed during follow up [37]. A similar finding was observed with the administration of poorly absorbed EGCG in a double-blind, placebo-controlled pilot study, where 20 patients with mild to moderately active UC were randomized to receive 56-days of daily oral polyphenon E (400 mg, or 800 mg in split doses) or a green tea extract containing 50% EGCG, vs. placebo (Table 2). The results yielded a favorable response rate in the treatment arm, as 66.7% in the polyphenon E group experienced a decrease in the UC disease activity index (P=0.03), with 53.3% of participants achieving statistically non-significant active remission (P=0.10) (Table 2) [39]. Despite the poor systemic bioavailability of the compound with oral administration, there was an appreciable reduction in the inflammatory burden of the disease, probably due to the increased colonic mucosal exposure of EGCG [39]. In both

Table 2 Clinical outcomes of flavonoid therapy

Ref.	Study	N	Participants	Intervention	Outcome
			Epigallocatechin-3-gallate		
[38]	Open pilot trial	13	Mild-to-moderate UC	9 weeks of anthocyanin-rich bilberries	63.4% achieved remission Improved Endoscopic Mayo score (P<0.001) Histologic Riley index and fecal calprotectin (P=0.049)
[40]	Double-blind, placebo-controlled pilot study	20	Mild-to-moderate active UC	56-days of daily oral polyphenon E (400 mg or 800 mg in split doses)	66.7% had decreased UC disease activity index (P=0.03) 53.3% had active remission (P=0.10)
			Curcumin		
[47]	Pilot study	10	5 ulcerative proctitis or proctosigmoiditis 5 Crohn's disease	Ulcerative disease group 550 mg of curcumin b.i.d. for 1 month Followed by 550 mg t.i.d. for 1 month Crohn's disease group 360 mg of curcumin t.i.d. for 1 month Followed by 360 mg q.i.d. for 2 months	UC group had improved: Symptoms based on global score from an administered questionnaire (P<0.02) Stool frequency and quality Normalized ESR and CRP Crohn's disease cohort had a mean reduction in: ESR 10 mm/h CRP 0.1 mg/dL Crohn's disease activity index by 55 points
[48]	Multi-center randomized, placebo-controlled, double-blind study	50	Mesalamine-treated active mild-to-moderate UC	3 g daily of curcumin for 1 month	Clinical remission (OR 42, 95%CI 2.3-760; *P*=0.01) Reduced SCCAI by≥3 points (OR 13.2, 95%CI 3.1-56.6; *P*<0.001). Partial Mayo score≤1 (OR 20.7, 95%CI 1.1-393; *P*=0.43)
[49]	Pilot study	45	Mild-to-moderately active ulcerative proctitis and proctosigmoiditis	140 mg/20 mL water curcumin enema (NCB-02) + 800 mg of oral 5-aminosalicylic acid b.i.d. for 8 weeks	Clinical remission 71.4% (P=0.03) Improved endoscopic disease activity 85.7% (P=0.04)
[50]	Randomized, multi-center, double-blind, placebo-controlled trial	89	Quiescent UC	45 received 2 g daily for 6 months 1 g of curcumin after breakfast 1 g after an evening meal+Sulfasalazine 44 received placebo+sulfasalazine or mesalamine for 6 months	Treatment improved Clinical activity index (P=0.038) Endoscopic index (P=0.0001) Recurrence 4.65% in the treatment group 20.51% in the placebo group (P=0.040)

(*Contd...*)

Table 2 (*Continued*)

