

Favorable results from the use of herbal and plant products in inflammatory bowel disease: evidence from experimental animal studies

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Abstract

The use of herbal therapy for inflammatory bowel disease is increasing worldwide. The aim of this study was to review the available literature on the efficacy of herbal therapy in experimental colitis. All relevant studies published in Medline and Embase up to June 2015 have been reviewed. The results of bowel histology and serum parameters have been recorded. A satisfactory number of published experimental studies, and a quite large one of both herbal and plant products tested in different studies have been reported. The results showed that in the majority of the studies, herbal therapy reduced the inflammatory activity of experimental colitis and diminished the levels of many inflammatory indices, including serum cytokines and indices of oxidative stress. The most promising plant and herbal products were *tormentil* extracts, wormwood herb, *Aloe vera*, germinated barley foodstuff, curcumin, *Boswellia serrata*, *Panax notoginseng*, *Ixeris dentata*, green tea, *Cordia dichotoma*, *Plantago lanceolata*, *Iridoid glycosides*, and mastic gum. Herbal therapies exert their therapeutic benefit via various mechanisms, including immune regulation, anti-oxidant activity, inhibition of leukotriene B4 and nuclear factor- κ B, and antiplatelet activity. Large, double-blind clinical studies assessing these natural substances should be urgently conducted.

Keywords Alternative medicine, herbal medicine, inflammatory bowel disease, Crohn's disease, ulcerative colitis, experimental colitis

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Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD) of unknown origin. Their conventional treatment is mainly based on the use of corticosteroids, immunosuppressants, antibiotics, and biologic agents. The cost of these treatments becomes extraordinary worldwide as the time passes. Moreover, the list of side-effects related to their use is quite extensive with some of them being life-threatening [1].

In recent years, many natural products, e.g. products derived from plants and herbals, are used by patients suffering from IBD. Experimental colitis in animals (mainly rats and mice) using two models of colitis (TNCB and DSS) has become a standard method to investigate the possible favorable effects of these herbal and plant products [2]. In this review, the authors have evaluated the most important studies concerning the effect of the use of natural products and plants in experimentally-induced colitis.

Methodology

A computerized search strategy using Medline and Embase databases up to June 2015 was implemented. The medical subject headings applied were: "herbal products", "herbal medicine", and "experimental colitis". Various other sources were also used in order to obtain information concerning the physical characteristics of these natural products. All the experimental animal studies investigating the effectiveness of herbal products in various models of colitis were included in the analysis. Data collection included the type of experimental colitis implemented, histological response, and serum levels of various pro-inflammatory cytokines and stress indices having been estimated before and after treatment.

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Results

From 1993 to June 2015, 80 studies dealing with 55 herbal and plant products used in the treatment of experimentally-induced colitis in animals were published. Almost half of them concerned plant and herbal products derived from countries in Europe, while the rest dealt with products derived from plants growing in Asian countries, mostly China and India. The most important data concerning the use of herbals and plants in the treatment of IBD patients in Europe and Asian countries are summarized below.

Plants and herbal products used in various models of colitis

The volume of experimental studies published so far includes 55 products of herbals or plants. Almost all experimental studies showed beneficial effects, thus making the authors of the relevant studies strongly recommend their use in large clinical trials.

Thyme (*Lamiaceae*)

Thyme is the common name of many taxa belonging to the *Thymbra* and *Thymus* genera, species that are frequently found in the western Mediterranean region [3]. In a TNBS model of colitis significantly milder histological lesions were noticed in the group receiving thyme compared to the group without treatment. No differences between animals receiving thyme decoction and animals receiving prednisolone were noticed [4].

Green tea

Green tea is made from the leaves of *Camellia sinensis* that have undergone minimal oxidation. The cardinal anti-oxidative ingredients are catechins, flavonoids and polyphenols. In an experimental colitis treatment with green tea extracts significantly attenuated diarrhea and loss of body weight accompanied by reduction in colonic myeloperoxidase (MPO) and tumor necrosis factor (TNF)- α production [5].

Lemon verbena (*Aloysia triphylla*)

Lemon verbena (*Aloysia citrodora*) comprises a flowering plant found mainly in western South America. Lemon verbena extracts have strong anti-oxidant capacity due to polyphenols contained in it. The results of DSS-induced colitis in rats showed that, although the histological lesions and MPO activity were not significantly improved, the herbal infusion increased colonic superoxide dismutase activity and decreased the levels of malondialdehyde [6].

Lemon grass (*Cymbopogon citratus*-*Poaceae*)

Lemon grass (*Cymbopogon citratus*) belongs to a family of fragrant grasses -*Poaceae* (*Gramineae*) plant family- of Indian origin. Lemon grass has been shown to suppress lymphocyte expression of gut homing molecules by inhibiting retinoic acid formation. In an experimental study, mice were treated with lemon grass for 26 weeks. Lemon grass attenuated the surface expression of beta7-integrin and CCR9 suggesting that it could ameliorate ileitis by inhibiting beta7-integrin expression [7].

Crataegi fructus (*Rosaceae*)

Crataegus is a large genus of shrubs and trees in the family of *Rosaceae*, native to temperate regions of the northern hemisphere in Europe, Asia, and North America. Active ingredients found in hawthorn include tannins, flavonoids, oligomeric proanthocyanidins, and phenolic acids. *Crataegi fructus* (hawthorn fruit) has been shown to decrease inflammation and improve leukotriene B4 levels in a murine model of colitis [8], having a potential of therapeutic utility in IBD.

Ginger extract (*Zingiber officinale*-*Zingiberaceae*)

Ginger or ginger root is the rhizome of the plant *Zingiber officinale*, consumed as a delicacy, medicine, or spice. In laboratory animals, the gingerols increase the motility of gastrointestinal tract having also analgesic, and antibacterial properties [9-13].

