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EDITORIAL

A review of the efficacy of traditional Iranian medicine for inflammatory bowel disease

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Abstract

The etiology of inflammatory bowel disease (IBD) is not yet known, but many factors such as defects in the immune system, oxidative stress, microbial content in the gastrointestinal tract, nuclear factor (NF)-κB, nitric oxide (NO), cyclooxygenase-2 (Cox-2), and leukotriene B4 (LB4) are thought to play a role in its pathogenesis. In traditional Iranian medicine (TIM), several medicinal plants are thought to be effective for the treatment of IBD. In this study, information on all of these remedies were derived from all available old sources such as documents or notes and books and were added to the information derived from modern medical databases covering all *in vitro*, *in vivo* and clinical trials. For some of these plants, only one or two mechanisms of action have been found such as in *Cassia fistula*, *Lepidium sativum*, and *Bunium persicum*. However, for some plants various mechanisms of action are known. For example, *Commiphora mukul* is effective in IBD due to its immunomodulatory, antioxidant, and antibacterial properties and it decreases NF-κB, NO and Cox-2. Another herb, *Plantago ovata*, has immunomodulatory, antioxidant, anti-inflammatory and wound healing activities and decreases NO and LB4. Considering the mechanisms of action of these plants, the combination of some of them may be useful because of their many mechanisms of action such as *Pistacia lentiscus*, *Bunium persicum*, *Solanum nigrum*, *Plantago ovata*, *Boswellia*, *Solanum nigrum*, *Plantago ovata* and *Commiphora mukul*. For some of the herbal products used in TIM such as oleogum resin from *Commiphora myrrha*, seeds of *Ocimum basilicum*, seeds of *Linum usitatissimum*, gum resin of *Dracaena cinnabari*, seeds of *Plantago major*, seeds of *Lallementia royleana*, and seeds of *Allium porrum*, there is no or not enough studies to confirm their benefits in IBD. It is suggested that an evaluation of the effects of these plants on different aspects of IBD should be performed.

Key words: Herbal medicine; Inflammatory bowel disease; Medicinal plants; Traditional Iranian medicine

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INTRODUCTION

Inflammatory bowel disease (IBD) refers to two chronic diseases that cause inflammation of the intestines: ulcer-

ative colitis (UC) and Crohn's disease (CD). The etiology of IBD is unclear. The most accepted hypothesis currently implicates a combination of one or more of the following factors: immune dysregulation (caused by genetic or environmental factors), abnormal gastrointestinal (GI) tract luminal factors (such as microorganisms constituting the GI tract flora), oxidative stress, and defects in the GI mucosal barrier that allow luminal factors to penetrate into the mucosa[1,2].

In our previous paper, we reviewed all medicinal plants used worldwide for the treatment of IBD[3] by including all *in vitro*, *in vivo*, and clinical studies that examined medicinal plants for the treatment of IBD. Added to that information, there is information and data that are only found in documents, notes, or books by traditional Iranian medicine (TIM) scientists. In TIM, there is a GI disease known as "Zahir" which seems to be identical to IBD regarding the explained symptoms of the disease. Zahir is defined as tenesmus of the rectum during defecation followed by secretion of mucosa and bloody diarrhea[4]. Various natural remedies have been used in TIM for IBD. These remedies have been used for many years by Iranian physicians such as Rhazes and Avicenna for the treatment of IBD in humans. Different mechanisms of action have been described in traditional Iranian publications accounting for the usefulness of these plants in IBD, which include anti-inflammatory, antiulcer, wound healing, and antidiarrheal activities[5,6]. In the present work, these remedies are revised individually and possible evidence of their efficacy in modern medicine is reviewed. For this purpose, electronic databases including Pubmed, Scopus, Embase, and Google Scholar were searched for each of the plants in TIM and all retrieved articles were examined to obtain studies giving any *in vitro*, *in vivo*, or clinical evidence of the efficacy of these herbs in the treatment of IBD. The retrieved studies directly evaluated these herbs on IBD animal models or humans, or indirectly surveyed their efficacy on the mechanisms involved in the pathogenesis of IBD.

FACTORS INVOLVED IN THE PATHOGENESIS OF IBD

Immune system

There is evidence of defective responses in both the innate and the adaptive immune systems in IBD[7]. The behavior of the cells mediating innate immunity such as neutrophils, macrophages, dendritic cells, and natural killer cells are altered, and defective mucosal T helper (Th) cell responses and greater expression of cytokines such as interleukin (IL)-1-β, IL-6, IL-12, tumor necrosis factor α (TNF-α) and interferon (IFN)-γ were demonstrated in patients with IBD[8,9]. Recent meta-analyses confirmed the efficacy of anti-TNF-α drugs for induction of remission in UC[10] but did not confirm them for induction of response and remission in CD[11].

Oxidative stress

Oxidative stress is a potential etiological and/or triggering factor for IBD, because the damaging effects of reactive oxygen molecules have been well established in the inflammation process[12-14]. Although some conflicting results exist, it seems that patients with IBD demonstrate excessive oxidized molecules compared with healthy control subjects in a variety of organic systems (e.g. GI tract, blood, and respiratory system)[12]. Recent studies have shown decreased total antioxidant capacity and increased reactive oxygen molecules in patients with IBD[13-15].