Ref.	Study	N	Participants	Intervention	Outcome
[51]	Retrospective, multicenter, cohort study	88	Active UC 29 mild disease (SCCAI 3-5) 51 moderate disease (SCCAI 6-11) 7 severe disease (SCCAI≥12)	8-12 weeks of 500 mg herbal extract+2-3 g of curcumin+0.5-2 g of QingDai 60 received 2 g curcumin+1 g QingDai 15 with moderate-to-severe disease received 3 g curcumin+2 g QingDai 13 with mild disease received 2 g curcumin+0.5 g QingDai	Clinical remission Achieved in 46.5% of entire cohort 13/29 (44.8%) in mild UC 28/58 (48.3%) in moderate-severe UC 17/43 (39.5%) in biologics/small molecules experienced UC patients 30/62 (48.4%) in concomitant steroid users Clinical Response Achieved in 60.2% of entire cohort 13/29 (44.8%) in mild UC 40/58 (69%) in moderate-severe UC 25/43 (58.1%) in biologics/small molecules experienced UC patients 39/62 (62.9%) in concomitant steroid users Endoscopic Outcome 8/25 had≥1 point decrease in Mayo endoscopic subscore 4/25 patients had Mayo endoscopic subscore 0 Fecal calprotectin 27/33 (81.8%) had≥50% decrease from baseline while on stable therapy+induction 13/15 (86.7%) had FC response 7/12 (58.3%) had FC remission 17/29 (58.6%) achieved FC≤100 μg/g Median improvement from 1000 μg/g to 75 μg/g (P<0.0001) Corticosteroid Outcome 13/26 (50%) were weaned from steroids after induction 7/26 (26.9%) achieved corticosteroid-free remission Disease Activity Improvement Median SCCAI from 7 to 2 among entire cohort (P<0.0001) Median SCCAI from 6 to 2 among patients on stable therapy (P<0.0001)
			Plantago Major Seed		
[52]	Randomized controlled trial	51	Mild and moderate UC	3,600 mg daily (Two 600 mg capsules before meals) +Routine medications for 8 weeks	Improved Lichtiger Colitis Activity Index: Abdominal tenderness (P=0.011) Distension (P=0.001) Anal pain (P=0.051) Visible blood after 8 weeks of treatment (P=0.001)
			Quercetin		
[53]	Open-label trial	10	Mild-to-moderate Crohn's disease or UC	200-400 g of mango pulp daily for 8 weeks	Reduced IL-8 by 16.2% (P=0.0475) GRO by 25.0% (P=0.0375) GM-CSF by 28.6% (P=0.0485) SCCAI from 4.4 to 2.8 (P=0.0447)
			Rose Oil		
[54]	Pilot double-blind randomized study	40	UC	1,000 mg rose oil soft capsules t.i.d. for 2 months	Improved Partial Mayo score (P<0.05) Inflammatory bowel disease questionnaire (IBDQ-9) (P<0.05) Fecal calprotectin levels (P=0.229)

(*Contd...*)

Table 2 (*Continued*)

Ref.	Study	N	Participants	Intervention	Outcome
			Silymarin		
[55]	Randomized double-blind, placebo-controlled clinical trial	80	UC in remission	140 mg of silymarin daily for 6 months	Complete remission (p=0.50) Improved: Disease activity index from 11.3±3.5 to 10.7±2.8 (P<0.05) Hemoglobin level 11.8±1.6 g/dL (P<0.05) ESR 23.7±11.5 mm/hour (P<0.05)

CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FC, fecal calprotectin; GM-CSF, granulocyte macrophage colony-stimulating factor; GRO, growth-related oncogene; IL, interleukin; OR, odds ratio; SCCAI, simple clinical colitis activity index; UC, ulcerative colitis

in vivo and *in vitro* studies, EGCG combined with apigenin was shown to inhibit cytokines and immune cells [40]. However, the results did not demonstrate statistically significant findings, possibly because the studies were of limited power.

On the other hand, bioavailability was seen to increase by >3.5-fold when polyphenon E capsules were consumed on an empty stomach preceding an overnight fast, in a study that assigned 30 healthy volunteers with an average age of 42 years to 400, 800 or 1200 mg daily doses [41]. Consumption of polyphenon E capsules containing 800 mg of EGCG was overall well tolerated on an empty stomach [41]. However, as this clinical trial was used to determine tolerance and side-effects associated with flavanol dosage in healthy controls, there were no data on clinical improvement in IBD symptoms or in inflammatory markers. Side-effects of EGCG-containing foods include nausea in patients taking 1200 mg and an increased risk of hepatotoxicity, characterized by elevated liver function tests, with doses of 800 mg daily [41,42]. Other published case reports have also noted a dose-independent risk for hepatotoxicity with intake concentrations between 140 mg and 1000 mg. However, the risk was seemingly increased by consumption on an empty stomach, while it is believed that the varying responses to the compound were dependent on inter-individual variability and genetic factors [43].