Two studies have investigated the role of ginger in experimental colitis. In the first one, rats received three different doses of ginger extracts, sulfasalazine, or vehicle, for 3 consecutive days before induction of colitis using intrarectal acetic acid administration. All parameters tested were improved in animals receiving ginger extracts, an effect comparable to sulfasalazine [14]. A second study found that ginger and zingerone improve the DSS colitis in rats in a dose-dependent manner. The favorable outcome was related to a reduction in the levels of nuclear factor- κ B (NF- κ B) and interleukin (IL)-1b [15].

Panax notoginseng

Panax notoginseng (*P. notoginseng*) belongs to the genus *Panax*. It is most commonly referred as *notoginseng*, being one of the best-known herbs. The dose in decoction for clinical use is 5-10 g. It contains dammarane-type ginsenosides as a major constituent. In a relevant study, one week after the administration of azoxymethane, the animals received DSS for 8 days or *P. notoginseng* extract, at 30 or 90 mg/kg. *P. notoginseng* reduced colonic inflammation, and inhibited loss of weight. Histological improvement went parallel to pharmacological observations [16].

Glabridin

Glabridin is a type of isoflavonoid found in the root extracts of licorice (*Glycyrrhiza glabra*). It has antimicrobial, and anti-inflammatory activities. Glabridin inhibits ICAM-1, nitric oxide (NO) production and *inducible NO synthase (iNOS)* gene expression in lipopolysaccharide-stimulated macrophages. In a rat model of colitis oral administration of glabridin in a dose of 10 or 50 mg/kg/day for 7 days significantly reduced mortality and loss of weight associated with histological improvement and reduction in colonic MPO activity and production of inflammatory mediators [17].

Scutellariae radix extracts (Lamiaceae)

Skullcaps are common herbal remedies in the systems of traditional medicine. Its root, known as radix *Scutellariae*, is the source of Chinese medicine Huang Qin. The main compounds responsible for the biological activity of skullcaps are flavonoids. *Scutellaria* root has been shown to modulate inflammatory activity. Isolated *Scutellaria* chemical compounds inhibit histamine and leukotriene release. In an experimental model of colitis in rats, treatment with *Scutellaria* relieved clinical symptoms, and improved histological damage [18].

Guggulsterone

Guggul is a tree that grows in India and exudes a resinous sap from its bark. The most significant constituents of the plant are sterols that have anti-inflammatory properties. In a relevant study, guggulsterone significantly reduced the severity of DSS-induced murine colitis. Tissue upregulation of NF- κ B, induced by DSS, was attenuated in guggulsterone-treated mice [19].

Arctium lappa L. (Asteraceae)

This species is native to the temperate regions of Europe, Middle East, China, India, and is commonly cultivated in Japan. The root contains a fair amount of polyphenols. The plant has antimicrobial and anti-oxidant activity. BALB/c mice were orally administered 100 mg/kg of *Arctium lappa* L. powder each day. After 7 days, colitis was induced by the administration of DSS. Significant differences in the disease activity indices between controls and *Arctium lappa* L.-treated animals were noticed. Treatment with *Arctium lappa* L. prevented mucosal inflammation, and reduced the levels of IL-6 and TNF- α [20].

Triptolide

Triptolide is the active component of extracts derived from the medicinal vine *Tripterygium wilfordii* Hook f. It induces apoptosis in T cells by activating DEVD cleaving caspases, and blocks TNF- α -mediated induction of c-IAP1 and c-IAP2, and

NF- κ B activation. Triptolide significantly reduced the severity of colitis in C3H/HeJ Bir IL-10-deficient mice. The mode of action seems to be related to the suppression of the IL-6/STAT3 signaling pathway, as well as the repressed gene expression of IL-17 *in vivo* [21].

Hesperidin

Hesperidin is a flavanone-type flavonoid that can be found in abundance in citrus fruits. It has natural anti-oxidative, antiviral, and anti-inflammatory characteristics. In a DSS-induced colitis, hesperidin significantly decreased disease activity index, MPO activity, malondialdehyde content and the level of IL-6 in serum [22].

Punica granatum (Lythraceae)

Punica granatum belongs to the family of *Lythraceae*. It contains large amounts of vitamin C and polyphenols. *Punica granatum* has anti-inflammatory, antibacterial, antifungal and anti-oxidative actions. In 2013, 44 clinical trials were registered with the National Institutes of Health to examine the effects of pomegranate extracts or juice consumption on a variety of human disorders [23-27]. In a relevant study, *Punica granatum* extracts and its ellagic acid rich fraction (100 mg/kg and 200 mg/kg p.o.) attenuated DSS-induced colonic inflammation along with an attenuation of histamine, MPO activity and oxidative stress [28].

Plantago lanceolata L (Plantaginaceae)

Plantago lanceolata L has been shown to have anti-inflammatory and anti-oxidative properties. It also inhibits protein kinase C, down-regulates the expression of intercellular adhesion molecule-1 and inhibits inflammation induced by 5-hydroxy-6,8,11,14-eicosatetraenoic acid and leukotriene B₄. In an experimental DSS colitis, intraperitoneal administration of *acteoside* (120, 600 μ g/mouse/d) resulted in a reduction in histological score compared to controls [29].

Yunnan Baiyao

Yunnan Baiyao is a traditional Chinese herbal remedy frequently used for treating hemorrhage and wounds. Oral administration of Yunnan Baiyao in drinking water significantly reduced the activity of both DSS- and TNBS-induced colitis by decreasing the levels of pro-inflammatory cytokines in the colonic mucosa [30].

Cordia dichotoma f. (Boraginaceae)

Cordia dichotoma f. is a small deciduous tree from India belonging to the family of *Boraginaceae*. Apigenin, the active

component of this plant has anti-oxidative, antifungal, and immunomodulating properties [31,32]. Leaves, seeds and fruits of the plant are rich in flavonoids, carbohydrates, fatty acids, and tannins [33,34]. In an experimental study, animals treated with the methanol fraction of the crude methanol extracts achieved lower histological scores and a satisfactory healing capacity. This fraction showed also a significant anti-oxidant potential [35]. A second study showed that apigenin (5 mg/kg, p.o.) exhibited both a significant healing capacity and reduction in inflammatory cytokines [36].

