Antioxidant Supplements and Gastrointestinal Diseases: A Critical Appraisal

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Abstract

The gastrointestinal tract digests and absorbs dietary nutrients, protects the body against physical and chemical damage from contents in its lumen, provides immunity against external antigens, and keeps an optimum environment for the gut microbiota. These functions cannot be performed normally in several diseases of which the following are discussed here: irritable bowel syndrome and inflammatory bowel disease, which includes Crohn's disease and ulcerative colitis. Because these diseases are associated with oxidative stress, a host of antioxidant supplements are used for maintenance and recovery of the gut functions. However, the benefits of these supplements have not been established. The available 80 human trials were rated for levels of confidence and for benefits of the antioxidant supplements. For Crohn's disease, the supplements for which clear benefits occurred in at least 2 studies were allopurinol, *Boswellia serrata* (frankincense or shallaki), *Artemesia* species (worm-wood), *Tripterygium wilfordii* (léi gōng téng), and omega-3 fatty acids. Similar beneficial supplements for ulcerative colitis were allopurinol, *Matricaria chamomilla* (chamomile), *Curcuma longa* (curcumin in turmeric), and omega-3 fatty acids. There was also a clear benefit for ulcerative colitis in 2 studies where a multiherbal Chinese medicine preparation and an Ayurvedic medicine preparation were used. For irritable bowel syndrome, there was only a marginal benefit of some of the antioxidant supplements. Thus, some antioxidant supplements may be beneficial at certain stages of specific diseases. This is consistent with the current concept that antioxidants act by inhibiting oxidative stress pathways in a tissue- and environment-specific manner and not by simply acting as scavengers.

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Introduction

The problems in the gastrointestinal (GI) tract can lead to many diseases, but in this review only irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), are considered. IBS affects 10–25% of the population globally with a slightly higher prevalence

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in females compared to males [1]. CD inflicts individuals in the prime of life between 10 and 30 years of age [2]. In developed countries, the prevalence of CD exceeds 4 million [3] and, surprisingly, the prevalence of CD has increased following the improvement in human hygiene and industrialization [3]. The worldwide prevalence of UC varies between 0.5 and 24.5 per 100,000 [3]. While CD is more common among smokers, UC is more common in ex-smokers and nonsmokers [4]. For these diseases, a variety of therapies are used to attain remission of the symptoms and/or avoid relapse once the patient is in remission. The current understanding of the pathology suggests that oxidative stress may contribute to these diseases [5]. This review contains a critical appraisal of the efficacies of these supplements based on the available literature on human trials. No studies were found on antioxidant supplements and celiac disease and hence it was not discussed here. This review covers the structure and function of the GI tract, diagnosis, pathophysiology, and current treatment of the diseases followed by a rationale for the use of antioxidant supplements. The efficacies of different supplements are discussed, leading to a synopsis, recommendations, and a critical appraisal. This not a meta-analysis type of study, but instead is based on opinions of the authors because the vast variety of antioxidant supplements were used for different GI diseases at different stages and examined by different methods.

Structure and Function of the Gastrointestinal Tract

The GI tract is a tube with mucosa lining its lumen, followed by a set of layers of submucosa, and smooth muscle with a rich supply of nerves and blood vessels. The mucosa enables the GI tract to perform its main functions: digestion and absorption of nutrients from the diet, protection of the body against physical and chemical damage from luminal contents, and provision of immunity against them [5, 6]. The lining is made up of a single layer of epithelial cells. The small intestinal epithelium is extensively folded to provide a very large absorptive surface area, resulting in distinct villus and crypt regions. The mucosa contains several types of cells: enterocytes, Paneth, goblet, and enteroendocrine [5–8]. A large proportion (80%) of the mucosal cells are enterocytes whose main role is the absorption of nutrients and unconjugated bile salts. They may also be involved in chemical processing of food and cooperate with other cells in the induction of immunological tolerance to the ingested proteins [5, 6]. Paneth cells synthesize and secrete substantial quanti-

ties of antimicrobial peptides which are key mediators of host-microbe interactions, including homeostatic balance with colonizing microbiota and innate immune protection from enteric pathogens [5, 8]. They also secrete factors that help sustain and modulate the epithelial stem and progenitor cells. Goblet cells secrete mucin 2 polymers which form mucus that plays a key role in mucosal immunology [7]. Based on their location, there are several types of goblet cells. In the colon, the surface goblet cells secrete continuously to maintain the inner mucus layer, whereas goblet cells of the colonic and small intestinal crypts secrete upon stimulation such as after endocytosis or in response to acetylcholine [7]. Thus, the mucus system itself and the regulation of its secretion differ between the small and the large intestine [5, 7]. Enteroendocrine cells, distributed throughout the GI tract, form a large endocrine organ to aid in the control of GI secretion and motility, the regulation of food intake, postprandial glucose levels, and metabolism. They also communicate directly with neurons innervating the GI tract and thus form part of the gut "brain axis." Beneath the endothelium is the lamina propria, which supports the mucosal epithelium. It consists of the extracellular matrix, blood and lymphatic vessels, neuronal and smooth muscle cells, and various immune cells (lymphocytes, macrophages) [5, 7, 8].

The mucosa is constantly being renewed as the stem cells in the crypt divide into progenitor cells, which can differentiate into secretory (Paneth, mucin-secreted goblet, and enteroendocrine cells) or absorptive (enterocyte) lineages [9]. The microenvironment surrounding the progenitor cells may determine the resulting cell types and their fate. The differentiated cells undergo apoptosis and are shed into the lumen in about 3 days. Damage to these structures, cross-talk between them, or imbalance in individual cell types diminishes barrier functions and sensitizes the GI tract with dietary antigens and GI normal microbiota, leading to various GI diseases [9].

Pathophysiology of Gastrointestinal Diseases

IBD is a multifactorial condition resulting from an interaction between genes and environmental factors [10]. Based on genome-wide association studies, there are 163 loci for IBD of which 110 are shared between CD and UC [11]. Single-nucleotide polymorphisms in the nucleotide-binding oligomerization domain gene (NOD2) may play an important role in CD. The NOD2 gene regulates barrier function, autophagy, and hyposensitization of

the gut to normal microflora and health of Paneth cells. Three alleles of NOD2 (Arg702Trp, Gly908Arg, and 980fs981) have been studied extensively [10]. A large segment of CD patients in Western countries carry at least one mutated NOD2 allele. Persons with 2 of the mutated alleles have a 20- to 40-fold higher risk of developing CD. Thus, mutations in NOD2 gene are strong genetic risk factors for CD. The NOD2 binds muramyl dipeptide, which is a component of bacterial cell wall peptidoglycan [10], thereby leading to an upregulation of NF-κB expression. NOD2 may directly influence the composition of the gut microbiota by regulating the production of a subgroup of intestinal antimicrobial peptides known as cryptdins, which are produced by Paneth cells in the intestinal crypts. The patients with CD may also show decreased populations of *Faecalibacterium prausnitzii* and *Roseburia* species and increase in bacteria such as *Escherichia coli* [11].

Unlike CD, UC is confined to the large bowel with diffuse inflammation of the colonic and rectal mucosa. It is associated with colorectal cancer risk, which increases with the duration of symptoms [12]. In a study on Indian patients with UC, the risk of colorectal cancer was 900 times higher than the general population [12]. The basic mechanisms of UC may be similar to those of CD: increased membrane permeability, immune exaggeration, and decreased autophagy [13]. The hepatocyte nuclear factor 4-alpha (HNF4A) gene has been associated with UC [13]. HNF4A may regulate epithelial permeability since it controls adherens junctions, tight junctions, and desmosomes, which play an important role in cell-cell junctions. In UC, the basement membrane may also be compromised by mutations in the E-cadherin encoding gene CDH1 and the laminin β1 subunit encoding gene LAMB1 [13]. Another defense is through the production of anti-inflammatory cytokines such as IL-10 and TG-Fβ, which activate TH17 (Treg cells) which in turn suppresses antigen-presenting cells and dendritic cells to secrete IL-17 [13]. The solute carrier family 9 member (SLC9A) 3 gene, encoding an epithelial sodium/hydrogen exchanger, has also been implicated in UC, but not in CD [13]. It was hypothesized that there is a considerable overlap between IBS and UC [5]. Compared to healthy controls, the mucosal biopsy samples obtained from the colon, rectum, and terminal ileum of IBS patients show more inflammation [5]. There may also be similarities between IBS and UC in the alterations in the serotonergic and cytokine-related pathways. Yet, IBS may lack the expression of several proteins which are markers of UC [5].

Microbiota and Gastrointestinal Diseases

There is a symbiotic relationship between the microbiota and the gut: the human host contributes the nutrients needed for the survival of the microbes, which in turn aid the host in nutrition (e.g., converting indigestible dietary fibers into short-chain fatty acids butyrate, propionate, and acetate), protection against pathogens, and regulation of the immune responses [10, 14]. A disruption in the ecological balance of the GI microbiota can lead to GI diseases or be caused by them. In IBD there is a decrease in the population of several protective bacteria and an increase in the population of harmful bacteria [14]. Food poisoning may be viral, but is mostly due to bacterial contamination in food and water. A large portion of the population also has *Helicobacter pylori* infection, which can lead to secondary diseases [10, 14, 15]. The infecting bacteria, or the antibiotics used to eliminate them, may also alter the balance of the indigenous microbiota. Often these problems are overcome on their own with time, but sometimes probiotic supplementation may be needed [10, 14–18].

Diagnosis of Gastrointestinal Diseases

IBS is a chronic condition of the large bowel that is characterized by abdominal pain, cramping, bloating, gas, diarrhea, and/or constipation [1]. Patients may be categorized as diarrheal-predominant, constipation-predominant, and as having both. Unlike IBD, there are no macroscopic or microscopic changes in the bowel tissue structure, and therefore IBS is also called a "functional disorder of gastrointestinal tract" [1, 19]. It is diagnosed by exclusion criteria for cancer, IBD, and infections.