Curcumin

Curcumin, an antioxidant and polyphenolic compound, a food additive that produces the major pigment in turmeric, was used as a nutraceutical in a pilot study that recruited 10 patients with IBD [44]. The patient cohorts, who were aged 28 to 54 years, included 5 patients with ulcerative proctitis or proctosigmoiditis and 5 others with CD. The group with UC was treated with 550 mg of curcumin b.i.d. for 1 month, followed by 550 mg t.i.d. for an additional month, whereas the CD cohort was administered 360 mg of curcumin t.i.d. for 1 month and 360 mg q.i.d. for 2 months (Table 2). The study found that all 5 subjects with UC had an overall improvement in symptoms, determined by a global score from an administered questionnaire (P<0.02), along with stool frequency and quality. Additionally, while no quantified values were provided, patients with UC had a normalized erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (Table 2). The CD cohort had a mean reduction of 10 mm/h in ESR, 0.1 mg/dL in CRP, and 55 points in their CD activity index (CDAI) [44]. Limitations of this study include a lack of both controls and elimination of confounding variables, and a lack of assessment of the compounded effect of flavonoids with concomitant pharmacotherapy.

A multicenter randomized, placebo-controlled, double-blind study assessing curcumin's ability to induce remission in 50 mesalamine-treated participants with active mild-to-moderate UC found that 14 of 26 patients receiving 3 g/day of curcumin for 1 month achieved clinical remission after an intention-to-treat analysis was conducted (OR 42, 95%CI 2.3-760; P=0.01) [45]. The primary outcome was defined by a reduction in Simple Clinical Colitis Activity Index (SCCAI) of ≥3 points, which was achieved in 17 patients in the curcumin group and 3 in the placebo group (OR 13.2, 95%CI 3.1-56.6; P<0.001) (Table 2). Endoscopic remission, as determined by a partial Mayo score ≤1, was observed in 8 of 22 patients in the curcumin group and 16 in the placebo group (OR 20.7, 95%CI 1.1-393; P=0.43). Nine of the participants (curcumin n=4; placebo n=5) in the study, however, underwent concomitant treatment with mesalamine, but no difference in outcomes was observed by the authors, who noted that the small size of this subgroup precluded statistical analysis [45].

A pilot study assessed the use of 140 mg/20 mL water curcumin enema (NCB-02) in 23 of 45 patients with mild-to-moderately active ulcerative proctitis and proctosigmoiditis, with concurrent usage of 800 mg of oral 5-aminosalicylic (5-ASA) acid b.i.d. [46]. The results found that, following 8 weeks of treatment, 92.9% of the treatment group achieved improved outcomes, compared to 50% in the placebo group (P=0.01), while 71.4% vs. 31.3% (P=0.03), and 85.7% vs. 50% (P=0.04), respectively, achieved clinical remission and improvement in their endoscopic disease activity (Table 2). These findings, however, were obtained using a per protocol analysis, as the initial intention-to-treat analysis demonstrated a non-inferior outcome between the treatment and placebo group who also received 5-ASA [46].

Curcumin was also explored as maintenance therapy in a randomized, multi-center, double-blind, placebo-controlled trial that enrolled 89 patients with quiescent UC [47]. Forty-five of the patients received a total of 2 g/day, 1 g of curcumin after breakfast and 1 g after an evening meal, plus sulfasalazine, while 44 received placebo along with sulfasalazine or mesalamine for 6 months (Table 2). The recurrence rates

using an intention-to-treat analysis were 2 of 43 (4.65%) in the treatment group and 8 of 39 (20.51%) participants in the placebo group (P=0.040) during the designated 6 months of therapy. The treatment arm also saw an improvement in both the clinical activity index (P=0.038) and the endoscopic index (P=0.0001). However, during a 6-month follow up, 8 additional patients in the treatment arm were noted to have had a disease flare in comparison to 6 in the placebo group [47]. Nevertheless, the treatment arm was observed to have a greater likelihood of maintaining disease remission.