***Withania somnifera* (Solanaceae)**

Withania somnifera is a plant belonging to the *Solanaceae* or nightshade family. It is used as a herb in Ayurvedic medicine, mainly in patients with irritable bowel syndrome, and gastrointestinal hemorrhage [37,38]. The main chemical constituents of the plant are alkaloids. The leaves of *Withania somnifera* show anti-inflammatory, antimicrobial, and immunomodulating activities [39]. Luvone *et al* showed that methanolic extracts of the roots of *Withania somnifera* activate the production of NO synthase by acting in the macrophages [40]. *Withania somnifera* on TNBS-induced colitis showed inhibition of lipid peroxidation, and H₂O₂ scavenging and histological improvement [41].

Embelin

Embelin is a phenolic compound found in the fruits of *Embelia tsjeriam-cottam*. Embelin inhibits cell growth, induces apoptosis, and activates caspase-9 in prostate cancer cells [42]. In a DSS colitis in rats, embelin administered for 7 days at a dose of 10, 30 or 50 mg/kg BW showed significant anti-inflammatory effects with down-regulation of the production and expression of inflammatory mediators and reduction in the histological score [43].

***Patrinia scabiosaefolia* Fisch**

Patrinia scabiosaefolia Fisch is a plant used in oriental traditional medicine. A large number of chemical substances, including oleanolic acid, hederagenin, sitosterol and campesterol-d-glycosides, have been extracted from the roots of the plant. Ethanol extracts of the roots of *Patrinia scabiosaefolia* significantly improved the histological score and oxidative stress, as well as the levels of pro-inflammatory cytokines in experimental colitis [44].

***Pistacia lentiscus* (Anacardiaceae)**

Plants within *Anacardiaceae* are trees, shrubs, and woody vines, with a resinous bark. The aromatic, ivory-coloured resin, also known as mastic, is harvested as a spice from

the cultivated mastic trees grown in the Greek island of Chios in the Aegean Sea. In an experimental study, four different dosages of *Pistacia lentiscus* powder were orally administered. A histological amelioration of colitis and significant differences in colonic indices occurred after 3 days of treatment. A daily administration of 100 mg of *Pistacia lentiscus* powder/kg BW decreased all inflammatory cytokines [45].

***Oenothera paradoxa* (EP)**

Oenothera is a genus of about 145 species of herbaceous flowering plants native to the Americas. It is the type genus of the family *Onagraceae*. EP preparations have been used in a variety of digestive diseases because of their anti-inflammatory and anti-oxidant activities. Administration of EP pomace polyphenol extracts in TNBS colitis significantly improved macroscopic and microscopic colitis scores, and MPO activity. The favorable result is a consequence of free radical scavenging. EP pomace polyphenol extract in patients with IBD might be beneficial when administered concurrently with conventional treatment [46].

***Moringa oleifera* lam**

Moringa oleifera is the most widely cultivated species of the genus *Moringa*. It is a fast-growing, drought-resistant tree native to the foothills of the Himalayas in India, having anti-inflammatory, immunomodulatory, and anti-oxidative properties. The effect of *Moringa oleifera* seeds hydro-alcoholic extracts and their chloroform fraction on acetic acid-induced colitis was investigated. All three doses of the extracts used (50, 100, and 200 mg/kg orally) were able to reduce the severity of colitis. The favorable effect might be attributed to its anti-inflammatory components [47].

***Aegle marmelos* fruit**

Aegle marmelos represents a species of trees native to India, the fruits of which are used both in traditional medicine and as a food source. Ethanol extracts of dried fruit pulp of *Aegle marmelos* decreased colonic mucosal damage and inflammation, colonic free radicals and MPO activity. The plant improves colitis through its antibacterial activity, promotion of colonic anti-oxidants and reduction of free radicals and MPO-induced colon damage [48].

Quercetin

Quercetin is a flavonoid that can be found in citrus, buckwheat and onions. It is a naturally occurring polar auxin transport inhibitor. Quercetin in a dose of 50 and 100 mg/kg for 10 days significantly improved clinical,

morphological, and biochemical abnormalities in TNBS colitis. The mechanism of action is related to its anti-oxidative abilities [49].

***Echinacea* spp.**

Echinacea is a genus of herbaceous flowering plants in the daisy family, *Asteraceae*. The *Echinacea* genus has nine species grown in North America. Two of them, *E. tenesseeensis* and *E. laevigata*, are listed in the USA as endangered species. They are traditionally used in the treatment and prevention from common cold, flu, and other infections. In an experimental study, disease activity index and IL-1 β and TNF- α were significantly improved in the *Echinacea*-colitis groups compared to controls suggesting that *Echinacea* spp. may have beneficial effects on active UC [50]. The same group of investigators in an acetic acid model of colitis found that macroscopic and histological scores, malondialdehyde levels and total anti-oxidant status were significantly better in *Echinacea*-colitis groups compared to controls [51].

Xilei San

Xilei San is an herbal preparation widely used in China for the treatment of ulcerative disorders, including UC. In a DSS-induced colitis, it was found that the intrarectal administration of *Xilei San* attenuated colitis by reducing both the histological damage score and the MPO activity. It also reduced the levels of proinflammatory cytokines, increased the mucosal repair-related cytokines and upregulated the epithelial Ki-67 expression. *Xilei San* might be of benefit in the form of topical treatment in patients with ulcerative proctitis [52].