IBD may be divided into CD and UC, which share several common symptoms except that the affected area in UC is the colon but in CD it may be the colon or ileum [20]. CD symptoms may include diarrhea, fever, fatigue, abdominal pain and cramping, blood in the stool (bright red blood in toilet bowl or darker blood mixed with stools), mouth sores, reduced appetite, weight loss, and anal fistulas [21]. For UC the part of the colon being inflamed is considered and the general symptoms are: diarrhea (often with blood or pus), abdominal pain and cramping, rectal pain, blood in the stool (bright red blood in toilet bowl or darker blood mixed with stools), urgency and inability to defecate, weight loss, fatigue, and fever [22]. There is no single test to diagnose CD or UC. The patient may undergo all or some of the following tests:

blood tests for anemia or infection, fecal occult blood test, colonoscopy (presence of clusters of inflammatory cells called granulomas point to CD), flexible sigmoidoscopy, computerized tomography, magnetic resonance imaging, capsule endoscopy, double-balloon endoscopy, and small bowel imaging. Diagnosis of either disease is made by ruling out other factors. Several indices and scoring systems of GI diseases have been used by investigators to determine the efficacies of supplements as indicated in Table 1.

Current Treatments of Gastrointestinal Diseases

CD and UC are chronic GI inflammatory diseases with periods of relapse and remission, and the treatments aim to achieve and maintain remission. The current treatments include a combination of anti-inflammatory (steroids), immunosuppressive agents (e.g., azathioprine, sulfasalazine, mesalamine, 6-mercaptopurine, and methotrexate) and anti-tissue necrosis factor-α (anti-TNF-α) even though some treatments may have serious adverse effects [23, 24]. For CD, a phase II clinical trial reported that 21 oligomeric antisense specific for SMAD7, which suppresses TGF-β1, achieved 65% remission as compared to 15% with placebo [25, 26]. The compound is ready for the phase III clinical trial. Probiotics and prebiotics may also be included in the treatment so as to normalize the GI microfloral ecosystem [14–18].

IBS treatment depends on the most bothersome symptoms of the patient. The treatment may include the use of antispasmodics, laxatives, dopamine antagonists, 5-hydroxy tryptamine-3 antagonists and/or 5-hydroxy tryptamine-4 agonists, sedatives, antibiotics, probiotics, modifications in diet and lifestyle, and complementary and alternative therapies [19]. For C-IBS, linaclotide and lubiprostone may be used and for D-IBS, cilansetron or ramosetron may be given. Rifaximin has emerged as a strong option for the treatment of IBS because of its broad-spectrum bactericidal activity in vitro, and its favorable tolerability profile [19]. Nitric oxide (NO) donors, opioid receptor agonists, and ketotifen have also been proposed for IBS treatment [19].

Rationale for the Use of Antioxidant Supplements in Gastrointestinal Diseases

Normal physiological processes result in the generation of reactive oxygen species (ROS) such as peroxide, superoxide, hydroxyl radical, and peroxynitrite. The ROS occur normally in the body at very low concentrations (nanomolar to micromolar) [27]. The body needs them for survival but excess ROS might have deleterious effects [28, 29] because the GI tract maintains an appropriate balance of the levels of ROS. The enzyme superoxide dismutase decreases the level of superoxide by catalyzing its conversion into molecular oxygen or hydrogen peroxide [27, 30]. Similarly, catalase also catalyzes the degradation of hydrogen peroxide into oxygen and water. Glutathione peroxidases decrease the levels of peroxides using reduced glutathione (GSH) [31]. This requires maintenance of an appropriate ratio of GSH and its oxidized form (GSSG). Whereas γ-glutamylcysteine ligase and GSH synthase are pivotal for the GSH synthesis, nicotinamide adenine dinucleotide phosphate (NADPH)-dependent GSSG reductase is key to the conversion of GSSG to GSH. Ascorbate may also quench ROS and is converted into a transient unstable species and then into dehydroascorbate. Dehydroascorbate reductase uses GSH to recycle it back into ascorbate [27]. The reduced peroxiredoxin can also quench hydrogen peroxide and gets oxidized in the process. Thioredoxin can convert the peroxiredoxin back by oxidation of thioredoxin which in turn is reduced by thioredoxin reductase and NADPH$^+$ [27]. The cysteine-cystine cycle also plays a key role in maintaining the appropriate balance of ROS [32].

High levels of ROS may damage cells by oxidizing lipids and DNA and protein in various tissues [27]. In the GI tract, the cellular redox potential may even determine the fate of the differentiating cells [9]. Wnt/β-catenin and Notch signaling pathways are major determinants of commitment of the cells for specialization. There may be a direct relationship among NADPH oxidase 1 (NOX-1)-dependent ROS generation, differential activation of Wnt/β-catenin or Notch signaling pathways, and intestinal proliferation and lineage commitment. Changes in the redox potentials of GSH/GSSG and cysteine/cystine (Cys/CySS) have been correlated with intestinal phenotypic transitions. Reducing potentials may favor cell proliferation, but a switch to oxidizing potentials may lead to cell growth arrest [9, 33].

Studies with animal models have shown that IBD leads to decreased glutathione concentrations, high DNA oxidation, lipid peroxidation, myeloperoxidase, and elevated TNF-α and malondialdehyde levels [34]. Catalase and superoxide dismutase levels are also altered in some models [34]. The gene ablation of inducible NO synthase (iNOS) in mice showed significant attenuation of UC indicating that iNOS and NO play a major role in UC [35]. In UC, the inflamed human lamina propria showed an increased

Table 1. Effects of antioxidant supplements on gastrointestinal diseases (see footnote for explanations)

Ref.	Disease	Trial characteristics	Outcome measures	Observation summary	Rating and comments
Allopurinol					
44	IBD	O: combination therapy after failed azathioprine monotherapy ($n = 11$) up to 8 months	6-TGN levels in erythrocytes	50 mg allopurinol with 50 mg azathioprine sufficient to raise 6-TGN level	++** Small sample size, no clinical results
45	IBD	O: combination therapy after failed monotherapy, given allopurinol + thiopurine ($n = 77$) up to 5 years	6-TGN levels in erythrocytes	Long-term combination therapy effective and well tolerated	++** No clinical results
46	IBD	O: azathioprine combination therapy ($n = 10$; 8 CD, 2 UC), 12 weeks	6-TGN levels in erythrocytes and hypoxanthine-guanine phosphoribosyltransferase	Increased hypoxanthine-guanine phosphoribosyltransferase and 6-TGN levels	++** No clinical results
85	UC	RDBP: prophylactic use of pouchitis ($n = 273$), 2 years	Pouchitis incidence and pouch function	No effects	±***** Restorative surgery in UC may result in pouchitis
48	UC	RDBP: combination therapy with mesalamine, patients in remission ($n = 199$), 12 months	Clinical and endoscopy after 1, 6 and 12 months	Combination therapy better for 6 but not 12 months	+***** High relapse rate in mesalamine alone in first 3 months
47	UC	RDB: sulfasalazine and prednisol enema ($n = 45$) ± allopurinol ($n = 46$) or DMSO ($n = 45$), 12 months	Remission and relapse rate	2 weeks: 51% in remission vs. 84% with allopurinol or DMSO; over 12 months 5% relapse with allopurinol or DMSO vs. 25% without	++*** No placebo, limited measurements
Aloe vera					
86	IBS	RDBP: ($n = 58$), 1–3 months	IBS, pain and distension scores, bowel habit satisfaction	Effects similar to placebo	±***
87	IBS	RDBP crossover: ($n = 110$), 5 + 5 months	Gastrointestinal Symptoms Rating Score, IBS Quality of Life, EuroQol	Effects similar to placebo	±**** Subjective questionnaires, high dropout
88	IBS	O: constipation-predominated refractory patients ($n = 33$), 8 weeks	Self-rated VAS scores	Pain and discomfort decreased significantly	+* No placebo, subjective questionnaires
89	UC	RDBP: ($n = 44$), 4 weeks	SCCAI, sigmoidoscope scores, and histological scores	Better than placebo for SCCAI and histological scores not for sigmoidoscopic scores	+*** Small sample size and short time
Andrographis paniculata (Indian echinacea, kirayat)					
90	UC	RDBC: compared with mesalamine ($n = 120$), 8 weeks	Colonoscopy, stools, abdominal pain, and distension	Effects similar to mesalamine	++**** This was a pilot study
91	UC	RDBP: extract 1,200 or 1,800 mg or placebo ($n = 224$), 8 weeks	Colonoscopy, stools, abdominal pain, and distension	1,800 mg gave better clinical response but adverse effects in half the patients	–**** Has in vitro inhibitory activity against TNF-α, IL-1β, and NF-κB
Vaccinium myrtillus (bilberry)					
92	IBS	O: bilberry and other compounds D-IBS ($n = 21$) and C-IBS ($n = 10$), 3 weeks	Stool frequency and consistency	Small improvement in C-IBS but not in D-IBS	±** Small sample, no control
93	UC	O: mild to moderate active UC ($n = 13$), 6 weeks treatment + 3 weeks	Remission, CAI, SIBDQ fecal calprotectin, endoscopy, histology score	63% remission at 6 weeks which did not last in the follow-up	+** No control, small sample size

Table 1 (continued)