A recent retrospective multicenter cohort study, evaluating the effectiveness of curcumin and QingDai (QD) in 87 patients who had active UC with an SCCAI ≥3 points, observed both clinical and biomarker remission [48]. The primary outcome of the study was to achieve clinical remission within 8-12 weeks of treatment with 500 mg of herbal extract dry powder daily containing varying doses of curcumin, ranging from 2-3 g, admixed with 0.5-2 g of QD. Sixty patients received 2 g curcumin and 1 g QD. Fifteen patients with moderate-severe UC (SCCAI scores >10) received 3 g curcumin and 2 g QD, whereas 13 patients with milder UC (SCCAI 3-4) received 2 g curcumin and 0.5 g QD (Table 2). Forty-one (46.5%) achieved clinical remission, whereas 53 (60.2%) had a clinical response. Twenty-six patients were on corticosteroids at baseline, of whom 7 experienced corticosteroid-free remission. In addition, of the participants who were on biologics, 39.5% achieved clinical remission, with 58.1% achieving a clinical response [48]. Median SCCAI decreased from 7 (interquartile range [IQR] 5-9) to 2 (IQR 1-3) (P<0.001), while the median fecal calprotectin decreased from 1000 μg/g (IQR 392-2772) to 75 μg/g (IQR 12-136). Of the 25 patients who had baseline endoscopic data (85% had moderate-severe UC) 9 maintained stable therapy. Eight of the 9 patients had endoscopic improvement (score decrease of ≥1 in Mayo endoscopic subscore), while 4 patients had endoscopic remission (Mayo endoscopic subscore of 0) (Table 2). Major adverse outcomes included 4 patients who experienced liver transaminase increases of >3 times the upper limit of normal, whereas 4 patients were hospitalized in the setting of worsening SCCAI scores. One patient was omitted from the efficacy analysis after starting ustekinumab [48]. Limitations of this study include its lack of clarity regarding the induction and maintenance doses, as well as the lack of a placebo control.

Plantago major seed

In a randomized controlled trial in which 3600 mg/day (two 600 mg capsules before each meal, t.i.d.) of Plantago major (large plantain) seed was administered to a group of 31 of 51 UC subjects with mild and moderate disease, the treatment group showed an improvement in abdominal tenderness (P=0.011), distension (P=0.001), anal pain (P=0.051), and visible blood (P=0.001) after 8 weeks of treatment (Table 2) [49]. However, there were no overall statistically significant differences between the treatment and placebo group randomized to receive wheat flour, for any of the respectively aforementioned primary outcomes (P=0.224, P=0.283, and P=0.455). Disease activity was assessed using the Lichtiger Colitis Activity Index at weeks 4 and 8 (Table 2). Initially 61 participants were recruited, with 51 completing the trial, (n=28 in the treatment group, n=23 in the placebo group). No side-effects were reported in either of the 2 groups, and seemingly discontinuation from the study was due to loss to follow up. Nonetheless, limitations of the study were the frequency of recommended intake, the low sample size, and the concomitant use of routine medications [49]. Additionally, the use of the per-protocol analysis reduced the relevance for real-world applications regarding patient adherence patterns.

Quercetin

The edible part of the mango, called *Mangifera indica* L., which contains quercetin, gallic acid, and kaempferol and galloyl glycosides, was used in an 8-week open label trial involving 10 participants with mild-to-moderate CD or UC at concentrations of 200-400 g of mango pulp daily (Table 2) [50]. There was an observed reduction in SCCAI from 4.4 to 2.8 (P=0.0447) without statistically significant findings in terms of overall improvement in symptoms and quality of life, based on participant responses from the Short IBD Questionnaire [53]. The following inflammatory markers were found to have been lowered with the mango pulp regimen: IL-8 by 16.2% (P=0.0475), growth-regulated oncogene (GRO) by 25.0% (P=0.0375), and granulocyte macrophage colony-stimulating factor (GM-CSF) by 28.6% (P=0.0485) (Table 2). Shortcomings of this study were its open-label nature and the fact that participants were advised to weigh and record the exact amount of mango pulp they consumed daily, which may have been a factor in the statistically non-significant quality-of-life scores noted in the study [50].

Rose oil

In a pilot double-blind study that randomized 1000 mg rose oil soft capsules t.i.d. for a total of 2 months to 20 of 40 UC participants (mean age 41±10 years) vs. placebo (liquid paraffin soft capsules; n=20), the treatment group experienced significant improvement in partial Mayo score (P<0.05) and the IBD questionnaire (IBDQ-9) (P<0.05) (Table 2) [51]. However, although mean fecal calprotectin levels were decreased by the completion of the study, the difference was not statistically significant (P=0.229). Additionally, the results for primary outcomes, demographic factors and disease course were not statistically significant when an intergroup analysis was conducted (P>0.05). Overall satisfaction was greatly improved among the treatment group (7.46±2.33 vs. 6.79±2.01), although this also showed no statistical significance. Only 28 patients completed the study, with ultimately 14 participants remaining in both groups. The most common side-effects of rose oil were increased frequency of defecation and abdominal cramping (10% in the treatment and 15% in the placebo groups), which were reportedly the leading causes of participant withdrawal from the study (P=0.56) [51].