Ixeris dentata

Ixeris is a genus of plants belonging to the dandelion family growing in Asia. It has been used in Asian countries against indigestion, pneumonia, and hepatitis. In a relevant study, the administration of *Ixeris* in DSS-induced colitis was able to significantly attenuate weight loss, colon shortening, and disease activity index score. It also significantly decreased the degree of colonic mucosa inflammation and inhibited the expressions of cyclooxygenase-2 and hypoxia-inducible factor-1 α in colonic tissue [53].

Xie-xin decoction

Ban Xia Xie-xin decoction is a traditional Chinese compound herbal regimen used mainly in the treatment of cold. "Modified Ban Xia Xie-xin decoction" comprises a recipe that combines related herbal medicines that could increase the effectiveness of the formula. Previous data indicate that modified Ban Xia Xie-xin decoction can restore

gastrointestinal function and mucosal integrity. Xie-xin decoction has also been used in China for the treatment of UC. Han *et al* administered Xie-xin decoction formula orally for 8 days in a dose of 2 or 4 g/kg/day. They found that Xie-xin decoction induced recovery of colitis and inhibited colonic inflammation by reducing the tissue levels of MPO and TNF- α and NF- κ B p65 and increasing the production of IL-10 [54]. Whether these positive effects on experimental colitis could be transferred to human UC remains to be seen.

Si Shen Wan

Si Shen Wan is a traditional Chinese herbal medicine formula widely used in a number of gastrointestinal disorders, including UC and chronic diarrhea. In an experimental study rats with TNBS-colitis were treated with Si Shen Wan for 10 days. It was found that colon wet weight and colonic damage score were lower compared to control group, while malondialdehyde and MPO concentrations in colonic tissue were also decreased in the treated groups compared to controls. Moreover, IL-4 and IL-10 mRNA expression in colonic tissues were increased suggesting that this formula could have a positive effect on human UC [55].

STW 5

STW 5 (Iberogast) is a liquid formulation consisting of nine herbs, namely bitter candytuft (*Iberis amara*), angelica root (*Angelicae radix*), milk thistle fruit (*Silybi mariani fructus*), celandine herb (*Chelidonii herba*), caraway fruit (*Carvi fructus*), liquorice root (*Liquiritiae radix*), peppermint herb (*Menthae piperitae folium*), balm leaf (*Melissae folium*) and chamomile flower (*Matricariae flos*). Iberis represents one of the main ingredients of it posing anti-inflammatory and anti-oxidative properties. STW 5 has been used in functional dyspepsia and irritable bowel syndrome. STW 5 and sulfasalazine (control group) were orally administered daily for 1 week before induction of DSS colitis and continued thereafter. STW 5 and sulfasalazine were equally effective in reducing the total histology score and the changes in biochemical parameters measured [56] supporting a role of STW 5 in the clinical setting of UC.

Iridoid glycosides

Iridoids are a class of secondary metabolites (monoterpenes) found in a wide variety of plants. Iridoids exhibit a wide range of biological actions, including cardiovascular, antihepatotoxic, hypoglycemic, analgesic, anti-inflammatory, antimutagenic, antispasmodic, antitumor, and antiviral. In an experimental study, iridoid glycosides (80, 160 and 240 mg/kg) were administered for 2 weeks. Treated rats showed a significant improvement in macroscopic damage and histological changes, and a reduction in MPO activity and malondialdehyde and

NO levels. Iridoid glycosides effectively inhibited mRNA expressions of NF- κ B p65, TNF- α and IL-6 in colon tissue. Higher doses of this herbal (160 mg/kg and 240 mg/kg) were superior to sulfasalazine [57]. This herbal might be of value in human UC.

***Teucrium persicum* (*T. persicum*)**

The genus *Teucrium* (*Labiatae*) includes about 300 species worldwide. It is distributed mainly in Central and South America, Southeastern Asia, and the Mediterranean region. *T. persicum* is used for treating headache, abdominal pain, diabetes, obesity, hyperlipidemia, inflammation, and rheumatoid arthritis having antibacterial, and anti-oxidant effects. The essential oils from *Labiatae* species are the main components among the 31 constituents characterized in the oil of *Teucrium persicum*. Three different doses of *Teucrium* (100, 200, and 400 mg/kg) were used for 10 days in an experimental model of colitis in rats. *Teucrium* at all doses improved histological changes, reduced colonic MPO activity and the concentrations of cellular lipid peroxides, TNF- α , and IL-1 β with a concurrent increase in ferric reducing anti-oxidant power value. This herbal needs to be clinically explored in patients with UC [58].

***Ziziphora clinopoides* (*Z. clinopoides*) methanolic extract**

Z. clinopoides methanolic extract is a traditional Iranian herbal derivate used mainly in inflammatory conditions. *Z. clinopoides* was orally administrated at doses of 75, 150, and 300 mg/kg/day for 7 days in a DSS model of colitis. The formula improved all parameters tested, including lipid peroxidation, total anti-oxidant capacity, total thiol molecules, anti-oxidant enzymes and tissue levels of TNF- α [59]. The results support the protective effect of this herb in IBD.

Fructus Mume pill

Fructus Mume pill has been used in China as a folk remedy for gastrointestinal diseases, including UC, over many years. Fructus Mume pill was approved for the treatment of gastrointestinal diseases in 2001 by the State Food and Drug Administration of China. The ingredients include *mume fructus*, *zanthoxylum fructus*, *coptidis rhizome*, *phellodendron cortex*, *asarum radix*, *zingiber rhizome*, *aconit tuber*, *ginseng radix*, *angelicae sinensis*, and *cinnamomum ramulus*. The effects and mechanism of action of Fructus Mume pill on TNBS-induced colitis were investigated. Fructus Mume pill improved all parameters in a greater degree compared to dexamethasone. It also restored the balance of intestinal bacteria population from the imbalance of G(+)/G(-) in rats with colitis. The mechanisms may be related to the down-regulation of Th1 immune response and opsonic effect of intestinal commensal bacteria [60].