Ref.	Disease	Trial characteristics	Outcome measures	Observation summary	Rating and comments
Boswellia serrata (*frankincense, shallaki, salai*)					
52	CC	RDBP: extract vs. placebo in collagenous colitis (*n* = 26), 6 weeks	Clinical remission, SF-36 questionnaire, colonoscopy, stools	More patients in remission 63.6 vs. 26.7%; no effect on colonoscopy or SF-36	++**** Small sample
94	CC	RDBP: collagenous colitis in remission (*n* = 82), 52 weeks	Remission maintenance, time to relapse, CDAI and IBDQ	Terminated early due to no difference	± **** Good safety profile
49	CD	RDBC: extract (*n* = 44) vs. mesalamine (*n* = 39), 8 weeks	CDAI noninferiority vs. mesalamine	CDAI decreased: 90 (treated) and 53 points (controls)	++***
53	CD	O: diet with curcumin, vitamins, microbiotics and others, juvenile CD (*n* = 6)	Clinical remission, weight gain	Prolonged remission (years) in most with continued therapy; improved patient growth	++** Small sample, requires maintaining diet, role of *Boswellia* not clear
54	UC	O: active UC, resin (*n* = 20) vs. sulfasalazine (*n* = 10), 6 weeks	Remission, stool properties, histopathology, serum and blood biochemistry	More effective for remission (14/20) than sulfasalazine (4/10)	++** Small trial, short time period
Capsicum annuum (*chili pepper*)					
95	IBS	RDBP: red pepper (*n* = 23) vs. placebo (*n* = 27), 6 weeks	Likert scale, pain, and bloating	Low efficacy at low doses, abdominal pain at higher doses	–*** Doses need to be optimized
96	IBS	RDBP: red pepper (*n* = 15) vs. placebo (*n* = 15), 5 weeks	Symptom score, epigastric pain, fullness, nausea	Relief more significant in pepper (60%) than placebo (30%)	+*** Small sample
97	IBS	RP crossover: Guajillo chili vs. placebo (*n* = 10), 7 days each phase	Rectal pain threshold and upper abdominal discomfort	Decreased pain threshold, but increased upper abdominal discomfort	–*** Small sample
Carnosine					
98	IBS	RDBP: dose escalation study 500, 1,000, 1,500 mg (*n* = 25), 12 weeks	Diarrhea symptoms	Diarrhea decreased after 1,500 mg	++*** Gulf War syndrome
Matricaria chamomilla (*chamomile*)					
62	UC	RDBC: chamomile + myrrh + coffee charcoal vs. mesalamine (*n* = 96), 12 months	Noninferiority measured by CCAI and relapse rates	Relapse rates similar to mesalamine	++***** Role of chamomile not clear
61	UC	RDBC: chamomile + myrrh + coffee charcoal vs. mesalamine (*n* = 39), 12 months	CD4 + T-cell compartment	With mesalamine there was a steady decrease with flare but different patterns with chamo.	++***** Role of chamomile not clear
Curcumin (isolated from Curcuma longa *which is turmeric)*					
58	IBD	O: UC (*n* = 5), CD (*n* = 5), 3 months	Clinical assessment and blood parameters	Improvement with curcumin	+** No controls, very small sample
59	IBD	O: pediatric UC/CD patients (*n* = 11), 6 weeks	Tolerability in pediatric patients and disease indices	Improvement in some patients, 3 g/day tolerated in all patients	±* Small study, no controls, limited determinations
55	IBS	RB: turmeric extract (72 or 144 mg) (*n* = 207), 8 weeks	Questionnaires on pain and discomfort, self-reported effectiveness	Similar improvement at both doses compared to initial baseline	+** IBS symptoms can fluctuate over time; no controls
56	UC	RDBP: mesalamine plus curcumin/ placebo refractory to mesalamine (*n* = 50), 1 month	Remission, SCCAI and endoscopy	Effective for all parameters	++**** Short duration of study
57	UC	RDBP: mesalamine with curcumin enema or placebo (*n* = 45), 8 weeks	UCDAI, improvement in endoscopic activity, remission	More improvement in all parameters than by placebo	++*** Short study duration

Table 1 (continued)

Ref.	Disease	Trial characteristics	Outcome measures	Observation summary	Rating and comments
Ferrous fumarate					
99	IBD	O crossover: ferrous fumarate vs. iron sucrose ($n = 19$), 14 days each in iron deficiency anemia IBD	CDAI, UCDAI, general well-being, abdominal pain, vascular oxidative stress	Ferrous fumarate increased disease activity, iron sucrose increased oxidative stress	–**
Camellia sinensis (green tea)					
100	UC	RDBP: EGCG ($n = 15$) or placebo ($n = 4$), 7 weeks	Remission, UCDAI; IBD questionnaire	Remission 8/15 vs. placebo 0/4 ($p = 0.1$); UCDAI decrease in 10/15 vs. 0/4 with placebo	++*** Small sample and short duration
Actinidia deliciosa (kiwifruit)					
101	IBS	O: IBS (constipation/ diarrhea) patients ($n = 41$), 5 weeks	Stool properties and frequency	Improved bowel function	+* Small sample size, no controls
Pistacia lentiscus (mastic gum)					
102	CD	O: active CD patients ($n = 18$), 4 weeks	CDAI, IL-6, TNF-a, CRP and total antioxidant potential	Improvement in all parameters	+** No adverse effects, small sample size, no controls
N-acetyl cysteine					
103	UC	RDBP: combination therapy with mesalamine ($n = 37$), 4 weeks	Modified Truelove Witts Severity Index, remission	Small benefits for the measured parameters	+*** Small sample and short duration
Oxpentifylline					
104	CD	O: active CD patients ($n = 16$), 4 weeks	CDAI, endoscopic inflammation	No improvement	±* It is a TNF-α inhibitor
Mentha piperita (peppermint)					
72	IBS	RDBP: oil vs. placebo ($n = 90$), 8 weeks	Pain and quality of life based on three types of questionnaires	Severity of pain decreased vs. placebo	+** High dropout rate
69	IBS	RDBP: oil vs. placebo, D-IBS patients ($n = 74$), 6 weeks + 2 week follow-up	Change in symptoms at 3, 6 and 8 weeks	Small but significant difference at 6 weeks; none after the follow-up	+*** Abstract only available, dose not quoted
71	IBS	RDBP: oil ($n = 35$) vs. placebo ($n = 37$) IBS-mixed or D-IBS, 4 weeks	Total IBS Symptom Score	Significantly better at 24 h; at 4 weeks: 40% reduction vs. 24% with placebo ($p = 0.0246$)	+*** Used a sustained release preparation
105	IBS	RDBP: oil vs. placebo, pediatric IBS ($n = 42$), 2 weeks	Neurological exam, gastrointestinal symptom rating scale, other variables	Pain decreased in 75% of treated group vs. 19% of placebo; no other changes	+*** Short and small trial
67	IBS	RDBP: oil ($n = 52$) vs. placebo ($n = 49$), 1 month	Pain, distension, stool frequency, flatulence, borborygmi	Symptoms improved significantly compared to placebo ($p < 0.05$)	++*** Well tolerated, short duration
68	IBS	RDBP: oil vs. placebo ($n = 18$), 3 weeks	Symptom severity, stool frequency	Worked better than placebo	+*** Small sample and short duration
70	IBS	RDBP oil vs. placebo ($n = 57$), 4 weeks + 4 week follow-up	Symptom changes and Total IBS Symptom Score at 0, 4, 8 weeks	Score decreased more at 4 (and 8 weeks) vs. 0 weeks ($p < 0.01$) vs. no change in placebo	++*** Even at 8 weeks still partial effect
Punica granatum (pomegranate)					
106	UC	RBP: peel extract vs. placebo ($n = 78$), 4 weeks + 6 week follow-up	Lichtiger CAI	CAI decreased marginally, better than placebo at 4 but not 10 weeks	±**

Table 1 (continued)

Ref.	Disease	Trial characteristics	Outcome measures	Observation summary	Rating and comments
Plantago ovata *(psyllium, isabgol)*					
107	IBS	RDBP: chronic constipation with/without IBS ($n = 20$), 1 month	Fecal weight and colonic transit time	Stool frequency increased and transit time decreased vs. no change with placebo	++*** Small sample
108	UC	OR: psyllium ($n = 35$) or mesalamine ($n = 37$) or both ($n = 30$), 1 year	Maintenance of remission	Failure rate: psyllium (40%), mesalamine (35%) vs. both (30%)	++***
Pycnogenol					
109	CD	O: pediatric patients in remission ($n = 15$) vs. healthy controls ($n = 15$), 10 weeks	Oxidative stress markers	Positive improvement	+* Small study, good study on CDAI vs. oxidative stress
Resveratrol (red wine)					
110	UC	RDBP: resveratrol vs. placebo, active UC ($n = 50$), 6 weeks	Serum inflammatory markers, IBDQ-9, CCAI	Greater reduction in TNF-α, CRP, NF-κB and CCAI vs. placebo, increase IBDQ	+**** Short duration, all changes were small
Superoxide dismutase					
11, 111	CD	O: 2 trials; patients refractory to steroids ($n = 26$), used with desferroxamine	CDAI, anatomic healing	No relapse in 12 and 1 relapse in 9 patients	+* Open trials, placebo, more recent trials not found
Potentilla erecta *(Tormentil)*					
112	UC	O: escalating dose trial 1,200; 1,800; 2,400; 3,000 mg ($n = 16$), 3 weeks each with 4 week washout	Side effects, CAI, CRP, tannins	CAI decreased during treatment and increased during washout, no side effects	+** Safety trial, small sample
Artemesia *species (Wormwood)*					
64	CD	RDBP: wormwood ($n = 20$) vs. placebo ($n = 20$) with decreasing steroids 10 weeks + 10 weeks no steroids, no wormwood	Change in prednisone use, CDAI, HAMD, IBDQ, VAS	18 treated patients stayed off steroids, CDAI, HAMD, IBDQ, and VAS improved, placebo patients deteriorated without steroids	++**** Longer duration study would be beneficial
65	CD	OC: usual medications with ($n = 10$) or without wormwood ($n = 10$), 6 weeks	TNF-α levels, CDAI, Hamilton Depression Scale, IBDQ	Improvement in all parameters with wormwood	++** Small sample and short duration

Types of trials: O, open, R, random, B, blind, DB, double blind, C, controlled, P, placebo controlled. Benefit ratings: ++, clear benefit, +, some benefit, ±, no benefit, –, adverse effects outweigh benefits. Quality of studies: *****, RDBP or RDB crossover or RDBC trials with good sample size and duration of several weeks to years, the number of stars decrease with the quality of trial. Indices and scoring systems of GI diseases: IBDQ (inflammatory bowel disease questionnaire) is the most comprehensive and contains 60 questions on current status and history of GI health, bowel movements and anxiety, general health, energy, ability to focus, medication, and other diseases [113]; CDAI (Crohn's Disease Activity Index) is a weekly sum of the scores based on lost fluid or the number of very soft stools, abdominal pain, arthritis/arthralgia, mucocutaneous lesions, iritis/uveitis, anal disease, external fistula, fever over 37.8°C, antidiarrheal use, abdominal mass, low hematocrit, and body weight [114]; CDEIS (Crohn's Disease Endoscopic Index of Severity) is based on locations of deep or superficial lengths of the surface involved in the disease and ulcerated surface [115]; IBS score is based on stomach pain, distension, bowel movement satisfaction and comfort, bowel habits and structure including passing of mucus and blood, effect of bowel movements on pain, and history of absence from work due to stomach problems [116]; SCCAI (Simple Clinical Colitis Activity Index) is based on bowel frequency during the day and during the night, urgency for defecation, blood in stool, general well-being, and extracolonic features [117]; SIBDQ is a shorter version of the CDAI questionnaire; UCDAI (Ulcerative Colitis Disease Activity Index) is based on stool frequency, rectal bleeding, mucosal appearance, and the physician's rating of disease activity [118]; Rutgeerts score, NRI (Nutrition Risk Index) EuroQol, Modified Truelove Witts Severity Index (also called Lichtiger CAI), DAI (Disease Activity Index), VAS score for pain, and Likert scale pain and bloating have also been used.