Microbes

Some studies have suggested a role for the microbial content of the GI tract in the pathogenesis of IBD[16]. The disease occurs in areas of the GI tract with the highest concentrations of luminal bacteria. Normal, nonpathogenic enteric bacteria can induce chronic intestinal inflammation in genetically susceptible hosts with defective immunoregulation, bacterial clearance, or mucosal barrier function. It has been shown that the concentration of intestinal bacteria in IBD is higher than normal and increases progressively with severity of the disease[17-19]. Probiotics have been found to be useful in the management of irritable bowel syndrome[20] and pouchitis[21]. Antibacterials and probiotics have been demonstrated to be effective in UC *via* modification of the gut bacterial flora[22,23]. However, current meta-analyses have only confirmed the efficacy of antibiotics for CD[24] and failed to demonstrate the efficacy of probiotics in maintaining remission and preventing clinical and endoscopic recurrence in CD[25].

Nuclear factor-κB

These proteins are a family of structurally related eukaryotic transcription factors that promote the expression of over 150 genes, many of which play important roles in the regulation of inflammation and apoptosis[26]. Excess or inappropriate activation of nuclear factor (NF)-κB has been observed in human IBD[27,28]. Thus, inhibitors of NF-κB can be used as a treatment strategy for the management of IBD.

Nitric oxide

Nitric oxide (NO) is a short-life molecule produced by the enzyme known as NO synthase (NOS), in a reaction that converts arginine and oxygen into citrulline and NO. There are three isoforms of the enzyme: neuronal NOS (nNOS), inducible NOS (iNOS), and endothelial NOS (eNOS). Interestingly, NO has both beneficial and detrimental roles in the body. It seems that constitutive forms of NO synthase (cNOS) including nNOS and eNOS are critical to normal physiology, while inhibition of these enzymes may cause cellular damage. On the other hand, induction of iNOS causes injury; therefore, specific inhibition of this enzyme can be beneficial. Three key observations confirm the detrimental role of iNOS in inflammation. Firstly, since large quantities of NO are produced by iNOS relative to the two cNOS isoforms, excess NO may contribute to inflammation through nitrosation,

Table 1 ***In vitro*** **studies on plants used in traditional Iranian medicine for the treatment of inflammatory bowel disease**

Study	Plant	Part	Results
Watt *et al*[39]	*Althaea officinalis*	Whole plant ethanol extract	Antibacterial activity against *E. coli*
Yoshikawa *et al*[40]	*Boswellia carterii*	Mono- and triterpenes isolated from this oleogum resin	↓NO production in lipopolysaccharide-activated mouse peritoneal macrophages
Chevrier *et al*[41]	*Boswellia carterii*	Ethanol extract of oleogum resin	Immunomodulatory properties
Camarda *et al*[42]	*Boswellia carterii*	Essential oil isolated from oleogum resin	Antimicrobial activities against various microorganisms including fungi, Gram-positive and Gram-negative bacterial strains
Moghtader *et al*[43]	*Bunium persicum*	Essential oil of seed	Strong anti-bacterial effects
Shahsavari *et al*[44]	*Bunium persicum*	Essential oil of seed	Antioxidant properties
Kumar *et al*[45]	*Cassia fistula*	Crude extract of fruit	Significant antimicrobial activity
Francis *et al*[46]	*Commiphora mukul*	Terpenoids and guggulusteroids	↓Lipid peroxidation and Cox inhibitory activities
Manjula *et al*[47]	*Commiphora mukul*	Crude extract of gum resin	↓Proliferative response of peripheral blood mononuclear cells,
Matsuda *et al*[48]	*Commiphora mukul*	Methanolic extract of gum resin	↓inflammatory mediators such as IFN-δ, IL-12, TNF-α, IL-1β and NO, ↓NO production in lipopolysaccharide-activated mouse peritoneal macrophages
Saeed *et al*[49]	*Commiphora mukul*	The essential oil, chloroform extract and seven sesquiterpenoids compounds of oleogum resin	Wide range of inhibitory activity against both Gram positive and Gram negative bacteria
Fattouch *et al*[50]	*Cydonia oblonga*	Pulp and peel polyphenolic extract	Radical scavenging and antimicrobial activities
Silva *et al*[51]	*Cydonia oblonga*	Pulp and peel methanolic extract	Antioxidant activity
Hamauzu *et al*[52]	*Cydonia oblonga*	Pulp and peel phenolic extract	Superior antioxidant functions to that of chlorogenic acid and ascorbic acid as standard antioxidants
Kaur *et al*[53]	*Foeniculum vulgare*	Aqueous and organic seed extracts	Antibacterial activity comparable to standard antibiotics
De Marino *et al*[54]	*Foeniculum vulgare*	n-butanol and aqueous extract of fruit	Moderate antioxidant activity
Baliga *et al*[55]	*Foeniculum vulgare*	Aqueous extract	↓NO
Fukuda *et al*[56]	*Juglans regia*	Polyphenols	↓Lipid peroxidation, ↑antioxidant activity
Zhou *et al*[57]	*Pistacia lentiscus*	Oleogum resin	↓Pro-inflammatory substances such as NO and prostaglandin E2, ↓expression of iNOS and Cox-2 at both protein and mRNA levels, potent hydroxyl radical scavenging activity
Westerhof *et al*[58]	*Plantago ovata*	Mucopolysaccharides of seed	Wound cleansing and healing properties, limits scarring
Al-Fatimi *et al*[59]	*Solanum nigrum*	Methanolic extract of fruit	Free radical scavenging activities in the DPPH assay
Heo *et al*[60]	*Solanum nigrum*	A glycoprotein (SNL glycoprotein) isolated from fruit	Scavenging effects on both superoxide anion and hydroxyl radical
Aquil *et al*[61]	*Terminalia chebula*	Ethanolic extract of fruit	Broad-spectrum antibacterial activity, synergistic interaction with tetracycline, chloramphenicol and ciprofloxacin against *S. aureus* and/or *E. coli*
Kim *et al*[62]	*Terminalia chebula*	Butanol fraction of fruit	Profound growth-inhibitory activity against six intestinal bacteria especially Clostridium perfringens and *E. coli*
Moeslinger *et al*[63]	*Terminalia chebula*	Aqueous extract of fruit	↓Inducible nitric oxide synthesis