Silymarin

Silymarin, a polyphenolic flavonoid derived from milk thistle, was studied in a randomized double-blind, placebo-controlled clinical trial for the management of UC in 80 patients considered to be in remission [52]. Forty-two of the participants were assigned to 140 mg of silymarin daily, while 38 participants received placebo (composed of lactose monohydrate, corn starch magnesium steerage) daily for 6 months (Table 2). Ten patients were lost from the study because of nausea in the silymarin group (n=4) and disease flare-up, while 6 in the placebo group left because of abdominal pain. The study observed an overall improvement in the disease activity index in the silymarin group from 11.3±3.5 to 10.7±2.8 ($P<0.05$). Thirty-five of 38 patients in the silymarin group achieved complete remission after 6 months, in contrast to 21 of 32 from the placebo group ($P=0.50$). Improvements were also seen in hemoglobin level (11.8±1.6 g/dL vs. 13.4±1.2 g/dL; $P<0.05$) and ESR (23.7±11.5 mm/h vs. 10.8±3.2 mm/h; $P<0.05$) in the silymarin group (Table 2) [52].

Discussion

Flavonoids have been shown to reduce inflammation in *in vitro* studies, while subverting the angiogenic and tumor microenvironments involved in IBD carcinogenesis. However, there remains a paucity of large, randomized placebo-controlled trials exploring the clinical effects of flavonoids in the immunomodulation of IBD. Limited searches have revealed studies that explored the pharmacokinetics and relative safety of these compounds in healthy human participants to determine tolerance. In most of the studies included in this narrative review, loss to follow up was often due to worsening of functional symptoms rather than organ injury or toxicity. For example, although EGCG has been shown to be associated with a dose-independent risk for the development of hepatotoxicity with ingestion on an empty stomach, other potential side-effects of flavonoids or phenolic compounds include liver failure, hemolytic anemia, contact dermatitis and hyper-estrogenism, which may preclude attempts to conduct larger randomized therapeutic trials [53]. Thus, a better understanding is needed of drug–drug interactions, dosing adjustments, minimal and maximal effective doses, toxicities, adverse effects, and interactions with cytochrome P450 (CYP450) systems for oxidation, as flavonoids are known to exert their chemopreventive effects through the inhibition of phase 1 metabolizing enzymes such as CYP450.

Several studies that were omitted from this narrative review did not have a standardized process for monitoring disease progression or improvement using clinical scores, indices, symptoms or histologic changes. Additionally, available clinical trials have had variable age groups and a lack of demographic data to determine applicability to specific patient populations. From the clinical trials documented in this narrative review, there were significant variabilities in the diagnostic, severity, and quality-of-life assessments for IBD. Overall, no statistically significant differences were seen between the treatment and placebo groups, probably because of the small sample sizes of the studies, although there were clinically significant improvements seen in the quality-of-life questionnaires as well as inflammatory indices. Clinical assessments that can improve the validity of the findings of the outcomes of the nutritional interventions include: endoscopic Mayo score, SCCAI, UC disease activity index, UC clinical activity index, disease activity index, CDAI, clinical activity index, short IBD questionnaire, histologic Riley index and fecal calprotectin, among other standardized lab measurements such as CRP, ESR, transforming growth factor-β, TNF-α, interferon-γ, NF-kB, IL-8, GRO, and GM-CSF. However, the use of these clinical and inflammatory assessments should be based on their relative sensitivity, specificity, and positive and negative predictive values to ensure reliability.