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infiltration by neutrophils and myeloperoxidase activity [24]. At early stages of CD, there is a patchy necrosis of leukocytes near the crypts and an increased number of macrophages and granulocytes [35]. These phagocytotic cells produce large amounts of NO and superoxide, resulting in the formation of peroxynitrite which can cause tyrosine nitration and also cause DNA damage. Thus, in CD and UC, there is an increased production of ROS and peroxynitrite by phagocytotic cells (neutrophils, monocytes, and macrophages) that infiltrate the mucosa. The inflammation also results in increased TNF-α which in turn can activate iNOS, thereby producing even larger amounts of NO. TNF-α also activates NF-κB, which translocates to the nucleus and activates mucosal inflammation genes such as the cytokines IL-6, IL-8 IL-1β, IL-10, TNF-α, ICAM, and P-selectin [34, 35]. This inflammatory pathway further triggers the generation of ROS. The importance of oxidative stress in this pathway is further confirmed by the use of sulfasalazine and mesalamine in the therapy for IBD [23, 24, 34, 35].

The conventional hypothesis is that antioxidant supplements simply scavenge ROS. However, based on the kinetic constraints, it is not possible for any concentrations of antioxidant supplements to scavenge ROS sufficiently to prevent biological damage [32]. An alternative hypothesis is that antioxidant supplements modulate endogenous mechanisms that either decrease the production of ROS or increase the enzymes that decompose ROS. One key pathway by which several antioxidants work involves the nuclear factor erythroid-related factor 2 (Nrf2) and the electrophile response element (EpRE), which is also called the antioxidant response element (ARE) [32, 33]. Nrf2 is normally bound to Keap1 in the cytoplasm, but polyphenols dissociate this complex to release Nrf2 which is then phosphorylated and transported to the nucleus where it binds EpRE and results in the transcription of genes for several enzymes which can either degrade ROS or prevent their production [32, 33]. Several antioxidants including curcumin, boswellic acids, planar aromatics, phenols, and rosmarinic acid can activate the Nrf2 pathway in animals [32, 36–39]. Antioxidant supplements may also decrease ROS levels through action on other enzymes [40]. For example, one of the enzymes that generates superoxide anions is xanthine oxidase, and allopurinol inhibits it [85]. Curcumin inhibits the inflammatory pathway by decreasing the activities of the aryl hydrocarbon receptor, IL-1β and COX, the AKT/mTOR pathway that controls the energy, and also the insulin growth factor and insulin pathways [40]. Resveratrol influences the aryl hydrocarbon receptor, COX, pro-

tein kinase C, adenosine monophosphate (AMP) kinase, and sirtuin 1 [40]. Since individual tissues differ in the activities of the enzymes involved, the action of antioxidant supplements may also be tissue and disease dependent. Hence, it is important to determine which antioxidant supplements are efficacious specifically against GI diseases.

Antioxidant Supplement Benefits: Analysis of Trials

Vitamins, minerals, and related compounds which act as cofactors for key enzymes are important to human health and these, as well as the effects of exercise, have been examined extensively [41–43]. Here the focus is human trials that examined the efficacies of various antioxidant supplements against GI diseases.

The initial general Medline search using the following keywords resulted in 372 references: "celiac or Crohn's or inflammatory bowel or irritable bowel or colitis" and "antioxidants" and "clinical trials". A modified search using the following keywords and the name of each antioxidant led to a total of 340 publications: "celiac" or "Crohn's" or "inflammatory bowel" or "irritable bowel" or "colitis", and "trial". However, very few of these searches were human clinical trials. Most of them were reviews or in vitro or animal studies. The original studies on human clinical trials are listed in Tables 1–3. These studies differed not only in the antioxidants tested, but also in the study methods, criteria, sample sizes, study duration, use of placebos or controls, rigor, and subjectivity (random, blind, open and questionnaires, types of clinical symptoms measured) [113–118]. Benefit ratings were provided for some guidance. A rating of "++" was given when there were either statistically significant benefits to the treated groups over the controls or there was a significant increase in the percent of patients with improvements and there were little or no adverse effects. The "+" rating was given for the cases where there were only marginal differences in some of the parameters, A rating of "±" was given when there were no statistically significant benefits. The studies where the adverse effects outweighed benefits received the rating "–".

Allopurinol

Allopurinol had been tested as a combined therapy with routinely used drugs such as sulfasalazines or steroids [44–48, 85]. In 3 open studies on IBD, allopurinol combination therapy increased thioguanine nucleotide (6-TGN) levels to greater than with monotherapy levels

with sulfasalazine, mesalamine or steroids (Table 1) [44–46]. In UC patients, combination therapy with allopurinol gave better relapse rates than sulfasalazine and prednisone enema alone, but the results on combination therapy with mesalamine were not as promising (Table 1) [47, 48]. Thus, allopurinol may be useful as an adjunct therapy to enhance the levels of the immunosuppressive metabolites like 6-TGN.

Boswellia serrata

Boswellia serrata resins contain boswellic acids such as acetyl-keto-β-boswellic acid which is a lipoxygenase inhibitor and may have anti-inflammatory properties [49]. *Boswellia* resins have been used in Ayurvedic medicine (shallaki or salai) [50] and in Europe (olibanum or frankincense) [51]. *Boswellia* extracts proved useful against collagenous colitis in one study but not in another (Table 1) [52, 94]. A random double-blind control study showed *Boswellia* extracts to be useful in CD but less efficacious than mesalamine [49]. Of greater interest is a small study on juvenile CD where capsules containing *Boswellia* plus several other ingredients were efficacious in maintaining remission over several years [53]. A small open study in patients with UC for ≥6 weeks indicated *Boswellia* extracts to be superior over sulfasalazine in maintaining remission [54]. Thus, *Boswellia* has been reported to be useful as a replacement for mesalamine and sulfasalazine in GI diseases, but its usefulness along with other antioxidants may be of greater value.

Curcumin

Curcumin is an antioxidant in turmeric (the rhizome of *Curcuma longa* or *Curcuma domestica*) which is used extensively as a spice. It inhibits inflammatory pathways by decreasing activities of the aryl hydrocarbon receptor, IL-1β, and COX; the AKT/mTOR pathway that controls the energy; and insulin pathways [40]. It is well tolerated. A random blind study with 207 patients over 8 weeks showed curcumin to be beneficial for IBS patients, but the study did not contain a placebo control [55]. In 2 independent random double-blind placebo controlled studies, combined therapy with curcumin and mesalamine was superior over mesalamine alone [56, 57]. In 2 small open studies curcumin showed marginal efficacy for IBD in adult and pediatric patients [58, 59]. It is noted that these 2 studies contained both UC and CD patients. Thus, the evidence for curcumin alone as a therapy for UC may be marginal, but the evidence is better for its usefulness in its combined therapy with mesalamine.

Chamomile

The term chamomile is used for members of Asteraceae, particularly *Matricaria chamomilla*. Their flowers contain antioxidant and anti-inflammatory compounds such as bisabolol, chamazulene, apigenin, and luteolin [60]. Two random double-blind controlled studies on UC patients found that a chamomile preparation which also contained myrrh and coffee charcoal was as effective as mesalamine [61, 62]. However, since the preparation contained many components, one cannot assign the beneficial effects to chamomile alone.

Wormwood

Wormwood or *Artemesia* species are members of Asteraceae and contain antioxidants such as artemesinin, myrcene, and camphor [63]. A small random double-blind placebo controlled study reported that therapy with wormwood extracts decreased or eliminated the need for steroids in CD patients [64]. Another open study also found wormwood to be beneficial for CD patients [65]. Both studies, however, had small sample sizes and short duration.

Peppermint

Peppermint (*Mentha piperita*) contains several antioxidants such as rosmarinic acid, eriocitrin, luteolin, and terpenes [66]. Table 1 lists 7 studies that examined the benefits of peppermint in IBS [67–72]. Based on these studies, at best peppermint has a marginal efficacy. However, it is important to note that there are no adverse reactions although there was a high dropout rate in one trial [72].

The following antioxidants have also been examined, but there is insufficient evidence concerning their benefits: *Aloe vera* [86–89] *Andrographis paniculata* [90, 91], bilberry [92, 93], *Capsicum* [95–97], carnosine [98], ferrous fumarate [99], green tea [100], kiwifruit [101], mastic gum [102], N-acetyl cysteine [103], oxpentifylline [104], pomegranate [106], psyllium [107, 108], Pycnogenol [109], resveratrol (red wine) [110], superoxide dismutase [11, 111], and tormentil [112] (Table 1).