E. coli: *Escherichia coli*; NO: Nitric oxide; Cox: Cyclooxygenase; IFN: Interferon; IL: Interleukin; TNF-α: Tumor necrosis factor α; iNOS: Inducible nitric oxide synthase; mRNA: Messenger ribonucleic acid; DPPH: 1,1-diphenyl-2-picrylhydrazyl; SNL: *Solanum nigrum* L.; *S. aureus*: *Staphylococcus aureus*.

oxidative damage, and enhanced inflammatory cytokines. Secondly, expression patterns of iNOS correlate with prolonged inflammation. Thirdly, inhibition of iNOS results in reduced inflammation[29,30]. There is evidence that IBD is associated with an overproduction of NO by iNOS[31]. Increased luminal and salivary NO has also been detected in IBD patients[32,33]. It was shown that inhibition of iNOS blunted dextran sulfate sodium (DSS) colitis in mice[34].

Cyclooxygenase-2

Cyclooxygenase-2 (Cox-2) is another involved factor in IBD acting through synthesis of prostaglandins. Thus, selective Cox-2 inhibitors, such as celecoxib, are another class of drugs that have been claimed to be effective in IBD[35,36].

Leukotriene B4

Leukotriene B4 is a pro-inflammatory mediator with a role in several inflammatory diseases such as IBD. Inhibition of this mediator can reduce inflammation and ameliorate IBD[37].

MODERN EVIDENCE FOR THE EFFICACY OF MEDICINAL PLANTS IN TIM USED FOR THE TREATMENT OF IBD

Pistacia lentiscus

Oleogum resin from *Pistacia lentiscus* (*P. lentiscus*) known as "Mastaki" is an efficacious remedy for the treatment of IBD in TIM[38]. Supplementation with oleogum resin from *P. lentiscus* delayed the onset and progression of the disease and helped prevent weight loss in the DSS model of colitis (Tables 1[39-63] and 2[64-81]). In addition, oleogum resin inhibited the production of pro-inflammatory substances such as NO and prostaglandin E2. Western blotting and reverse transcription polymerase chain reaction (RT-PCR) analyses have shown that oleogum resin from *P. lentiscus*

Table 2 *In vivo* studies on plants used in traditional Iranian medicine for the treatment of inflammatory bowel disease