EGCG and curcumin appear to have been the most studied flavonoids, with associated clinically significant improvements seen in quality-of-life scores and inflammatory markers. However, much like all the studies included in this narrative review, different doses, treatment frequencies, disease characteristics and length of treatment have made it difficult to identify an effective regimen and treatment length, although 8 weeks of treatment was seemingly the most common length of time used for most treatment protocols for all flavonoids and phenolic compounds discussed in this narrative review. Curcumin has had clinically significant outcomes in achieving remission in UC patients and was observed to increase the likelihood of maintaining disease remission. The doses associated with these outcomes were respectively 2 g/day for 6 months and 3 g/day for 1 month. However, there are limited studies that have explored sustained disease remission and the effects of maintenance treatment for participant cohorts with disease recurrence. Moreover, the studies that explored disease activity, inflammatory markers and quality-of-life assessments did not focus on non-inferiority or superiority of flavonoids in relation to current pharmacotherapeutics, although plantago major seed and curcumin compounds (e.g., CurQD) did show some data on synergism and treatment response among UC patients. The applicability of CurQD is limited by its lack of statistical significance analysis and study design, which was not placebo-controlled. Furthermore, dietary, and supplementary intake during these studies were not monitored to control for the effects of confounding variables. Therefore, the use of flavonoids as standalone therapy cannot be substantiated at this time.

In addition, some of the articles included in this narrative review used a per-protocol analysis, which limits their overall applicability to real-life circumstances, although it does add value to understanding the effects of nutritional therapies in patients who abide by strict adherence. The use of intention-to-treat (ITT) analysis helps to better understand the effect of the studied treatment with variable adherence patterns, but it appears that the use of ITT in some studies reduced the power, and consequently the statistically significant differences between the treatment and placebo groups. At this juncture, the application of these studies to IBD populations remains

limited, as the strength of the association with flavonoid use and disease modification remains to be further supported. Thus, these compounds should only be used with specific attention paid to the patient, disease type and characteristics, and comorbidities to determine the appropriateness of flavonoid use as therapies, with the caveat that inter-individual variability will exist among different subgroups.

Concluding remarks

There have been randomized control trials that have investigated the adjunctive effects of flavonoids when combined with approved pharmacotherapies, but larger scale placebo-controlled, double-blind comparative, non-inferior and superior clinical trial studies are needed to fully understand the impact of flavonoids on IBD immunomodulation. More studies with a stratified approach are also needed to assess treatment responsiveness based on disease activity. This is notwithstanding the need for randomized controlled trials with larger participant cohorts. Additionally, to improve the validity and reliability of future studies, a standardization of clinical assessments should be employed, using quality assessments for identifying IBD disease activity.