Polyunsaturated Fatty Acids or Fish Oil Supplements

Omega-3 and omega-6 polyunsaturated fatty acids (PUFA) are present in fish oil and also to some degree in plant flax seeds (*Linum usitatissimum*). PUFA and fish oil have been examined for their therapeutic effects on CD, UC, and IBS (Table 2) [73–78, 119–126, 129, 130]. Some of the studies examined PUFA along with several other ingredients and hence it is not possible to ascertain

Table 2. Effects of PUFA supplements on gastrointestinal diseases (see footnote to Table 1 for explanations)

Ref.	Disease	Trial characteristics	Outcome measures	Observation summary	Rating and comments
75	CD	RDBP: n–3 FA, 2 trials (n = 363) (n = 375), 58 weeks	Maintenance of remission	No effect on relapse rates	±***** No other medication
74	CD	RDBP: n–3 FA, high risk of relapse (n = 78), 1 year	Relapse rate	59 vs. 26% placebo stayed in remission	++**** Similar dropout rates between groups
73	CD	RDBP: 5-ASA or 5-ASA + n–3 FA, pediatric (n = 38), 1 year	Relapse rate	Lower (61%) relapse with n–3 FA than without (95%)	++**** Relapse delayed with n–3 FA
119	CD	RCP: n–3 FA (n = 70) vs. low-carb diet (n = 65) vs. placebo (n = 69), 1 year; prednisone for 1st 2 months	Remission maintenance, CDAI and CRP	n–3 FA not better than placebo; diet was better as long as maintained	±****
120	CD	RDB: impact powder with/without extra n–3 FA + arginine + RNA + protein (n = 31), 9 weeks	CDAI, leptin levels, BMI	Extract may have marginal benefits for CDAI	+*** Role of n–3 FA not clear
121	CD	RDBP: impact powder + AO or impact powder + AO + n–3 FA or placebo, patients in remission (n = 70), 3 months	Antioxidant levels, FA incorporation	Increase in antioxidant levels with AO treatment; n–3 FA resulted in better FA profile	±*** 33% dropout rate
122	CD	RDB: impact powder with n–3 or n–6 FA (n = 31), active CD into remission (or decreased CDAI), 9 weeks	Clinical and biochemical markers for inflammation	n–3 FA and n–6 FA inhibited proinflammatory cytokines and decreased CDAI	++*** Too many ingredients
123	CD	RDB: impact powder with n–3 or n–6 FA (n = 31), 9 weeks with prednisolone tapering	Insulin-like growth factors	All measured factors increased with both; no difference between groups	+*** Role of PUFA not clear; too many ingredients used
124	CD/UC	RDB: seal oil (n = 20) vs. cod oil (n = 18), 2 weeks	Joint pain	Joint pain improved somewhat with both	+**
125	CD/UC	RP: seal oil (n = 10) vs. soy oil (n = 9), 10 days	Joint pain	Improvement with seal oil but not soy oil	+** Seal oil still better than baseline 6 months later
78	UC	RO crossover: compare n–3 FA from fish oil vs. sulfasalazine (n = 10), 2 months	Blood parameters, CRP, total fecal nitrogen excretion	Sulfasalazine worked better than n–3 FA	±** Small study
126	UC	RDBP: fish oil (n = 9) vs. placebo (n = 9), with standard meds, 6 months	Disease activity, clinical, histology, cytokines	All measured parameters decreased	+** Confirmed in [127, 128]
77	UC	RDBP crossover: sulfasalazine with or without fish oil (n = 9), 2 + 2 months	Antioxidant status in active UC, disease activity	Fish oil improved only the antioxidant status activity	+**** Small study
129	UC	RDBP: supplement with fish oil, selenium, vit. E, vit. C, gum arabic, fructooligosaccharides vs. placebo (n = 121), 6 months	Prednisone use, DAI and histology	Prednisone use decreased	+**** Too many ingredients
130	UC	O: MAX-EPA capsules, patients refractory to other treatment (n = 9), 8 weeks	Safety, tolerability, stool diaries, sigmoidoscopy, symptom response	Marked to moderate improvement in 7 patients, decreased steroid dose in 4	++** Pilot study, well tolerated
76	UC	RDBP crossover: MAX-EPA vs. placebo, active UC, usual meds continued (n = 18), 4 + 4 months, 1 month washout	Flexible sigmoidoscopy, symptom review, rectal biopsy, pEG2, leukotriene B4	Leukotriene B4 decreased, histology improved, weight gain; no changes with placebo	++**** Small study

Table 3. Chinese and Ayurvedic medicine (see footnote to Table 1 for explanations)

Ref.	Disease	Trial characteristics	Outcome measures	Observation summary	Rating and comments
Léi gōng téng (Tripterygium wilfordii)					
82	CD	RC: glycosides vs. azathioprine ($n = 90$), 52 weeks	Clinical and endoscopic recurrence postsurgery	Efficacy similar to azathioprine	++*** High dropout rate – only 47 finished the study
79	CD	RSBC: glycosides ($n = 21$) vs. mesalamine ($n = 18$), postoperative CD, 52 weeks	Clinical and endoscopic measurements, CDAI, Rutgeerts score	Fewer recurrences than with placebo (4 vs. 9), Rutgeerts score better, CDAI similar	+*** Small trial
80	CD	RC: glycosides vs. mesalamine ($n = 45$), postoperative CD, 52 weeks	CDAI clinical markers, ileocolonoscopy at end or (suspected) recurrence	Efficacy similar to mesalamine for up to 1 year	++*** Based on abstract, small trial (paper in Chinese)
81	CD	RBC: glycosides ($n = 21$) vs. sulfasalazine ($n = 18$), up to 52 weeks	CDAI, ESR, CRP ileocolonoscopy at end or (suspected) recurrence	Glycosides prevented recurrence better than sulfasalazine	++*** Based on abstract, small trial (paper in Chinese)
Chinese herbal medicine blends					
131	IBS	RDBP: custom ($n = 38$), standard ($n = 45$) or placebo ($n = 33$), 16 weeks	Bowel symptoms, global improvement, interference in life style	Custom and standard herbal treatments equally better than placebo	+**** Standard preparation from 20 herbs
132	IBSC	RDBP: herbal blend (7) capsules ($n = 61$) vs. placebo ($n = 64$), 8 weeks	Global symptom improvement questionnaires, symptom severity scale and Bristol Stool Form Scale	Symptoms improved significantly over placebo although pain did not change	+**** Prospective study
133	IBS	RDBP: Tiaohe Ganpi Hexin decoction ($n = 20$) vs. placebo ($n = 20$), 4 weeks	Traditional Chinese medicine syndrome score, disappearance rate of symptoms, clinical symptom score	Some improvement seen in all parameters	+*** Small short-term study
134	IBSD	RDBP: Changjishu ($n = 78$) vs. placebo ($n = 26$), 21 days	Effectiveness of capsule covering	Worked better than placebo	+***
135	IBSD	RDBP: 11-herb formula ($n = 60$) vs. placebo ($n = 59$), 8 weeks	Global symptom assessment, SF-36 questionnaire	No difference from placebo	±***
83	UC	RDBP: ulcerative proctitis, xilei san suppository ($n = 15$) or placebo ($n = 15$), 6 months	Remission at day 14, relapse rate after 180 days, Riley's index for endoscopic and histologic exams, IBDQ	At day 14 remission higher in xilei san, at day 180 – 81.8% in remission vs. 16.7% placebo, other measures also improved	++**** Very small trial, not clear if this is an antioxidant
136	UC	O: Shuxuening injection ($n = 47$) vs. no injection ($n = 44$), meds continued + healthy controls ($n = 20$), 14 days	Mayo scoring system, endoscopy, IL-6, TNF-α, SOD, MDA	Treatment group had significantly better results than untreated group (also improved)	+* Paper in Chinese, composition of drug not clear
Ayurvedic herbal blends					
137	IBS	O: Bilvadileha ($n = 45$) Rome III, 12 weeks	IBS severity score, Ayurvedic parameters	Symptoms were significantly improved (only 2% reported no effect of treatment)	+* Bilvadileha (10 herbs), no controls
84	UC	O: oral administration of herbs plus *Ficus glomerata* enema while on usual meds ($n = 50$), 4 weeks	Changes in clinical parameters, lab tests, use of other drugs	Reduction in bowel movement frequency, blood in urine, steroid use (100%), sulfasalazine (80%), pain, weight loss	++** Small open short-term trial
138	IBS	RDBP: Ayurvedic vs. standard therapy ($n = 169$), 6 weeks	Diarrhea, pain, and gas	Ayurvedic better for D-IBS, standard for pain, both better for gas than placebo	+*** Only abstract available

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whether the observed effects were due to PUFA. Several other studies had small sample sizes and/or were not properly controlled. Only 3 random double-blind placebo controlled trials were found [73–75]. One study found mesalamine to control remission in pediatric CD patients but 95% of patients relapsed within 1 year. Adjunct therapy with PUFA decreased this relapse rate to 61% [73]. The multicentered Epanova Program in Crohn's (EPIC) Study included 2 trials named EPIC1 and EPIC2 in which patients were in remission. In 1 year, relapse occurred in 32% with PUFA and 36% with placebo in EPIC1, and 48% with PUFA and 49% with placebo in EPIC2 [75]. Thus, PUFA were ineffective in maintaining the remission. Another study used enteric coated PUFA capsules for remission maintenance in patients who had a high risk of relapse and found PUFA to be more effective than placebo [74]. Thus, there is only a marginal evidence for a low-grade efficacy of PUFA against CD. The evidence seems to be similar or slightly better for PUFA efficacy against UC (Table 2). Of interest is a small random double-blind placebo crossover study where patients on prednisone or sulfasalazine reported significant improvement with PUFA [76]. Another random double-blind placebo crossover study showed that PUFA improved the oxidative stress status in active UC patients receiving sulfasalazine [77]. Another small study showed that PUFA have some efficacy against UC, but it is less than that of sulfasalazine [78]. Thus, the efficacy of PUFA or fish oil against CD or UC is, at best, marginal; however, none of the studies reported any adverse effects of PUFA supplementation.

Chinese and Ayurvedic Medicines

Léi gōng téng *(Tripterygium wilfordii)*, which is rich in antioxidant polyglycosides, has been tested for its efficacy against CD (Table 3). The trials were random (some of them blind) with very small to medium sample sizes over a period of 1 year. Léi gōng téng performed better than azathioprine, mesalamine, and sulfasalazine [79–82]. It is cautioned that Léi gōng téng has male antifertility properties and this side effect is not monitored in these studies.

The remaining Chinese and Ayurvedic medicines reported in Table 3 contain multiple herb blends. There were 2 studies [83, 84] on UC in which the herbal medicines were significantly efficacious. The first was a study [83] on ulcerative proctitis patients using an enema of the multiherb drug xilei san. In this random double-blind placebo controlled trial, xilei san (Chinese medicine) showed improvement within 14 days, and after 6 months the remission rate was 81.8% with xilei san versus only 16.7% with the placebo. There was an overall improvement based on several parameters measured. The second was an open study [84] that used an Ayurvedic medicine containing the herbs *Aegle marmelos* Correa plus *Bacopa monnieri* plus a *Ficus glomerata* enema. In this study the patients were allowed to continue with steroids or sulfasalazine as needed. In 4 weeks, the patients showed significant improvement in their symptoms and stopped taking the other drugs. However, the sample sizes in both the studies were small and longer-term assessment is also needed. There are several other studies shown in Table 3 in which marginal or no benefits of the multiherbal preparations were observed on IBS or UC [131–138]. Thus, the multiple herbs were a mixture and even when they worked the active principles in them were not identified.