Study	Model	Species	Plant	Part	Results
Wang *et al*[64]	Carrageenan- or dextran- induced paw edema	Rat	*Althaea rosea*	Ethanolic extract of flower	Anti-inflammatory and analgesic effect
Fan *et al*[65]	Complete Freund's adjuvant-induced inflammation	Rat	*Boswellia carterii*	Gum resin extract	Lengthened paw withdrawal latency, ↓paw edema, ↓spinal Fos protein expression, no noticeable adverse effects observed
Banno *et al*[66]	TPA-induced inflammation	Mouse	*Boswellia carteri*	Compounds isolated from methanol extract of the resin	Marked anti-inflammatory activity
Kiela *et al*[67]	DSS- and TNBS-induced colitis	Mouse	*Boswellia serrata*	Gum resin extract	Ineffective in ameliorating colitis, ↑the basal and IL-1β-stimulated NF-κB activity in intestinal epithelial cells in vitro as well as reverse proliferative effects of IL-1β, hepatotoxicity effect with pronounced hepatomegaly and steatosis was observed
Mencarelli *et al*[68]	TNBS-induced colitis	Mouse	*Commiphora mukul*	Guggulsterone	↓Severity of disease and the fecal score and colon inflammation, ↓IL-2, IL-4 and IFN-γ as well as T cell proliferation
Cheon *et al*[69]	DSS-induced colitis	Mouse	*Commiphora mukul*	Guggulsterone	↓NF-κB signaling pathway, attenuates acute colitis
Birdane *et al*[70]	Ethanol-induced gastric lesions	Rat	*Foeniculum vulgare*	Aqueous extract	↓Gastric mucosal lesion, ↓lipid peroxidation, ↑antioxidant activity
Choi *et al*[71]	Carrageenan-induced paw edema, arachidonic acid-induced ear edema, formaldehyde-induced arthritis, DNFB-induced contact hypersensitivity reaction	Mouse	*Foeniculum vulgare*	Fruit methanolic extract	Anti-inflammatory and central analgesic effect, ↓lipid peroxidation, ↑antioxidant activity
Al-Yahya *et al*[72]	Carrageenan-induced paw edema	Rat	*Lepidium sativum*	Ethanolic extract of seed	Anti-inflammatory and analgesic activities, potentiate gastric ulcer induced by indomethacin
Kim *et al*[73]	DSS-induced colitis	Mouse	*Pistacia lentiscus*	Oleogum resin	Delayed the onset and progression of the disease, prevent weight loss
Al-Said *et al*[74]	Gastric mucosal damage induced by pyloric ligation, aspirin, phenylbutazone, and reserpine	Rat	*Pistacia lentiscus*	Oleogum resin	↓Intensity of gastric mucosal damage
Rodríguez-Cabezas *et al*[75]	TNBS-induced colitis	Rat	*Plantago ovata*	Seed	Ameliorated the development of colonic inflammation, ↓some of the pro-inflammatory mediators such as NO, leukotriene B4, and TNF-α; ↑production of short chain fatty acids, butyrate and propionate
Rodríguez-Cabezas *et al*[76]	TNBS-induced colitis	Rat	*Plantago ovata*	Seed	↓Colonic myeloperoxidase activity, restoration of colonic glutathione levels
Joo *et al*[77]	DSS-induced colitis	Mouse	*Solanum nigrum*	A glycoprotein (SNL glycoprotein) isolated from fruit	↓NO production, ↓free radical formation, suppressive effect on activities of NF-κB, regulates the expression of iNOS and Cox-2
Jainu *et al*[78]	Acetic acid-induced gastric ulcers	Rat	*Solanum nigrum*	Fruit extract	↓Gastric lesions induced by cold restraint stress (76.6%), indomethacin (73.8%), pyloric ligation (80.1%) and ethanol (70.6%) with equal or higher potency than omeprazole, ↓gastric secretory volume and acidity and pepsin secretion, ↑rate of healing of ulcers, ↓H(+)K(+)ATPase activity, ↓gastrin secretion
Akhtar *et al*[79]	Aspirin-induced gastric ulcers	Rat	*Solanum nigrum*	Powder from aerial parts and its methanolic extract	↓Ulcer index, ↓acid and pepsin secretions
Mahesh *et al*[80]	-	Rat	*Terminalia chebula*	Aqueous extract of fruit	Modulate oxidative stress and enhance antioxidant status in the liver and kidney
Bhattacharya *et al*[81]	-	Rat	*Terminalia chebula*	Ethanolic extract of fruit	↑Rate of healing of gastric lesion induced by indomethacin, ↓lipid peroxidation

TNBS: 2,4,6-Trinitrobenzene sulfonic acid; DNBS: 2,4-dinitrobenzene sulfonic acid; DSS: Dextran-sulfate sodium, TPA: 12-O-tetradecanoylphorbol-13-acetate; IL: Interleukin; NF-κB: Nuclear factor κB; IFN: Interferon; DNFB: 2,4-dinitrofluoro benzene; NO: Nitric oxide; TNF-α: Tumor necrosis factor α; iNOS: Inducible nitric oxide synthase; SNL: *Solanum nigrum* L.; Cox: Cyclooxygenase.

inhibited the expression of iNOS and Cox-2 at both the protein and mRNA levels. It has shown potent hydroxyl radical scavenging activity; however, it has scavenged NO and superoxide radicals very poorly (Table 1)[57]. Oleogum resin from *P. lentiscus* at an oral dose of 500 mg/kg produced a significant reduction in the intensity of gastric mucosal damage induced by pyloric ligation, aspirin, phenylbutazone, and reserpine in rats (Table 2)[74]. Treating CD

patients with oleogum resin from *P. lentiscus* resulted in the reduction of TNF-α secretion ($P = 0.028$). Macrophage migration inhibitory factor (MIF) release was significantly increased ($P = 0.026$) meaning that random migration and chemotaxis of monocytes/macrophages was inhibited. No significant changes were observed in IL-6, monocyte chemotactic protein-1 (MCP-1), and intracellular antioxidant glutathione (GSH) concentrations showing that oleogum resin from *P. lentiscus* acts as an immunomodulator on peripheral blood mononuclear cells (PBMCs) by a TNF-α inhibitory and a MIF stimulatory activity[82]. Another study performed on CD patients demonstrated a significant reduction in the CD activity index (CDAI) ($P = 0.05$) due to oleogum resin from *P. lentiscus* as compared to pretreatment values. Plasma IL-6 and C-reactive protein (CRP) were significantly decreased. Total antioxidant potential (TAP) was significantly increased ($P = 0.036$). No patient or control exhibited any side effects[83]. A double-blind clinical trial was carried out on patients with symptomatic and endoscopically proven duodenal ulcers, to compare therapeutic responses to oleogum resin from *P. lentiscus* and placebo over a period of 2 wk. The results from this study demonstrated symptomatic relief in 80% of patients treated with oleogum resin from *P. lentiscus* and in 50% patients treated with placebo. Endoscopically proved healing occurred in 70% of patients treated with oleogum resin from *P. lentiscus* and in 22% patients treated with placebo. The differences between the treatments were highly significant ($P < 0.01$). Oleogum resin from *P. lentiscus* was well tolerated and did not produce side effects. This study showed that oleogum resin from *P. lentiscus* has an ulcer healing effect (Table 3[82-88]).