References

1. Mulder DJ, Noble AJ, Justinich CJ, Duffin JM. A tale of two diseases: the history of inflammatory bowel disease. *J Crohns Colitis* 2014;**8**:341-348.
2. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. *Nature* 2011;**474**:307-317.
3. Frolkis A, Dieleman LA, Barkema HW, et al; Alberta IBD Consortium. Environment and the inflammatory bowel diseases. *Can J Gastroenterol* 2013;**27**:e18-e24.
4. Rogler G, Biedermann L, Scharl M. New insights into the pathophysiology of inflammatory bowel disease: microbiota, epigenetics and common signalling pathways. *Swiss Med Wkly* 2018;**148**:w14599.
5. Friedrich M, Pohin M, Powrie F. Cytokine networks in the pathophysiology of inflammatory bowel disease. *Immunity* 2019;**50**:992-1006.
6. Oliveira SB, Monteiro IM. Diagnosis and management of inflammatory bowel disease in children. *BMJ* 2017;**357**:j2083.
7. Kilby K, Mathias H, Boisvenue L, Heisler C, Jones JL. Micronutrient absorption and related outcomes in people with inflammatory bowel disease: a review. *Nutrients* 2019;**11**:1388.
8. Legaki E, Gazouli M. Influence of environmental factors in the development of inflammatory bowel diseases. *World J Gastrointest Pharmacol Ther* 2016;**7**:112-125.
9. Limdi JK. Dietary practices and inflammatory bowel disease. *Indian J Gastroenterol* 2018;**37**:284-292.
10. Nazarenkov N, Seeger K, Beeken L, et al. Implementing dietary modifications and assessing nutritional adequacy of diets for inflammatory bowel disease. *Gastroenterol Hepatol (N Y)* 2019;**15**:133-144.
11. Sáez-González E, Mateos B, López-Muñoz P, et al. Bases for the adequate development of nutritional recommendations for patients with inflammatory bowel disease. *Nutrients* 2019;**11**:1062.
12. Abegunde AT, Muhammad BH, Bhatti O, Ali T. Environmental risk factors for inflammatory bowel diseases: Evidence based literature review. *World J Gastroenterol* 2016;**22**:6296-6317.
13. Tapas AR, Sakarkar DM, Kakde RB. Flavonoids as nutraceuticals: a review. *Trop J Pharm Res* 2008;**7**:1089-1099.
14. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. *J Nutr Sci* 2016;**5**:e47.
15. Robak J, Gryglewski RJ. Bioactivity of flavonoids. *Pol J Pharmacol* 1996;**48**:555-564.
16. Jarmakiewicz-Czaja S, Piątek D, Filip R. The influence of nutrients on inflammatory bowel diseases. *J Nutr Metab* 2020;**2020**:2894169.
17. Kandaswami C, Lee LT, Lee PP, et al. The antitumor activities of flavonoids. *In Vivo* 2005;**19**:895-909.
18. Ross JA, Kasum CM. Dietary flavonoids: bioavailability, metabolic effects, and safety. *Ann Rev Nutr* 2002;**22**:19-34.
19. Havsteen BH. The biochemistry and medical significance of the flavonoids. *Pharmacol Ther* 2002;**96**:67-202.
20. Viuda-Martos M, Ruiz-Navajas Y, Fernández-López J, Pérez-Alvarez JA. Functional properties of honey, propolis, and royal jelly. *J Food Sci* 2008;**73**:R117-R124.
21. Mirossay L, Varinská L, Mojžiš J. Antiangiogenic effect of flavonoids and chalcones: an update. *Int J Mol Sci* 2017;**19**:27.
22. Ivey KL, Jensen MK, Hodgson JM, Eliassen AH, Cassidy A, Rimm EB. Association of flavonoid-rich foods and flavonoids with risk of all-cause mortality. *Br J Nutr* 2017;**117**:1470-1477.
23. Rice-Evans CA, Miller NJ, Paganga G. Structure-antioxidant activity relationships of flavonoids and phenolic acids. *Free Radic Biol Med* 1996;**20**:933-956.
24. Hoensch HP, Weigmann B. Regulation of the intestinal immune system by flavonoids and its utility in chronic inflammatory bowel disease. *World J Gastroenterol* 2018;**24**:877-881.
25. Ishige K, Schubert D, Sagara Y. Flavonoids protect neuronal cells from oxidative stress by three distinct mechanisms. *Free Radic Biol Med* 2001;**30**:433-446.
26. Peterson J, Dwyer J. Flavonoids: dietary occurrence and biochemical activity. *Nutr Res* 1998;**18**:1995-2018.
27. Yao LH, Jiang YM, Shi J, et al. Flavonoids in food and their health benefits. *Plant Foods Hum Nutr* 2004;**59**:113-122.
28. Nijveldt RJ, van Nood E, van Hoorn DE, Boelens PG, van Norren K, van Leeuwen PA. Flavonoids: a review of probable mechanisms of action and potential applications. *Am J Clin Nutr* 2001;**74**:418-425.
29. Hollman PC, Katan MB. Dietary flavonoids: intake, health effects and bioavailability. *Food Chem Toxicol* 1999;**37**:937-942.
30. Okushio K, Matsumoto N, Kohri T, Suzuki M, Nanjo F, Hara Y. Absorption of tea catechins into rat portal vein. *Biol Pharm Bull* 1996;**19**:326-329.
31. Pan MH, Lai CS, Ho CT. Anti-inflammatory activity of natural dietary flavonoids. *Food Funct* 2010;**1**:15-31.
32. Vezza T, Rodríguez-Nogales A, Algieri F, Utrilla MP, Rodriguez-Cabezas ME, Galvez J. Flavonoids in inflammatory bowel disease: a review. *Nutrients* 2016;**8**:211.
33. Neuman MG. Immune dysfunction in inflammatory bowel disease. *Transl Res* 2007;**149**:173-186.
34. Monteleone G, Caprioli F. T-cell-directed therapies in inflammatory bowel diseases. *Clin Sci (Lond)* 2010;**118**:707-715.
35. Singh B, Read S, Asseman C, et al. Control of intestinal inflammation by regulatory T cells. *Immunol Rev* 2001;**182**:190-200.
36. Hering NA, Schulzke JD. Therapeutic options to modulate barrier defects in inflammatory bowel disease. *Dig Dis* 2009;**27**:450-454.
37. Salaritabar A, Darvishi B, Hadjiakhoondi F, et al. Therapeutic potential of flavonoids in inflammatory bowel disease: A comprehensive review. *World J Gastroenterol* 2017;**23**:5097-5114.
38. Biedermann L, Mwinyi J, Scharl M, et al. Bilberry ingestion improves disease activity in mild to moderate ulcerative colitis - an