Critical Appraisal and Synopsis

The results reported on the effects of antioxidant supplements in GI diseases in Tables 1–3 are very heterogeneous. There may be many reasons for this. First, the definitions of different GI diseases overlap and possibly so do the diagnosis, etiology, and pathophysiology. The consequence is that different researchers have used a variety of indices to monitor the efficacies of the antioxidants. Some of the methods were quite subjective. Also, a lack of uniformity in the studies in following the Cochrane criteria for clinical trials added to the confusion. This led to assigning the ++, +, ±, and – ratings for the efficacies and separate star ratings for the rigor and quality of each study so that the reader may choose which substances they should explore more thoroughly. The reader is further cautioned that most studies did not comment on the quality of the antioxidant substances being used. These might vary with the subspecies used, suppliers, age of the products, and how the extracts were prepared.

Combined therapy of current treatments with allopurinol (that may decrease the generation of superoxide) has proved useful for CD and UC patients. Curcumin may also have provided a benefit for UC patients in combined therapy with mesalamine. Other substances for which benefits against CD might be *Boswellia* (frankincense or shallaki), *Artemesia* sp. (wormwood), *T. wilfordii* (Léi gōng téng), and fish oil, and for UC such antioxidants might be allopurinol, *M. chamomilla* (chamomile), and fish oil. Some studies showed benefits of multiherbal Chinese and Ayurvedic medicines in UC but the studies were not replicated in large clinical trials. For IBS patients, a number of substances that have small benefits and no adverse effects are listed in Tables 1 and 3.

Recommendations

Based on these findings, 3 levels of recommendations have been made. The first recommendation is that allopurinol and possibly curcumin should be used for combined therapy in IBD patients with the current treatments using mesalamine, azathioprine, sulfasalazine, and steroids. Secondly the combined therapy trials should be considered using the current treatments and the following antioxidants: *Boswellia*, *Artemesia*, *T. wilfordii*, fish oil, and chamomile. Studies on more promising antioxidants should be replicated that include Chinese and Ayurvedic medicine-based antioxidants. The third recommendation is that there was insufficient evidence for the benefits of several antioxidants against IBS, but these did not have any adverse effects.

References

1 Chial HJ, Camilleri M: Gender differences in irritable bowel syndrome. J Gend Specif Med 2002;5:37–45.

2 Molodecky NA, Soon IS, Rabi DM, et al: Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012; 142:46–54.

3 Loftus EV Jr: Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology 2004;126:1504–1517.

4 Lunney PC, Kariyawasam VC, Wang RR, et al: Smoking prevalence and its influence on disease course and surgery in Crohn's disease and ulcerative colitis. Aliment Pharmacol Ther 2015;42:61–70.

5 Kamiya T: The overlap in the genetic pathogenesis of ulcerative colitis and irritable bowel syndrome. Dig Dis Sci 2013;58:3379–3381.

6 Miron N, Cristea V: Enterocytes: active cells in tolerance to food and microbial antigens in the gut. Clin Exp Immunol 2012;167:405–412.

7 Birchenough GM, Johansson ME, Gustafsson JK, et al: New developments in goblet cell mucus secretion and function. Mucosal Immunol 2015;8:712–719.

8 Clevers HC, Bevins CL: Paneth cells: maestros of the small intestinal crypts. Annu Rev Physiol 2013;75:289–311.

9 Circu ML, Aw TY: Redox biology of the intestine. Free Radic Res 2011;45:1245–1266.

10 Hrncirova L, Krejsek J, Splichal I, et al: Crohn's disease: a role of gut microbiota and Nod2 gene polymorphisms in disease pathogenesis. Acta Medica (Hradec Kralove) 2014; 57:89–96.

11 Emerit J, Pelletier S, Tosoni-Verligue D, et al: Phase II trial of copper zinc superoxide dismutase (CuZnSOD) in treatment of Crohn's disease. Free Radic Biol Med 1989;7:145–149.

12 Desai D, Shah S, Deshmukh A, et al: Colorectal cancers in ulcerative colitis from a low-prevalence area for colon cancer. World J Gastroenterol 2015;21:3644–3649.

13 Barrett JC, Lee JC, Lees CW, et al: Genome-wide association study of ulcerative colitis identifies three new susceptibility loci, including the HNF4A region. Nat Genet 2009;41: 1330–1334.

14 Serban DE: Microbiota in inflammatory bowel disease pathogenesis and therapy: is it all about diet? Nutr Clin Pract 2015;30:760–779.

15 Rokkas T, Gisbert JP, Niv Y, et al: The association between *Helicobacter pylori* infection and inflammatory bowel disease based on meta-analysis. United European Gastroenterol J 2015;3:539–550.

16 Dore MP, Goni E, Di Mario F: Is there a role for probiotics in *Helicobacter pylori* therapy? Gastroenterol Clin North Am 2015;44:565–575.

17 Giorgetti G, Brandimarte G, Fabiocchi F, et al: Interactions between innate immunity, microbiota, and probiotics. J Immunol Res 2015; 2015:501361.

18 Pandey V, Berwal V, Solanki N, et al: Probiotics: healthy bugs and nourishing elements of diet. J Int Soc Prev Community Dent 2015;5: 81–87.

19 Lazaraki G, Chatzimavroudis G, Katsinelos P: Recent advances in pharmacological treatment of irritable bowel syndrome. World J Gastroenterol 2014;20:8867–8885.

20 Ellinghaus D, Bethune J, Petersen BS, et al: The genetics of Crohn's disease and ulcerative colitis – status quo and beyond. Scand J Gastroenterol 2015;50:13–23.

21 Elmgreen J, Both H, Binder V: Familial occurrence of complement dysfunction in Crohn's disease: correlation with intestinal symptoms and hypercatabolism of complement. Gut 1985;26:151–157.

22 Sanford P: Crohn's disease or ulcerative colitis? Check your patient's symptoms. Gastroenterol Nurs 1990;12:204.

23 Brookes MJ, Green JR: Maintenance of remission in Crohn's disease: current and emerging therapeutic options. Drugs 2004;64:1069–1089.

24 Burger M, Schmidt C, Teich N, et al: Medical therapy of active ulcerative colitis. Viszeralmedizin 2015;31:236–245.

25 Vermeire S: Oral SMAD7 antisense drug for Crohn's disease. N Engl J Med 2015;372: 1166–1167.

26 Monteleone G, Pallone F: Mongersen, an oral SMAD7 antisense oligonucleotide, and Crohn's disease. N Engl J Med 2015;372:2461.

27 Halliwell B: The chemistry of free radicals. Toxicol Ind Health 1993;9:1–21.

28 Fridovich I: Oxygen: how do we stand it? Med Princ Pract 2013;22:131–137.

29 Liochev SI: Free radicals: how do we stand them? Anaerobic and aerobic free radical (chain) reactions involved in the use of fluorogenic probes and in biological systems. Med Princ Pract 2014;23:195–203.

30 Walia M, Kwan CY, Grover AK: Effects of free radicals on coronary artery. Med Princ Pract 2003;12:1–9.

31 Couto N, Wood J, Barber J: The role of glutathione reductase and related enzymes on cellular redox homoeostasis network. Free Radic Biol Med 2016;95:27–42.

32 Forman HJ, Davies KJ, Ursini F: How do nutritional antioxidants really work: nucleophilic tone and para-hormesis versus free radical scavenging in vivo. Free Radic Biol Med 2014; 66:24–35.

33 Nkabyo YS, Ziegler TR, Gu LH, et al: Glutathione and thioredoxin redox during differentiation in human colon epithelial (Caco-2) cells. Am J Physiol Gastrointest Liver Physiol 2002;283:G1352–G1359.

34 Balmus IM, Ciobica A, Trifan A, et al: The implications of oxidative stress and antioxidant therapies in inflammatory bowel disease: clinical aspects and animal models. Saudi J Gastroenterol 2016;22:3–17.

35 Piechota-Polanczyk A, Fichna J: Review article: the role of oxidative stress in pathogenesis and treatment of inflammatory bowel diseases. Naunyn Schmiedebergs Arch Pharmacol 2014;387:605–620.

36 Boyanapalli SS, Paredes-Gonzalez X, Fuentes F, et al: Nrf2 knockout attenuates the anti-inflammatory effects of phenethyl isothiocyanate and curcumin. Chem Res Toxicol 2014; 27:2036–2043.

37 Soetikno V, Sari FR, Lakshmanan AP, et al: Curcumin alleviates oxidative stress, inflammation, and renal fibrosis in remnant kidney through the Nrf2-keap1 pathway. Mol Nutr Food Res 2013;57:1649–1659.

38 Ding Y, Chen M, Wang M, et al: Neuroprotection by acetyl-11-keto-β-boswellic acid, in ischemic brain injury involves the Nrf2/HO-1 defense pathway. Sci Rep 2014;4:7002.

39 Fetoni AR, Paciello F, Rolesi R, et al: Rosmarinic acid up-regulates the noise-activated Nrf2/HO-1 pathway and protects against noise-induced injury in rat cochlea. Free Radic Biol Med 2015;85:269–281.

40 Howitz KT, Sinclair DA: Xenohormesis: sensing the chemical cues of other species. Cell 2008;133:387–391.

41 Masri OA, Chalhoub JM, Sharara AI: Role of vitamins in gastrointestinal diseases. World J Gastroenterol 2015;21:5191–5209.

42 Lan A, Blachier F, Benamouzig R, et al: Mucosal healing in inflammatory bowel diseases: is there a place for nutritional supplementation? Inflamm Bowel Dis 2015;21:198–207.

43 Bi L, Triadafilopoulos G: Exercise and gastrointestinal function and disease: an evidence-based review of risks and benefits. Clin Gastroenterol Hepatol 2003;1:345–355.