***Angelica sinensis* polysaccharide**

Angelica sinensis is a herb belonging to the family of *Apiaceae*, growing in cool high altitude mountains in China, Japan, and Korea where Chinese and Japan medicine has been used for over thousands years. In Chinese traditional medicine, the plant has been used for the treatment of various disorders. In an experimental study the effect of the plant for 21 days was compared to 5-aminosalicylic acid. All inflammation indices were significantly ameliorated in colitis rats treated with *Angelica sinensis* polysaccharide at the doses of 400 and 800 mg/kg, and colonic epidermal growth factor protein expression was up-regulated. *Angelica sinensis* polysaccharide can ameliorate TNBS colitis due to its anti-oxidative, and immunomodulating effects and by promoting wound repair [61].

Oren-gedoku-to

Oren-gedoku-to (a mixture of ingredients derived from plants) has been long used in many Asian countries for the treatment of inflammatory and ulcerative disorders. In an experimental study in rats, oren-gedoku-to was orally administered for two weeks. The plant induced a quick healing process and a reduction in inflammatory cell infiltration, due to the reduction in IL-8, LTB₄, and PGE₂. Oren-gedoku-to might be of benefit in IBD patients as a combination treatment [62].

Sasa quelpaertensis

Sasa quelpaertensis Nakai is a species of bamboo grasses grown in South Korea. *Sasa* leaves have antidiabetic, anticancer, and anti-inflammatory effects. In a DSS-induced colitis mice were pretreated with 100 or 300 mg/kg of *Sasa quelpaertensis* Nakai for 2 weeks. Then, the animals received either *Sasa quelpaertensis* Nakai or sulfasalazine (100 mg/kg) with 2.5% DSS in drinking water for 7 days b.i.d. Treatment with *Sasa quelpaertensis* Nakai attenuated the severity of colitis and suppressed serum and tissue levels of TNF- α , NOS, cyclooxygenase, and phosphorylated c-Jun N-terminal kinases, p38, extracellular-signal-regulated kinases 1/2, and I κ B α in colon tissues [63].

Phytosterols

Phytosterols are steroid compounds which occur in a number of plants. So far, more than 200 sterols and related compounds have been identified. They have low-density lipoprotein cholesterol lowering effect, and strong anti-inflammatory properties. A mixture of phytosterols on a DSS murine model of colitis was administered before, during and after the induction of experimental colitis. It significantly reduced the severity of the disease and improved clinical and histological parameters [64].

Cranberry

Cranberries are a group of evergreen dwarf shrubs or trailing vines in the subgenus *Oxycoccus* of the genus *Vaccinium* cultivated in many parts of the world. They are used mainly for the prevention and treatment of urinary tract infections. In an experimental DSS-colitis both cranberry extract and dried cranberries-fed groups reduced disease activity index. It was also found that dried cranberries were more effective than cranberry extract in reducing colonic MPO activity and the production of pro-inflammatory cytokines compared with controls [65]. Cranberries can prevent and reduce the symptoms of patients with IBD.

FAHF-2

FAHF-2 is a herbal formula based on a classical traditional Chinese herbal formula *Wu Mei Wan*. The efficacy of FAHF-2 was investigated in the CD45RbRAG1 transfer colitis model. FAHF-2-treated mice exhibited decreased weight loss, reduced inflammation on histology, as well as TNF- α , IL-17, IL-6, and interferon (IFN)- γ production. This herbal formula inhibited both adaptive and innate immune proinflammatory cytokine responses in peripheral blood mononuclear cells due to blockage of NF- κ B activation [66]. FAHF-2 might represent a novel treatment of IBD.

Icariin

Icariin is a flavonol glycoside derived from species of plants belonging to the genus *Epimedium*, *Berberidaceae*. Oral administration of icariin (the major bioactive compound of *Epimedium* family) inhibited disease progression and diminished the histological lesions. It also reduced the levels of pro-inflammatory cytokines and expression of p-p65, p-STAT1 and p-STAT3 in colon tissues. Icariin inhibited the phosphorylations of STAT1 and STAT3 in CD4(+) T cells [67]. These immune effects suggest that icariin could be of value in the treatment of IBD.

Artemisinin

Artemisinin is a chemical from a traditional Chinese herbal medicine, named *Artemisia annua L.*, exhibiting anti-inflammatory and immunomodulatory effects on patients with autoimmune disorders with very few side-effects. *Artesunate* at a dose of 150 mg/kg/day significantly ameliorated DSS and TNBS colitis by reducing macroscopic and microscopic inflammation, and the expression of NF- κ B p65 and p-I κ B- α and IFN- γ , IL-17, and TNF- α . *Artesunate* inhibited TNF- α production by LPS-activated macrophages suggesting that it could be of value in the treatment of IBD [68].

Sophora alopecuroides L.

Sophora alopecuroides L. is a traditional Chinese herbal remedy used in enteritis and dysentery for many years. Sophocarpine represents the main ingredient of *S. alopecuroides L.* In a DSS colitis model, sophocarpine (60, 30, and 15 mg/kg of body weight) and sulfasalazine (520 mg/kg) were orally administered once daily for 7 days. Sophocarpine significantly reduced disease activity index and decreased MPO activity and serum levels of IL-1 and IL-6 [69]. The plant acts through the regulation of pro- and anti-inflammatory cytokine production.

2, 3, 5, 4'-tetrahydroxystilbene-2-O-beta-D-glucoside (THSG)

THSG is a water-soluble active component extracted from dried tuber root of *Polygonum multiflorum* that possesses anti-inflammatory effects. In a relevant study, mice were administered 10, 30, 60 mg/kg of THSG or 100 mg/kg of mesalazine or saline once daily for 7 days. It was shown that THSG restored weight loss and improved histopathological lesions. Moreover, THSG decreased the levels of malondialdehyde exerting its beneficial effects through upregulation of PPAR- γ mRNA levels and inhibition of the NF- κ B pathway in a greater degree compared to mesalazine [70]. THSG might be considered as a promising new compound for the treatment of IBD.