open pilot study. *J Crohns Colitis* 2013;**7**:271-279.
39. Dryden GW, Lam A, Beatty K, Qazzaz HH, McClain CJ. A pilot study to evaluate the safety and efficacy of an oral dose of (-)-epigallocatechin-3-gallate-rich polyphenon E in patients with mild to moderate ulcerative colitis. *Inflamm Bowel Dis* 2013;**19**:1904-1912.
40. Hoensch H, Oertel R. Anti-inflammatory effects of tea-flavonoids. *Dtsch Med Wochenschr* 2012;**137**:2738-2740.
41. Chow HH, Hakim IA, Vining DR, et al. Effects of dosing condition on the oral bioavailability of green tea catechins after single-dose administration of Polyphenon E in healthy individuals. *Clin Cancer Res* 2005;**11**:4627-4633.
42. Lovera J, Ramos A, Devier D, et al. Polyphenon E, non-futile at neuroprotection in multiple sclerosis but unpredictably hepatotoxic: Phase I single group and phase II randomized placebo-controlled studies. *J Neurol Sci* 2015;**358**:46-52.
43. Oketch-Rabah HA, Roe AL, Rider CV, et al. United States Pharmacopeia (USP) comprehensive review of the hepatotoxicity of green tea extracts. *Toxicol Rep* 2020;**7**:386-402.
44. Holt PR, Katz S, Kirshoff R. Curcumin therapy in inflammatory bowel disease: a pilot study. *Dig Dis Sci* 2005;**50**:2191-2193.
45. Lang A, Salomon N, Wu JC, et al. Curcumin in combination with mesalamine induces remission in patients with mild-to-moderate ulcerative colitis in a randomized controlled trial. *Clin Gastroenterol Hepatol* 2015;**13**:1444-1449.e1.
46. Singla V, Pratap Mouli V, Garg SK, et al. Induction with NCB-02 (curcumin) enema for mild-to-moderate distal ulcerative colitis - a randomized, placebo-controlled, pilot study. *J Crohns Colitis* 2014;**8**:208-214.
47. Hanai H, Iida T, Takeuchi K, et al. Curcumin maintenance therapy for ulcerative colitis: randomized, multicenter, double-blind, placebo-controlled trial. *Clin Gastroenterol Hepatol* 2006;**4**:1502-1506.
48. Yanai H, Salomon N, Lahat A, et al. Real-world experience with Curcumin-QingDai combination for patients with active ulcerative colitis: a retrospective multicentre cohort study. *Aliment Pharmacol Ther* 2023;**58**:175-181.
49. Baghizadeh A, Davati A, Heidarloo AJ, Emadi F, Aliasl J. Efficacy of Plantago major seed in management of ulcerative colitis symptoms: a randomized, placebo controlled, clinical trial. *Complement Ther Clin Pract* 2021;**44**:101444.
50. Kim H, Venancio VP, Fang C, Dupont AW, Talcott ST, Mertens-Talcott SU. Mango (Mangifera indica L.) polyphenols reduce IL-8, GRO, and GM-SCF plasma levels and increase Lactobacillus species in a pilot study in patients with inflammatory bowel disease. *Nutr Res* 2020;**75**:85-94.
51. Tavakoli A, Shirzad M, Taghavi A, et al. Efficacy of rose oil soft capsules on clinical outcomes in ulcerative colitis: a pilot randomized, double-blinded, placebo-controlled clinical trial. *Galen Med J* 2019;**8**:e1307.
52. Rastegarpanah M, Malekzadeh R, Vahedi H, et al. A randomized, double blinded, placebo-controlled clinical trial of silymarin in ulcerative colitis. *Chin J Integr Med* 2015;**21**:902-906.
53. Galati G, O'Brien PJ. Potential toxicity of flavonoids and other dietary phenolics: significance for their chemopreventive and anticancer properties. *Free Radic Biol Med* 2004;**37**:287-303.