44 Curkovic I, Rentsch KM, Frei P, et al: Low allopurinol doses are sufficient to optimize azathioprine therapy in inflammatory bowel disease patients with inadequate thiopurine metabolite concentrations. Eur J Clin Pharmacol 2013;69:1521–1531.

45 Hoentjen F, Seinen ML, Hanauer SB, et al: Safety and effectiveness of long-term allopurinol-thiopurine maintenance treatment in inflammatory bowel disease. Inflamm Bowel Dis 2013;19:363–369.

46 Seinen ML, de Boer NK, Smid K, et al: Allopurinol enhances the activity of hypoxanthine-guanine phosphoribosyltransferase in inflammatory bowel disease patients during low-dose thiopurine therapy: preliminary data of an ongoing series. Nucleosides Nucleotides Nucleic Acids 2011;30:1085–1090.

47 Salim AS: Role of oxygen-derived free radical scavengers in the management of recurrent attacks of ulcerative colitis: a new approach. J Lab Clin Med 1992;119:710–717.

48 Jarnerot G, Strom M, Danielsson A, et al: Allopurinol in addition to 5-aminosalicylic acid based drugs for the maintenance treatment of ulcerative colitis. Aliment Pharmacol Ther 2000;14:1159–1162.

49 Gerhardt H, Seifert F, Buvari P, et al: Therapy of active Crohn disease with Boswellia serrata extract H 15 (in German). Z Gastroenterol 2001;39:11–17.

50 Gupta PK, Samarakoon SM, Chandola HM, Ravishankar B: Clinical evaluation of Boswellia serrata (Shallaki) resin in the management of Sandhivata (osteoarthritis). Ayu 2011;32: 478–482.

51 Miller JM, Goodell HB: Frankincense and myrrh. Surg Gynecol Obstet 1968;127:360–365.

52 Madisch A, Miehlke S, Eichele O, et al: Boswellia serrata extract for the treatment of collagenous colitis. A double-blind, randomized, placebo-controlled, multicenter trial. Int J Colorectal Dis 2007;22:1445–1451.

53 Slonim AE, Grovit M, Bulone L: Effect of exclusion diet with nutraceutical therapy in juvenile Crohn's disease. J Am Coll Nutr 2009; 28:277–285.

54 Gupta I, Parihar A, Malhotra P, et al: Effects of gum resin of Boswellia serrata in patients with chronic colitis. Planta Med 2001;67:391–395.

55 Bundy R, Walker AF, Middleton RW, et al: Turmeric extract may improve irritable bowel syndrome symptomology in otherwise healthy adults: a pilot study. J Altern Complement Med 2004;10:1015–1018.

56 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.

57 Singla V, Pratap M, 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.

58 Holt PR, Katz S, Kirshoff R: Curcumin therapy in inflammatory bowel disease: a pilot study. Dig Dis Sci 2005;50:2191–2193.

59 Suskind DL, Wahbeh G, Burpee T, et al: Tolerability of curcumin in pediatric inflammatory bowel disease: a forced-dose titration study. J Pediatr Gastroenterol Nutr 2013;56: 277–279.

60 Srivastava JK, Shankar E, Gupta S: Chamomile: a herbal medicine of the past with bright future. Mol Med Rep 2010;3:895–901.

61 Langhorst J, Frede A, Knott M, et al: Distinct kinetics in the frequency of peripheral CD4+ T cells in patients with ulcerative colitis experiencing a flare during treatment with mesalazine or with a herbal preparation of myrrh, chamomile, and coffee charcoal. PLoS One 2014;9:e104257.

62 Langhorst J, Varnhagen I, Schneider SB, et al: Randomised clinical trial: a herbal preparation of myrrh, chamomile and coffee charcoal compared with mesalazine in maintaining remission in ulcerative colitis – a double-blind, double-dummy study. Aliment Pharmacol Ther 2013;38:490–500.

63 Altunkaya, A, Yýldýrým, B, Ekici K, et al: Determining essential oil composition, antibacterial and antioxidant activity of water wormwood extracts. GIDA 2014;39:17–24.

64 Omer B, Krebs S, Omer H, et al: Steroid-sparing effect of wormwood (Artemisia absinthium) in Crohn's disease: a double-blind placebo-controlled study. Phytomedicine 2007;14: 87–95.

65 Krebs S, Omer TN, Omer B: Wormwood (Artemisia absinthium) suppresses tumour necrosis factor alpha and accelerates healing in patients with Crohn's disease – a controlled clinical trial. Phytomedicine 2010;17:305–309.

66 Riachi LG, De Maria CA: Peppermint antioxidants revisited. Food Chem 2015;176:72–81.

67 Liu JH, Chen GH, Yeh HZ, et al: Enteric-coated peppermint-oil capsules in the treatment of irritable bowel syndrome: a prospective, randomized trial. J Gastroenterol 1997;32: 765–768.

68 Rees WD, Evans BK, Rhodes J: Treating irritable bowel syndrome with peppermint oil. Br Med J 1979;2:835–836.

69 Alam MS, Roy PK, Miah AR, et al: Efficacy of peppermint oil in diarrhea predominant. Mymensingh Med J 2013;22:27–30.

70 Cappello G, Spezzaferro M, Grossi L, et al: Peppermint oil (Mintoil) in the treatment of irritable bowel syndrome: a prospective double blind placebo-controlled randomized trial. Dig Liver Dis 2007;39:530–536.

71 Cash BD, Epstein MS, Shah SM: A novel delivery system of peppermint oil is an effective therapy for irritable bowel syndrome symptoms. Dig Dis Sci 2016;61:560–571.

72 Merat S, Khalili S, Mostajabi P, et al: The effect of enteric-coated, delayed-release peppermint oil on irritable bowel syndrome. Dig Dis Sci 2010;55:1385–1390.

73 Romano C, Cucchiara S, Barabino A, et al: Usefulness of omega-3 fatty acid supplementation in addition to mesalazine in maintaining remission in pediatric Crohn's disease: a double-blind, randomized, placebo-controlled study. World J Gastroenterol 2005;11: 7118–7121.

74 Belluzzi A, Brignola C, Campieri M, et al: Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. N Engl J Med 1996;334:1557–1560.

75 Feagan BG, Sandborn WJ, Mittmann U, et al: Omega-3 free fatty acids for the maintenance of remission in Crohn disease: the EPIC Randomized Controlled Trials. JAMA 2008;299: 1690–1697.

76 Stenson WF, Cort D, Rodgers J, et al: Dietary supplementation with fish oil in ulcerative colitis. Ann Intern Med 1992;116:609–614.

77 Barbosa DS, Cecchini R, El Kadri MZ, et al: Decreased oxidative stress in patients with ulcerative colitis supplemented with fish oil omega-3 fatty acids. Nutrition 2003;19:837–842.

78 Dichi I, Frenhane P, Dichi JB, et al: Comparison of omega-3 fatty acids and sulfasalazine in ulcerative colitis. Nutrition 2000;16:87–90.

79 Ren J, Wu X, Liao N, et al: Prevention of postoperative recurrence of Crohn's disease: Tripterygium wilfordii polyglycoside versus mesalazine. J Int Med Res 2013;41:176–187.

80 Tao QS, Ren JA, Ji ZL, et al: Maintenance effect of polyglycosides of Tripterygium wilfordii on remission in postoperative Crohn disease (in Chinese). Zhonghua Wei Chang Wai Ke Za Zhi 2009;12:491–493.

81 Liao NS, Ren JA, Fan CG, et al: Efficacy of polyglycosides of Tripterygium wilfordii in preventing postoperative recurrence of Crohn disease (in Chinese). Zhonghua Wei Chang Wai Ke Za Zhi 2009;12:167–169.

82 Zhu W, Li Y, Gong J, et al: *Tripterygium wilfordii* Hook. f. versus azathioprine for prevention of postoperative recurrence in patients with Crohn's disease: a randomized clinical trial. Dig Liver Dis 2015;47:14–19.

83 Fukunaga K, Ohda Y, Hida N, et al: Placebo controlled evaluation of Xilei San, a herbal preparation in patients with intractable ulcerative proctitis. J Gastroenterol Hepatol 2012; 27:1808–1815.

84 Patel KB, Patel M, Mehta CS, et al: Ayurvedic management of ulcerative colitis – a non-randomized observational clinical study. Forsch Komplementmed 2013;20:144–147.

85 Joelsson M, Andersson M, Bark T, et al: Allopurinol as prophylaxis against pouchitis following ileal pouch-anal anastomosis for ulcerative colitis. A randomized placebo-controlled double-blind study. Scand J Gastroenterol 2001;36:1179–1184.

86 Davis K, Philpott S, Kumar D, et al: Randomised double-blind placebo-controlled trial of aloe vera for irritable bowel syndrome. Int J Clin Pract 2006;60:1080–1086.

87 Hutchings HA, Wareham K, Baxter JN, et al: A randomised, cross-over, placebo-controlled study of *Aloe vera* in patients with irritable bowel syndrome: effects on patient quality of life. ISRN Gastroenterol 2011;2011: 206103.

88 Khedmat H, Karbasi A, Amini M, et al: *Aloe vera* in treatment of refractory irritable bowel syndrome: trial on Iranian patients. J Res Med Sci 2013;18:732.

89 Langmead L, Feakins RM, Goldthorpe S, et: Randomized, double-blind, placebo-controlled trial of oral aloe vera gel for active ulcerative colitis. Aliment Pharmacol Ther 2004;19:739–747.

90 Tang T, Targan SR, Li ZS, et al: Randomised clinical trial: herbal extract HMPL-004 in active ulcerative colitis – a double-blind comparison with sustained release mesalazine. Aliment Pharmacol Ther 2011;33:194–202.

91 Sandborn WJ, Targan SR, Byers VS, et al: Andrographis paniculata extract (HMPL-004) for active ulcerative colitis. Am J Gastroenterol 2013;108:90–98.

92 Hawrelak JA, Myers SP: Effects of two natural medicine formulations on irritable bowel syndrome symptoms: a pilot study. J Altern Complement Med 2010;16:1065–1071.

93 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.

