Annals of Gastroenterology (2015) **28,** 210-220

Herbal and plant therapy in patients with inflammatory bowel disease

Aikaterini Triantafyllidi[a], Theodoros Xanthos[a], Apostolos Papalois[b], John K. Triantafillidis[c]

University of Athens Medical School; ELPEN Pharma; Iaso General Hospital, Athens, Greece

Abstract

The use of herbal therapy in inflammatory bowel disease (IBD) is increasing worldwide. The aim of this study was to review the literature on the efficacy of herbal therapy in IBD patients. Studies on herbal therapy for IBD published in Medline and Embase were reviewed, and response to treatment and remission rates were recorded. Although the number of the relevant clinical studies is relatively small, it can be assumed that the efficacy of herbal therapies in IBD is promising. The most important clinical trials conducted so far refer to the use of mastic gum, tormentil extracts, wormwood herb, *aloe vera*, *triticum aestivum*, germinated barley foodstuff, and *boswellia serrata*. In ulcerative colitis, *aloe vera* gel, *t*riticum aestivum, andrographis paniculata extract and topical Xilei-san were superior to placebo in inducing remission or clinical response, and curcumin was superior to placebo in maintaining remission; *boswellia serrata* gum resin and *plantago ovata* seeds were as effective as mesalazine, whereas oenothera biennis had similar relapse rates as ω-3 fatty acids in the treatment of ulcerative colitis. In Crohn's disease, mastic gum, *Artemisia absinthium*, and *Tripterygium wilfordii* were superior to placebo in inducing remission and preventing clinical postoperative recurrence, respectively. Herbal therapies exert their therapeutic benefit by different mechanisms including immune regulation, antioxidant activity, inhibition of leukotriene B4 and nuclear factor-kappa B, and antiplatelet activity. Large, double-blind clinical studies assessing the most commonly used natural substances should urgently be conducted.

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

Ann Gastroenterol 2015; 28 (2): 210-220

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic idiopathic inflammatory bowel diseases (IBD) involving the large bowel (UC) or the small and large bowel (CD), in which patients require both induction and maintenance treatment [1]. The conventional treatment of IBD includes the use of corticosteroids, immunosuppressants, antibiotics, and biologic agents (anti-tumor necrosis factor (TNF)-α). However, the use of these drugs is accompanied by a certain number of side effects, with some of them being quite severe [1].

[a]MSc Cardiopulmonary Resuscitation, University of Athens Medical School (Aikaterini Triantafyllidi, Theodoros Xanthos); [b]Experimental-Research Laboratory ELPEN Pharma (Apostolos Papalois); [c]Inflammatory Bowel Disease Unit, "IASO General" Hospital (John K. Triantafillidis), Athens, Greece

Conflict of Interest: None

Correspondence to: Prof. John K. Triantafillidis, 354 Iera Odos, Haidari, 12461, Greece, e-mail: jktrian@gmail.com

Received 14 August 2014; accepted 3 November 2014

The term complementary or alternative medicine (AM) refers to both diagnostic and therapeutic strategies existing outside medical centers where conventional medicine is practiced [2]. Natural products, e.g. products derived from plants and herbals, are increasingly used by IBD patients.

In this review, the authors evaluate the clinical studies concerning the natural products used by IBD patients as an alternative treatment method for either induction or maintenance treatment.

Methodology

A computerized search strategy using Medline and Embase databases up to April 2014 was implemented. The medical subject headings applied were: "alternative medicine" or "herbal medicine" and "inflammatory bowel disease", or "Crohn's disease", or "ulcerative colitis". In order to obtain information concerning the physical characteristics of the herbal investigated in the clinical studies, relevant reviews published in the international scientific literature were used. All full-length randomized,

placebo-controlled or controlled against a conventional treatment clinical studies were included in the analysis. Then, studies deemed eligible for inclusion were manually searched. Studies were divided into those that have assessed the use of herbal therapy for the induction of remission and maintenance of remission in UC, and the induction of remission and prevention from operative recurrence for CD. Data collection included types of herbal administered, treatment duration, length of follow up, remission and response rates, and adverse effects.