Commiphora mukul

Gum resin from *Commiphora mukul* (*C. mukul*) known as "Moghl" is another natural product used in TIM for IBD[4,89]. Guggulsterone (GS), a steroid isolated from the gum resin of *C. mukul*, has been investigated in two models of intestinal inflammation induced in mice by trinitrobenzene sulfonic acid (TNBS) and oxazolone. The results showed that GS protects mice against the development of signs and symptoms of colon inflammation. GS effectively attenuated the severity of disease, the fecal score and colon inflammation as assessed by measuring the macroscopic and microscopic damage scores. *In vitro*, mechanistic studies carried out using CD4+ cells isolated from the intestinal lamina propria demonstrated that GS effectively regulates the function of effector T cells. The net biological effects resulting from exposure to GS includes attenuation of the generation of IL-2, IL-4 and IFN-γ as well as T cell proliferation (Table 1)[68]. GS blocked the NF-κB signaling pathway and attenuated DSS-induced acute murine colitis (Table 2)[69]. Several compounds in the gum resin from *C. mukul* have shown lipid peroxidation and Cox inhibitory activities[46]. The anti-inflammatory effect of *C. mukul* gum has been studied in PBMCs and showed an inhibitory effect on the proliferative response of PBMC. Further studies on inflammatory mediators such as IFN-γ, IL-12, TNF-α, IL-1β and NO showed down-regulation, whereas no inhibition was observed in the case of the anti-inflammatory cytokine IL-10[47]. The methanolic extract of the gum resin from *C. mukul* was found to inhibit NO production in lipopolysaccharide-activated mouse peritoneal macrophages[48]. The essential oil, chloroform extract, and seven sesquiterpenoid compounds isolated from the oleogum resin of *C. mukul* demonstrated a wide range of inhibitory activity against both gram positive and gram negative bacteria (Table 1)[49].

Foeniculum vulgare

The fruit of *Foeniculum vulgare* (*F. vulgare*) known as "Razianeh" in TIM has been used for the treatment of IBD[87]. The aqueous and organic seed extracts have shown significant antibacterial activity comparable to standard antibiotics[53]. n-Butanol and aqueous fruit extracts of *F. vulgare* showed moderate radical scavenging properties *in vitro* (Table 1)[54]. Pretreatment with aqueous extracts of *F. vulgare* significantly reduced ethanol-induced gastric lesions in rats. In addition, this extract significantly reduced lipid peroxidation and increased antioxidant activity[70]. Oral administration of *F. vulgare* fruit methanolic extract to mice exhibited inhibitory effects against acute and subacute inflammatory diseases and type Ⅳ allergic reactions and showed a central analgesic effect. Moreover, it significantly increased the plasma antioxidant activity and decreased lipid peroxidation (Table 2)[71]. The aqueous extract of *F. vulgare* showed a significant NO scavenging effect *in vitro* (Table 1)[55].

Terminalia chebula

The black fruit of *Terminalia chebula* (*T. chebula*) known as "Halile siah" in TIM has been used for the treatment of IBD[4]. The aqueous extract of *T. chebula* has been shown to effectively modulate oxidative stress and enhance antioxidant status in the liver and kidney of aged rats[80]. The ethanolic extract of *T. chebula* accelerated the rate of healing of gastric lesions induced by indomethacin and inhibited lipid peroxidation in the gastric tissue of rats (Table 2)[87]. In addition, the ethanolic extract has been tested against specific multidrug-resistant bacteria, including methicillin-resistant *Staphylococcus aureus* (*S. aureus*) and extended spectrum β-lactamase-producing enteric bacteria and has shown broad-spectrum activity. This extract has also shown synergistic interaction with tetracycline, chloramphenicol and ciprofloxacin against *S. aureus* and/or *Escherichia coli* (*E. coli*)[61]. In addition, the butanol fraction of *T. chebula* fruit had profound growth-inhibitory activity against six intestinal bacteria, especially *Clostridium perfringens* and *E. coli*[62]. An aqueous extract from *T. chebula* was found to inhibit inducible nitric oxide synthesis by decreasing iNOS protein and iNOS mRNA levels (Table 1)[63].