Bojanguunbi-tang (BGT)

Anjang-san is composed of *Geranii Herba*, *Terminaliae Fructus*, *Dolichoris Semen*, *Alpiniae Katsumadaii Semen*, *Myristicae Semen*, *Glycyrrhizae Radix*, and *Zizyphi Semen*, mainly used in acute and chronic diarrhea, including irritable bowel syndrome. BGT, a mixture of 16 herbs, is one of the most frequently used herbal preparations in South Korea for patients with "colitis". In the one and only available study, BGT was orally administered b.i.d. for 7 days in the DSS model and for 3 days in the TNBS model at a dose of 50, 150, or 450 mg/kg, respectively. BGT improved all parameters investigated in both types of colitis, including histology, weight loss and shortening of colon length [71].

Huangqin-Tang decoction

Huangqin-Tang decoction represents a traditional Chinese herbal formulation consisting of the roots of *Scutellaria baicalensis* Georgi, *Glycyrrhiza uralensis* Fisch., *Paeonia lactiflora* Pall., and the fruit of *Ziziphus jujuba* Mill. It has been used in the treatment of many gastrointestinal disorders, including diarrhea, fever, vomiting, and nausea. Huangqin-Tang decoction has also been used in the treatment of IBD in Chinese patients. In a recent experimental study, it was found that Huangqin-Tang decoction significantly reduced the severity of colitis. In addition, Huangqin-Tang decoction

reduced the percentages of Th1 and Th17 cells and lowered the levels of Th1/Th17-associated cytokines. This plant acts via its effects on CD4(+) T cells subsets [72].

Malva sylvestris

Malva sylvestris is a plant consumed as an herbal supplement in traditional Persian medicine because of its antiulcer and colon cleansing properties. In an acetic acid model of colitis 3 groups of rats received aqueous, n-hexane, or ethanolic fractions of the plant before the induction of colitis. Isolated polysaccharide of the plant was also tested before and after the induction of colitis. The aqueous fraction was effective in preventing the appearance of inflammatory lesions. Polysaccharide also reduced inflammation, especially as a pretreatment. This plant could be suggested for patients with UC [73].

Protodioscin

Dioscoreaceae, a kind of yam plants, has been used in the treatment of inflammatory conditions. Methyl protodioscin has been extracted and purified from the rhizome of *Dioscorea collettii* var. *hypoglauca*. Methyl protodioscin ameliorated intestinal inflammation in DSS colitis, increased the survival rate and accelerated mucosal healing and epithelial proliferation in experimental colitis. Moreover, it inhibited the NF- κ B activation, pro-inflammatory cytokines expression and bacterial translocation [74].

Tragopogon graminifolius

Tragopogon graminifolius is considered to be an efficacious remedy for gastrointestinal ulcers in Iranian traditional medicine. In a relevant study, rats orally received a standardized ethanol extract of *Tragopogon graminifolius* aerial part at 20, 30, or 50 mg/kg/d. The plant reduced macroscopic and microscopic scores of colitis and MPO activity [75]. *Tragopogon graminifolius* reduced the degree of colitis via its anti-inflammatory, immunomodulatory, anti-oxidant, and mucosal healing activities.

***Boswellia serrata* (B. serrata)**

B serrata belongs to a family of trees producing resin rich in carbohydrates, essential oils and acids ("boswellic acids"), the latter being the active component of the plant. *B. serrata* has been used in chronic inflammatory disorders, including UC and CD. In an experimental study in rats, the treatment with extracts of *B. serrata* (34.2 mg/kg/day) significantly reduced lipid peroxidation, NO and iNOS levels and the improvement in bowel histology [76]. Another experimental study also showed that the recruitment of adherent leukocytes and platelets into inflamed colonic venules was reduced in

mice treated with acetyl-11-keto-beta-boswellic acid, while P-selectin upregulation was diminished [77].

Curcumin

Curcumin is the yellow pigment associated with the curry spice, turmeric, and to a lesser extent ginger. It is a small molecule that has effects similar to other polyphenols. So far, two studies have investigated the effect of curcumin on experimental colitis. In the first one, a significant improvement in the disease activity index and histological score was observed. Moreover, the increase in phospho-STAT3 activity, DNA-binding activity of STAT3 dimers, MPO activity, IL-1 β , and TNF- α expression was significantly reduced [78]. In the second study, the curcumin-treated group showed a significant decrease in the disease activity index, histological score, MPO activity, and expressions of NF- κ B mRNA, IL-27 mRNA, TLR4 protein, NF- κ B p65 protein, and IL-27 p28 protein compared to the untreated colitis group. The anti-inflammatory actions of curcumin on colitis may involve an inhibition of the TLR4/NF- κ B signaling pathway and IL-27 expression [79].

Germinated barley foodstuff

Germinated barley foodstuff is a prebiotic product made from malt, which contains glutamine-rich protein and hemicellulose-rich fiber. In an experimental model of colitis induced by transferring CD4+ CD45RB (high) T cells to mice, germinated barley foodstuff reduced inflammation by modulating the colonic microflora [80]. Germinated barley foodstuff may effectively enhance luminal butyrate production, and thereby accelerate colonic epithelial repair in colitis [81]. The favorable results may be also related to its inhibitory effects on mucosal mast cells, and the destruction of the mucosal connective tissues [82].

Anthocyanins

Anthocyanins can be found in relatively high quantities in bilberries, having both anti-oxidative and anti-inflammatory properties. The ingestion of anthocyanins reduced intestinal inflammation in acute and chronic DSS-colitis with decreased histological scores and cytokine secretion [83]. In another study, anthocyanin extracts of blueberry rendered a protection against TNBS-induced colonic damage at a dosage of 40 mg/kg [84].