94 Holtmeier W, Zeuzem S, Preiss J, et al: Randomized, placebo-controlled, double-blind trial of *Boswellia serrata* in maintaining remission of Crohn's disease: good safety profile but lack of efficacy. Inflamm Bowel Dis 2011;17:573–582.

95 Bortolotti M, Porta S: Effect of red pepper on symptoms of irritable bowel syndrome: preliminary study. Dig Dis Sci 2011;56:3288–3295.

96 Schmulson MJ, Valdovinos MA, et al: Chili pepper and rectal hyperalgesia in irritable bowel syndrome. Am J Gastroenterol 2003; 98:1214–1215.

97 Bortolotti M, Coccia G, Grossi G, et al: The treatment of functional dyspepsia with red pepper. Aliment Pharmacol Ther 2002;16: 1075–1082.

98 Baraniuk JN, El Amin S, Corey R, et al: Carnosine treatment for Gulf War illness: a randomized controlled trial. Glob J Health Sci 2013;5:69–81.

99 Erichsen K, Ulvik RJ, Nysaeter G, et al: Oral ferrous fumarate or intravenous iron sucrose for patients with inflammatory bowel disease. Scand J Gastroenterol 2005; 40:1058–1065.

100 Dryden GW, Lam A, Beatty K, et al: 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.

101 Chang CC, Lin YT, Lu YT, et al: Kiwifruit improves bowel function in patients with irritable bowel syndrome with constipation. Asia Pac J Clin Nutr 2010;19:451–457.

102 Kaliora AC, Stathopoulou MG, Triantafillidis JK, et al: Chios mastic treatment of patients with active Crohn's disease. World J Gastroenterol 2007;13:748–753.

103 Guijarro LG, Mate J, Gisbert JP, et al: N-acetyl-L-cysteine combined with mesalamine in the treatment of ulcerative colitis: randomized, placebo-controlled pilot study. World J Gastroenterol 2008;14:2851–2857.

104 Bauditz J, Haemling J, Ortner M, et al: Treatment with tumour necrosis factor inhibitor oxpentifylline does not improve corticosteroid dependent chronic active Crohn's disease. Gut 1997;40:470–474.

105 Kline RM, Kline JJ, Di Palma J, et al: Enteric-coated, pH-dependent peppermint oil capsules for the treatment of irritable bowel syndrome in children. J Pediatr 2001;138: 125–128.

106 Kamali M, Tavakoli H, Khodadoost M, et al: Efficacy of the *Punica granatum* peels aqueous extract for symptom management in ulcerative colitis patients. A randomized, placebo-controlled, clinical trial. Complement Ther Clin Pract 2015;21:141–146.

107 Tomas-Ridocci M, Anon R, Minguez M, et al: The efficacy of *Plantago ovata* as a regulator of intestinal transit. A double-blind study compared to placebo (in Spanish). Rev Esp Enferm Dig 1992;82:17–22.

108 Fernandez-Banares F, Hinojosa J, Sanchez-Lombrana JL, et al: Randomized clinical trial of *Plantago ovata* seeds (dietary fiber) as compared with mesalamine in maintaining remission in ulcerative colitis. Spanish Group for the Study of Crohn's Disease and Ulcerative Colitis (GETECCU). Am J Gastroenterol 1999;94:427–433.

109 Kolacek M, Muchova J, Dvorakova M, et al: Effect of natural polyphenols (Pycnogenol) on oxidative stress markers in children suffering from Crohn's disease – a pilot study. Free Radic Res 2013;47:624–634.

110 Samsami-Kor M, Daryani NE, Asl PR, et al: Anti-inflammatory effects of resveratrol in patients with ulcerative colitis: a randomized, double-blind, placebo-controlled pilot study. Arch Med Res 2015;46:280–285.

111 Emerit J, Pelletier S, Likforman J, et al: Phase II trial of copper zinc superoxide dismutase (CuZn SOD) in the treatment of Crohn's disease. Free Radic Res Commun 1991;12–13:563–569.

112 Huber R, Ditfurth AV, Amann F, et al: Tormentil for active ulcerative colitis: an open-label, dose-escalating study. J Clin Gastroenterol 2007;41:834–838.

113 Lehmann M, Walther M, Ulitzsch S, Thomas A, Hauser W, Stallmach A: Validation and first results of the German QUOTE-IBD to measure quality of care from the perspective of patients with inflammatory bowel disease (in German). Z Gastroenterol 2013;51:196–203.

114 Lahiff C, Safaie P, Awais A, et al: The Crohn's disease activity index (CDAI) is similarly elevated in patients with Crohn's disease and in patients with irritable bowel syndrome. Aliment Pharmacol Ther 2013;37:786–794.

115 Mary JY, Modigliani R: Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). Gut 1989;30:983–989.

116 Francis CY, Morris J, Whorwell PJ: The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. Aliment Pharmacol Ther 1997;11:395–402.

117 Walmsley RS, Ayres RC, Pounder RE, et al: A simple clinical colitis activity index. Gut 1998;43:29–32.

118 Tursi A, Brandimarte G, Papa A, et al: Treatment of relapsing mild-to-moderate ulcerative colitis with the probiotic VSL#3 as adjunctive to a standard pharmaceutical treatment: a double-blind, randomized, placebo-controlled study. Am J Gastroenterol 2010;105:2218–2227.

119 Lorenz-Meyer H, Bauer P, Nicolay C, et al: Omega-3 fatty acids and low carbohydrate diet for maintenance of remission in Crohn's disease. A randomized controlled multicenter trial. Study Group Members (German Crohn's Disease Study Group). Scand J Gastroenterol 1996;31:778–785.

120 Nielsen AA, Nielsen JN, Gronbaek H, et al: Impact of enteral supplements enriched with omega-3 fatty acids and/or omega-6 fatty acids, arginine and ribonucleic acid compounds on leptin levels and nutritional status in active Crohn's disease treated with prednisolone. Digestion 2007;75:10–16.

121 Geerling BJ, Badart-Smook A, van Deursen C, et al: Nutritional supplementation with n-3 fatty acids and antioxidants in patients with Crohn's disease in remission: effects on antioxidant status and fatty acid profile. Inflamm Bowel Dis 2000;6:77–84.

122 Nielsen AA, Jorgensen LG, Nielsen JN, et al: Omega-3 fatty acids inhibit an increase of proinflammatory cytokines in patients with active Crohn's disease compared with omega-6 fatty acids. Aliment Pharmacol Ther 2005;22:1121–1128.

123 Eivindson M, Gronbaek H, Nielsen JN, et al: Insulin-like growth factors (IGFs) and IGF binding proteins in active Crohn's disease treated with omega-3 or omega-6 fatty acids and corticosteroids. Scand J Gastroenterol 2005;40:1214–1221.

124 Brunborg LA, Madland TM, Lind RA, et al: Effects of short-term oral administration of dietary marine oils in patients with inflammatory bowel disease and joint pain: a pilot study comparing seal oil and cod liver oil. Clin Nutr 2008;27:614–622.

125 Bjorkkjaer T, Brunborg LA, Arslan G, et al: Reduced joint pain after short-term duodenal administration of seal oil in patients with inflammatory bowel disease: comparison with soy oil. Scand J Gastroenterol 2004;39: 1088–1094.

126 Almallah YZ, Richardson S, O'Hanrahan T, et al: Distal procto-colitis, natural cytotoxicity, and essential fatty acids. Am J Gastroenterol 1998;93:804–809.

127 Almallah YZ, El Tahir A, Heys SD, et al: Distal procto-colitis and n-3 polyunsaturated fatty acids: the mechanism(s) of natural cytotoxicity inhibition. Eur J Clin Invest 2000; 30:58–65.

128 Almallah YZ, Ewen SW, El Tahir A, et al: Distal proctocolitis and n-3 polyunsaturated fatty acids (n-3 PUFAs): the mucosal effect in situ. J Clin Immunol 2000;20:68–76.

129 Seidner DL, Lashner BA, Brzezinski A, et al: An oral supplement enriched with fish oil, soluble fiber, and antioxidants for corticosteroid sparing in ulcerative colitis: a randomized, controlled trial. Clin Gastroenterol Hepatol 2005;3:358–369.

130 Salomon P, Kornbluth AA, Janowitz HD: Treatment of ulcerative colitis with fish oil n–3-omega-fatty acid: an open trial. J Clin Gastroenterol 1990;12:157–161.

131 Bensoussan A, Talley NJ, Hing M, et al: Treatment of irritable bowel syndrome with Chinese herbal medicine: a randomized controlled trial. JAMA 1998;280:1585–1589.

132 Bensoussan A, Kellow JE, Bourchier SJ, et al: Efficacy of a Chinese herbal medicine in providing adequate relief of constipation-predominant irritable bowel syndrome: a randomized controlled trial. Clin Gastroenterol Hepatol 2015;13:1946–1954.

133 Liang ZF, Chen RH, Xu YS, et al: Tiaohe Ganpi Hexin Decoction in treatment of irritable bowel syndrome with diarrhea: a randomized controlled trial (in Chinese). Zhong Xi Yi Jie He Xue Bao 2009;7:819–822.

134 Gao WY, Lin YF, Chen SQ, et al: Effects of Changjishu soft elastic capsule in treatment of diarrhea-predominant irritable bowel patients with liver-qi stagnation and spleen deficiency syndrome: a randomized double-blinded controlled trial (in Chinese). Zhong Xi Yi Jie He Xue Bao 2009;7:212–217.

135 Leung WK, Wu JC, Liang SM, et al: Treatment of diarrhea-predominant irritable bowel syndrome with traditional Chinese herbal medicine: a randomized placebo-controlled trial. Am J Gastroenterol 2006; 101:1574–1580.

136 Xie ZH, Wang TJ, Zheng YX, et al: Shuxuening injection combined with routine therapy in treating patients with active ulcerative colitis: an analysis of efficacy (in Chinese). Zhongguo Zhong Xi Yi Jie He Za Zhi 2014; 34:1164–1167.

137 Tiwari R, Pandya DH, Baghel MS: Clinical evaluation of Bilvadileha in the management of irritable bowel syndrome. Ayu 2013;34: 368–372.

138 Yadav SK, Jain AK, Tripathi SN, et al: Irritable bowel syndrome: therapeutic evaluation of indigenous drugs. Indian J Med Res 1989;90:496–503.