Lepidium sativum

The seed of *Lipidium sativum* known as "Tokhm taretizak" is another famous drug used in TIM for IBD[90]. The ethanolic extract from the seed of this plant has

Table 3 Clinical studies on plants used in traditional Iranian medicine for the treatment of inflammatory bowel disease

Study	Study design	No. of patients	Disease	Plant	Part of plant	Control group	Duration of treatment	Result
Kaliora *et al*[82]	Open, comparing CD patients with healthy volunteers	10 patients and 8 controls	CD	*Pistacia lentiscus*	Oleogum resin	-	4 wk	↓TNF-α secretion, ↑macrophage migration inhibitory factor release meaning that random migration and chemotaxis of monocytes/ macrophages was inhibited
Kaliora *et al*[83]	Open, comparing CD patients with healthy volunteers	10 patients and 8 controls	CD	*Pistacia lentiscus*	Oleogum resin	-	4 wk	Significant reduction of CD Activity Index, ↓Plasma IL-6 and C-reactive protein, ↑total antioxidant potential, no side effects observed
Madisch *et al*[84]	Double-blind, randomized, placebo-controlled, multicenter	31	Collagenous colitis	*Boswellia serrata*	Gum resin extract	Placebo	6 wk	The proportion of patients in clinical remission was higher in the *Boswellia serrata* extract group than in the placebo group; Compared to placebo, *Boswellia serrata* extract treatment had no effect on histology and quality of life
Gupta *et al*[85]	Randomized	30	Chronic colitis	*Boswellia serrata*	Gum resin	Sulfasalazine	6 wk	Eighteen out of 20 patients treated with *Boswellia* gum resin showed an improvement in one or more of the parameters including stool properties, histopathology as well as scanning electron microscopy, hemoglobin, serum iron, calcium, phosphorus, proteins, total leukocytes and eosinophils; In the sulfasalazine group, 6 out of 10 patients showed similar results in the same parameters, 14 out of 20 patients treated with *Boswellia* gum resin achieved remission, while in the case of sulfasalazine the remission rate was 4 out of 10
Gupta *et al*[86]	Randomized	30	UC	*Boswellia serrata*	Gum resin	Sulfasalazine	6 wk	All tested parameters including stool properties, histopathology, scanning microscopy of rectal biopsies, and blood parameters including hemoglobin, serum iron, calcium, phosphorus, proteins, total leukocytes and eosinophils improved after treatment with *Boswellia serrata* gum resin. The rate of remission was similar in the two studies group (82% in the *Boswellia serrata* group *vs* 75% in the sulfasalazine group)
Al-Habbal *et al*[87]	Double-blind controlled	38	Duodenal ulcer	*Pistacia lentiscus*	Oleogumresin	Placebo	2 wk	Symptomatic relief in 80% of patients on oleogum resin from *P. lentiscus* and 50% in patients on placebo, endoscopically proven healing occurred in 70% of patients on oleogum resin from *P. lentiscus* and 22% of patients on placebo, no side effects observed
Fernández-Bañares *et al*[88]	Open label, multicenter, randomized	92	UC	*Plantago ovata*	Seed	Mesalamine	12 mo	40% relapse rate in the *P. ovata* seed group and 35% in the mesalamine group and 30% in the *Plantago ovata* plus mesalamine group

UC: Ulcerative colitis; CD: Crohn's disease; iNOS: Inducible nitric oxide synthase; Cox: Cyclooxygenase.

shown significant anti-inflammatory and analgesic activities in rats. However, it has been shown to potentiate gastric ulcer induced by indomethacin in these animals (Table 2). The mechanism of action of this seed seems to be inhibition of prostaglandin synthesis[72].

Plantago ovata and *P. psyllium*

The seed isolated from *Plantago ovata* (*P. psyllium*) and *P. psyllium* called "Esfarzah" is also used as an effective drug in the treatment of IBD[56,90]. Dietary fiber supplementation with 5% *P. ovata* seeds ameliorated the development of colonic inflammation in transgenic rats as evidenced by an improvement in intestinal cytoarchitecture. This effect was associated with a decrease in some of the pro-inflammatory mediators involved in the inflammatory process such as NO, leukotriene B4, and TNF-α. The

intestinal contents from fiber-treated colitis rats showed a significantly higher production of short chain fatty acids, butyrate and propionate, than non-treated colitis animals. *In vitro* studies revealed a synergistic inhibitory effect of butyrate and propionate on TNF-α production[75]. A significant reduction in colonic myeloperoxidase activity and restoration of colonic glutathione levels were also shown by this supplementation in a similar study (Table 2)[76]. Mucopolysaccharides derived from the husk of *P. ovata* have properties beneficial for wound cleansing and wound healing. It also limits scarring (Table 1)[58]. An open label, multicenter, randomized clinical trial was conducted to compare the efficacy and safety of *P. ovata* seeds (10 g *bid*) with mesalamine (500 mg *tid*) in maintaining remission in UC. After 12 mo, the relapse rate was 40% (14 of 35 patients) in the *P. ovata* seed group, 35% (13 of 37) in the mesalamine group, and 30% (9 of 30) in the *P. ovata* plus mesalamine group. The results of this study showed that *P. ovata* seeds might be as effective as mesalamine in maintaining remission in UC (Table 3)[88].

Bunium persicum

The fruit of *Bunium persicum* (*B. persicum*) known as "zireh kermani" is another natural product used for the treatment of IBD in TIM[6]. It is an economically important medicinal plant growing wild in the dry regions of Iran. The essential oil of *B. persicum* has strong anti-bacterial effects. This property could be the result of relatively high amounts of terpinenes and cumin aldehyde in the essential oil[43]. In addition, this essential oil has shown antioxidant properties. It was able to reduce the oxidation rate of soybean oil in the accelerated condition at 60℃ (Table 1)[44].