Aloe vera

Aloe vera represents a quite popular folk remedy for inflammatory conditions despite the lack of studies reporting its efficacy *in vivo*. It seems that dietary supplementation of aloe components ameliorates intestinal inflammation in a

DSS-induced experimental colitis, with aloein being the most potent constituent [85].

Cellular and molecular mechanisms

The abovementioned studies showed that individual chemical substances derived from plants and herbals may have antibacterial, anti-oxidative, anti-inflammatory, and immunoregulatory properties, the latter being a pivotal contributor to their therapeutic beneficial. Experimental models of colitis confirmed the central role of nuclear and intracellular signaling pathways with transcription and transduction activity in the prevention and management of IBD.

The most significant cellular and molecular mechanisms are summarized in Table 1 and subsequently analyzed.

Alterations of gut microbiota

A number of natural agents, such as red ginseng, could improve gut microbiota in rats with experimental colitis by enhancing *Lactobacillus* and *Bifidobacterium* colonization, and suppressing *Escherichia coli* (*E. coli*) growth. Intake of blueberry as dietary supplementation results in a significant decrease in *Clostridium perfringens*, *Enterococcus* spp. and *E. coli*, as well as an increase in butyric acid in a genetic experimental model of IBD [86].

Table 1 Main cellular and molecular mechanisms of herbals and plants used in experimental models in colitis

Mechanism of action	Herbals and plants	Reference
Anti-oxidative action	Green dwarf banana flour	81
	Cattail rhizome flour (<i>Typha angustifolia</i>)	82-85
	<i>Tragopogon graminifolius</i> extract	
	Blueberry extract	
Modulation of nitregic system	Apple polyphenols	92
	Flavonoids (quercitrin)	93
Alterations of gut microbiota	Red ginseng	76
	Blueberry	77-80
Anti-inflammatory action	Anthocyanin-enriched bilberry and blueberry extract	83,84
	<i>Ginkgo biloba</i> extract	
	Ginseng extract	
	<i>Curcuma longa</i> constituents	
Modulation of cellular signaling pathways	Ellagic acid	94-97
	Curcumin	102
	Flavonoids	103
	Green tea and other dietary polyphenols	
	Glucosinolates of Chinese cabbage	
Immunomodulation	Apple constituents	89
	<i>Panax quinquefolius</i>	90

Anti-inflammatory and anti-oxidant actions

Herbal dietary supplements, including anthocyanin-enriched bilberry extract, *Ginkgo biloba* extract, *ginseng* extract, *Curcuma longa* constituents and *anthocyanins*-enriched blueberry extract, exert their effect by suppressing the expression of inflammatory mediators [87]. Many dietary natural products (e.g. *Tragopogon graminifolius*, pomegranate, and blueberry extract) act through the enhancement of anti-oxidant performance, prevention of DNA oxidative damage and lipid peroxidation, as well as free radical scavenging [88].

Immunomodulation and modulation of the nitregic system

T cells apoptosis represents a key cellular mechanism of dietary agents for alleviating immune cascade with mitochondrial mediated and death receptor-mediated pathways. Natural products harboring cyclooxygenase inhibiting activity could regulate apoptosis of activated inflammatory cells. Other natural supplements, including polyphenols and flavonoids like quercitrin, showed an upregulation of endothelial NOS expression along with suppression of *iNOS* expression and reduction in *iNOS*-derived NO [89,90].

Modulation of cellular signaling pathways

A number of herbal supplements could have a therapeutic potential on IBD by modulating mitogen-activated protein kinases subfamily proteins resulting in remission of chronic inflammation. Other natural products are of benefit in IBD by acting on nuclear pathway of inflammatory reaction. Ellagic acid, curcumin, flavonoids and green tea polyphenols can modulate I κ B phosphorylation and deactivate IKK enzyme [91].

Another nuclear factor (nuclear factor-erythroid 2-related factor-2) (Nrf2) enhances cellular defense via the expression of cytoprotective molecules, such as stress-response molecules and activation of phase-II detoxifying enzymes. Dietary polyphenols could regulate Nrf2 resulting in the attenuation of colonic mucosa inflammation [92].

Cellular and molecular mechanisms of individual herbals and plants

Individual herbal and plants usually pose more than one cellular and molecular mechanism explaining their anti-inflammatory and immunomodulating action. The most important paradigms of multiple actions are given in Table 2.

Safety and side-effects of herbal treatment

Herbal therapy, in general, could carry risks and produce side-effects similar to other forms of alternative therapy and those of placebo or mesalazine. Liver and renal failure has been

Table 2 Cellular, molecular and systemic effects of plant and herbal preparations used in experimental colitis models

Herbal and plant	Cellular, molecular and systemic effects	Reference
<i>Boswellia serrata</i> (Boswellic acid)	• Selective inhibition of 5-lipoxygenase	76
	• Anti-inflammatory effects • Direct inhibition of intestinal motility • Reduction of chemically induced edema and inflammation in the intestine in rodents	77
Curcumin	Decreased activity	78
	• Interferon- γ • Mitogen-activated protein kinase • IL-1, IL-4, IL-5, IL-6, IL-12 • Tumor necrosis factor- α • Myeloperoxidase • Lipid peroxidase activity • Inducible nitric oxide synthase • Cyclooxygenase-2 • Toll-like receptor-4 • Nuclear factor- κ B • Binds to thioredoxin reductase and irreversibly changes its activity Increased activity • IL-10, IL-4 • Prostaglandin E2	79
Germinated barley foodstuff	• Increases luminal butyrate production by modulating the microfloral distribution	81
	• Prebiotic action • High water holding capacity	82
<i>Oenothera biennis</i>	• The mature seeds contain 7–10% γ -linolenic acid	46
<i>Plantago ovata</i>	• Anti-inflammatory and anti-oxidative properties • Inhibits the protein kinase C • Down-regulates the expression of intercellular adhesion molecule-1 • Inhibits the inflammation produced from 5-hydroxy-6,8,11,14-eicosa-tetraenoic acid and leukotriene B4	29
Anthocyanins	• Anti-oxidative effects	83
	• Anti-inflammatory effects	84
<i>Xilei San</i>	• Anti-inflammatory effects	52
		53
<i>Aloe vera</i>	• <i>In vitro</i> inhibition of prostaglandin E2 and IL-8 secretion	85
Mastic gum	• Anti-inflammatory	3
	• Anti-oxidative	4