Cassia fistula

Fruit from *Cassia fistula* (*C. fistula*) known as "Flous" is another drug for the treatment of IBD in TIM[87]. The only known mechanism related to the beneficial effect of this plant is its antimicrobial properties. Crude extract of *C. fistula* exhibited significant antimicrobial activity (Table 1)[45].

Cydonia oblonga

Fruit from *Cydonia oblonga* known as "Beh" is also used for the treatment of IBD[91]. This fruit has shown radical scavenging and antimicrobial activities[50]. The phenolic extract exhibited the strongest antioxidant activity among the other extracts[51]. The antioxidant functions of its phenolic extracts were superior to that of chlorogenic acid and ascorbic acid as standard antioxidants (Table 1)[52].

Solanum nigrum

The fruit of *Solanum nigrum* (*S. nigrum*) known as "Tajrizi" is another natural product for the treatment of IBD in TIM[4,5]. A glycoprotein isolated from this fruit [*Solanum nigrum* L. (SNL) glycoprotein] has demonstrated a dose-dependent inhibitory effect on NO production and free radical formation in DSS-induced colitis in mice. It exhibited a suppressive effect on the activities of NF-κB and regulated the expression of iNOS and Cox-2 in the downstream signaling pathway (Table 2)[77]. *S. nigrum* fruits showed effective free radical scavenging activities in the 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay which seemed to be related to the SNL glycoprotein[59]. The SNL glycoprotein has remarkable scavenging effects on both the superoxide anion and hydroxyl radical, but exhibited slightly higher scavenging effects on the superoxide anion generated by the enzymatic hypoxanthine/xanthine oxidase system than on hydroxyl radicals generated by the Fenton reaction (Table 1)[60]. Treatment with *S. nigrum* extract significantly inhibited the gastric lesions induced by cold restraint stress (76.6%), indomethacin (73.8%), pyloric ligation (80.1%) and ethanol (70.6%) with equal or higher potency than omeprazole in experimental ulcer models. It also showed concomitant attenuation of gastric secretory volume, acidity and pepsin secretion in ulcerated rats. In addition, it accelerated the healing of acetic acid-induced ulcers after 7 d of treatment. Furthermore, it significantly inhibited H^+K^+ATPase activity and decreased gastrin secretion in the ethanol-induced ulcer model. The severity of the reaction of the ulcerogen and the reduction in ulcer size by *S. nigrum* extract was evident from histological findings (Table 2)[78,79].

Juglans regia

The kernel of *Juglans regia* (*J. regia*) known as "gerdou" has been used for the treatment of IBD in TIM[62]. Polyphenol compounds isolated from n-butanol extract of *J. regia* demonstrated a significant decrease in lipid peroxidation and a remarkable increase in antioxidant potential (Table 1)[56].

Boswellia carterii

Oleogum resin from *Boswellia carterii* (*B. carterii*) and *Boswellia serrata* (*B. serrata*) known as "Kondor" in TIM is another efficacious remedy for IBD[6,90]. Various studies have shown the anti-inflammatory effect of this oleogum resin (Table 2)[65,66]. Some new mono- and triterpenes isolated from this oleogum resin have exhibited NO production inhibitory activity in lipopolysaccharide-activated mouse peritoneal macrophages[40]. The ethanol extract of this oleogum resin has immunomodulatory properties *in vitro*[41]. The antimicrobial activities of the essential oil isolated from the oleogum resin of *B. carterii* have been demonstrated against various microorganisms including fungi, and gram-positive and gram-negative bacterial strains (Table 1)[42]. The results of a study evaluating the effectiveness of *Boswellia* extracts in controlled settings of DDS- or TNBS-induced colitis in mice suggested that *Boswellia* is ineffective in ameliorating colitis in these models. Moreover, individual boswellic acids were demonstrated to increase the basal and IL-1β-stimulated NF-κB activity in intestinal epithelial cells *in vitro* as well as reverse the proliferative effects of IL-1β. In addition, a hepatotoxic effect of *Boswellia* with pronounced hepatomegaly and steatosis was observed (Table 2)[67]. Patients with chronic diarrhea and histologically proven collagenous colitis were randomized to receive either oral *B. serrata* extract 400 mg three times daily for 6 wk or placebo. After 6 wk, the proportion of patients in clinical remission was higher in the

Table 4 Mechanisms of action of the plants used for the treatment of inflammatory bowel disease in traditional Iranian medicine

Plant	Activities								
	Immunomodulatory[1]	Antioxidant[2]	Antibacterial	↓NF-κB	↓NO	↓Cox-2	↓LB4	Anti-inflammatory	Wound healing
Althaea spp.			*					*	
Boswellia carterii and *Boswellia serrata*	*		*		*			*	
Bunium persicum		*	*						
Cassia fistula			*						
Commiphora mukul	*	*	*	*	*	*			
Cydonia oblonga		*	*						
Foeniculm vulgare		*	*		*			*	*
Juglans regia		*							
Lepidium sativum								*	
Pistacia lentiscus	*				*	*			*
Plantago ovata	*	*			*		*	*	*
Solanum nigrum		*		*	*	*			*
Terminalia chebula			*		*				*

[1]Modulating immune system by effects on factors of innate immunity including neutrophils, macrophages, dendritic cells, and natural killer cells are altered and defective mucosal helper T (Th) cell responses and greater expression of cytokines such as interleukin (IL)-1-β, IL-6, IL-12, tumor necrosis factor α (TNF-α) and interferon (IFN)-γ; [2]Decreasing factors involved in oxidative stress and lipid peroxidation and/or increased factors enhanced antioxidant capacity. Asterisks indicate having that kind of effect under the column heading. LB4: Leukotriene B4; NO: Nitric oxide; Cox-2: Cyclooxygenase-2; NF-κB: Nuclear factor κB.

B. serrata extract group than in the placebo group ($P = 0.04$). Compared to placebo, *B. serrata* extract treatment had no effect on histology and quality of life[84]. Thirty patients with chronic colitis were randomized to receive either a preparation of the gum resin from *B. serrata* (900 mg daily divided in three doses for 6 wk) or sulfasalazine (3 g daily divided in three doses for 6 wk). Of 20 patients treated with *Boswellia* gum resin, 18 patients showed an improvement in one or more of the parameters including stool properties, histopathology as well as scanning electron microscopy, in addition to hemoglobin, serum iron, calcium, phosphorus, proteins, total leukocytes, and eosinophils. In the sulfasalazine group, 6 of 10 patients showed similar results in the same parameters. Of 20 patients treated with *Boswellia* gum resin, 14 achieved remission, while in the case of sulfasalazine, the remission rate was 4 of 10[85]. In a similar study, patients with UC received either *B. serrata* gum resin preparation (350 mg three times daily for 6 wk) or sulfasalazine (1 g three times daily) and all tested parameters including stool properties, histopathology, scanning microscopy of rectal biopsies, blood parameters including hemoglobin, serum iron, calcium, phosphorus, proteins, total leukocytes and eosinophils improved after treatment with *B. serrata* gum resin. The rate of remission was similar in the two studies group (82% in the *B. serrata* group *vs* 75% in the sulfasalazine group) (Table 3)[86].

Althaea spp.

The flower and seed of various species of *Althaea* known as "Khatmi" in TIM have been claimed to be efficacious in IBD[87]. The ethanol extract of *Althaea officinalis* demonstrated significant antibacterial activity against *E. coli* (Table 1)[39]. The ethanol extract of the flower of *Althaea rosea* showed anti-inflammatory and analgesic effects in carrageenan- or dextran-induced rat paw edema (Table 2)[41].

CONCLUSION

Various herbal preparations have been used in TIM for the treatment of IBD. For many of the plants used in these formulations, there are various studies demonstrating their efficacy in IBD. These studies included *in vitro*, *in vivo*, and clinical trials which are summarized in detail in Tables 1-3, respectively. Table 4 briefly shows the modes of action of these plants in IBD. These medicines have shown their usefulness in IBD by different mechanisms of action including inhibiting the production of NO, Cox-2 and leukotriene B4, immunomodulatory properties, antimicrobial activities, antioxidant activities, and antiulcer and wound healing properties. As shown in Table 4, for some of these plants, only one or two mechanisms of action have been found such as in *Juglans regia*, *Cassia fistula*, *Lepidium sativum*, and *Bunium persicum*. However, in some of the plants various mechanisms of action are known. For example *Commiphora mukul* is effective in IBD due to its immunomodulatory, antioxidant, and antibacterial properties and it decreases NF-κB, NO and Cox-2. Another herb, *Plantago ovata*, has immunomodulatory, antioxidant, anti-inflammatory and wound healing activities and decreases NO and leukotriene B4. Considering the mechanisms of action of these plants, the combination of some of them may be useful due the numerous mechanisms involved in IBD, such as *Pistacia lentiscus*, *Bunium persicum*, *Solanum nigrum*, *Plantago ovata*, *Boswellia*, *Solanum nigrum*, *Plantago ovata* and *Commiphora mukul*.

Based on the published studies, some plants are likely to be more effective in the management of current IBD cases such as *Pistacia lentiscus*, *Plantago ovata* and *Commiphora mukul*. No exact relationship was found between the class of plants investigated and their efficacy which supports

the hypothesis of a complicated pathogenesis of IBD.

No potential adverse events have been reported for these remedies. There is only one study showing the ineffectiveness of the gum resin from *B. serrata* in ameliorating colitis in mouse DSS- and TNBS-induced colitis. Moreover, this study demonstrated its hepatotoxic effect[67]. However, other studies on gum resin from this plant have demonstrated its benefit in IBD such as inhibiting NO production[40], immunomodulatory properties[41], antimicrobial[40], anti-inflammatory activities[65,66], and inducing clinical remission[84,85].

For some of the herbal products used in TIM such as oleogum resin from *Commiphora myrrha*, seeds of *Ocimum basilicum*, seeds of *Linum usitatissimum*, gum resin from *Dracaena cinnabari*, seeds of *Plantago major*, seeds of *Lallementia royleana*, and seeds of *Allium porrum*, there are no or not enough studies to confirm their benefits in IBD. It is suggested that an evaluation of the effects of these plants on different aspects of IBD should be performed.

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