described with some of them, fortunately not with those used in the treatment of IBD patients. However, the most important “side-effect” of the use of herbal preparations is the abandonment of the drugs used in the treatment of IBD by the patients themselves, a fact leading to a deterioration of the underlying disorder. Toxic effects could also be associated with the inclusion of prescription medicines in some herbal preparations, such as corticosteroids, and glibenclamide. Toxic products, such as mercury, arsenic, and lead, can be found in some plant preparations. The long-term safety of herbal treatment, including possible mutagenicity and carcinogenicity, has not been adequately explored. The most important side-effects of some herbals and plants used in experimental colitis are shown in Table 3.

Discussion

The review of the relevant literature revealed that at least fifty different herbal and plant preparations were used in

experimental colitis. These plants were originated mainly in Asia, America, and Europe, including Mediterranean basin. The great majority of plant and herbals tested have been previously successfully used for centuries for the treatment of IBD, being part of the so-called traditional medicine.

In the studies described in this review, the methodology used was suitable and complete. In most of them, a control group, either placebo or active drug, was used. A number of cytokines and indices of the presence of inflammation and oxidative stress were estimated in the serum along with a detailed histopathology of bowel specimens. Although the models of colitis used are basically chemical models, they are very well-accepted worldwide, because they have similarities with clinical and laboratory parameters of the human IBD.

The effectiveness of the herbal preparations was quite satisfactory in all studies being similar to the active drug or significantly better compared to placebo. Because of their multiple biological properties, herbs and plants might be emerged as the alternative for treatment of IBD. However, as

Table 3 Safety of plants and herbals used in experimental colitis

Herbal and plant	Side-effects	Safety	Reference
<i>Boswellia serrata</i>	Rich in guggalsterones that increase the thyroid function leading to weight loss	Satisfactory	76 77
Germinated barley foodstuff	No side-effects related to this plant have been observed	Excellent	81 82
<i>Oenothera biennis</i>	Safety has not been evaluated in pregnant or nursing women	Satisfactory	46
<i>Plantago ovata</i>	Hypersensitivity after inhaled or ingested psyllium. Temporary gas and/or bloating	Satisfactory	29
Anthocyanins	No serious adverse events have been described	Satisfactory	83 84
<i>Xilei San</i>	Well-tolerated topically without safety concerns	Satisfactory	52
Mastic gum	No side-effects have been reported	Excellent	4
Green tea	Side-effects occasionally could occur with high doses	Moderate	5
Phytosterols	Sometimes constipation, nausea, flatulence, heartburn	Satisfactory	64
Ginger extract	Safe for most people. Mild side-effects including heartburn, diarrhea, and general stomach discomfort have been reported. Menstrual bleeding in some women	Satisfactory	9-13
<i>Echinacea</i>	Safe for most people when used short-term. Fever, nausea, vomiting, unpleasant taste, diarrhea, sore throat, dry mouth, headache, dizziness, insomnia, disorientation, and arthralgias have been reported	Satisfactory	50
Quercetin	Safe for most people when taken by mouth short-term (500 mg twice/d for 12 wks). Headache and tingling of the arms and legs have been reported. Very high doses might cause kidney damage	Excellent	49
Curcumin	Safe when taken by mouth or applied to the skin appropriately for up to 8 months. Nausea, dizziness, or diarrhea might appear in a small proportion of patients	Excellent	78
Cranberry	Safe. Patients taking warfarin must not drink cranberry juice as an increased incidence of bruising has been reported due to the presence of salicylic acid	Excellent	65

Satisfactory, Side-effects no different from an established active drug, Moderate, Larger number of side-effects requiring close follow-up during treatment; Excellent, No different from placebo

herbal preparations are the mixture containing a huge range of biological compounds, it might not be known which component offers the exact pharmacological effects or clinical benefits. The determination of herb components, dosage and course of herb treatment becomes a challenge for clinical employment.

Finally, we propose that, in order to build a database for a successful therapy of IBD with plant-derived remedies, the treatment results observed by physicians and/or patients should be reported in medical journals. Such evidence-based scientific observations and case reports may encourage the pharmaceutical companies, naturopaths, and government agencies to undertake large scale clinical trials to assess the long-term safety and efficacy of the alternative therapies for treating CD and UC in humans.

Concluding remarks

Regarding the published data on the effect of various herbals and plants used in experimental models of colitis we

can conclude that the number of studies was satisfactory, and the results of all studies concerning the estimated clinical, histological and serum parameters were beneficial. It must be emphasized that all herbals with favorable efficacy in clinical trials produced similar beneficial results in experimental colitis [93].

Treatment of IBD patients is quite expensive. The cost of herbal therapy is probably similar or even smaller compared to that of conventional treatment of IBD. Studies investigating the real cost of herbal therapy must be also conducted. Large double-blind clinical studies assessing the most commonly used herbals are needed. Pharmaceutical companies must aid to the current knowledge by supporting relevant studies even if their financial gain would be much less compared to other kinds of treatment. International scientific societies and governmental organizations should take seriously the locally available opportunities of drug development by financially supporting clinical studies. There is a need for more essential representation of alternative medicine in under- and postgraduate medical education. With discerned safety of herbs, herb medicine itself or in combination with conventional therapies would largely benefit IBD patients.

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