Results

From 1993 to April 2014, we identified 27 clinical studies dealing with herbal therapy in IBD. There were 17 studies of herbal therapy in UC and 10 studies in CD, including 1,874 individuals in total (Table 1). The mean age of subjects was 43 years. No significant differences concerning the number of male and female patients participating in the trials was recorded.

The most important of the available data concerning the use of herbals and plants in the treatment of IBD patients are summarized below.

UC

So far a total number of 17 clinical studies related to the treatment of either active or inactive UC with the use of herbal products have been published. The total number of patients included was 1421. These studies compared the effectiveness of herbal treatment with either drugs used regularly by patients with UC or placebo. In a minority of studies, herbal treatment was tested while the patients were receiving their regular treatment. The number of patients included in each study varied between a few dozen to more than 200. In studies dealing with induction treatment of active disease, the duration of treatment varied between 4 and 12 weeks, while in studies dealing with maintenance treatment fluctuated between 6 and 12 months.

Table 1 Number of clinical studies performed so far and number of patients included

Disease	Number of studies	Number of patients
UC (active disease)	11	1008
UC (maintenance treatment)	6	413
CD (active disease)	6	222
CD (post-operative maintenance treatment)	4	231
Total	27	1874

UC, ulcerative colitis; CD, Crohn's disease

Treatment of active disease

The total number of studies referring to the treatment of active UC was 11 and the number of patients included was 1008 (Table 1).

Aloe vera (Xanthorrhoeaceae)

Aloe vera is a herbal preparation with significant anti-inflammatory effects. The leaves of the plant contain an abundance of phytochemical substances including acetylated mannans, polymannans, anthraquinone C-glycosides, anthrones, anthraquinones (emodin), and lectins, most of which are under intense search.

In a double-blind, randomized, placebo-controlled trial, 44 hospital outpatients with mild to moderately active UC were randomly given oral *aloe vera* gel or placebo, 100 mL b.i.d. for 4 weeks, in a 2:1 ratio. Oral administration of *aloe vera* produced a clinical response more often than placebo; it also reduced the histological disease activity and appeared to be safe [3].

This herbal seems to be effective in some proportion of patients with active UC. Further studies are necessary using different doses in larger number of patients.

Triticum aestivum (Poaceae)

Triticum aestivum, common as bread wheat, is an annual grass belonging to the *Poaceae* family. It can be found in the form of liquid or powder. It contains chlorophyll, aminoacids, vitamins and various enzymes. The plant can be used as food, or as a drug with unique therapeutic potentials for which, however, there is no strong scientific support. It can be found as a fresh product, tablets, frozen juice, or powder.

In a randomized, double-blind, placebo-controlled study, 23 patients with active distal UC were allocated to receive either 100 mL of wheat grass juice (*Triticum aestivum*), or placebo, daily, for 1 month. Ten of 11 patients in the active treatment showed endoscopic improvement in comparison with 3 of 10 in the placebo group. Treatment was associated with significant reduction in the overall disease activity index and in the severity of rectal bleeding. Apart from nausea, no other serious side effects were noticed [4].

Andrographis paniculata (Acanthaceae)

Andrographis paniculata, a plant belonging to the family of *Acanthaceae*, grows mainly in India και Sri Lanka, as well as in South and South-Eastern Asia.

A recent randomized, double-blind, placebo-controlled study compared the extract of *Andrographis paniculata* (HMPL-004) with placebo in 224 adult patients with mild to moderately active UC. Treatment with HMPL-004 in a dose of 1800 mg per day resulted in a statistically significantly better clinical response compared to placebo (60% vs. 40%; P=0.018), although the proportion of remission after 8 weeks did not differ in the two groups [5].

The second study was also a randomized, double-blind, multicenter study of an 8-week duration with parallel groups. The study showed that HMPL-004 had similar effectiveness with mesalazine (response 76% vs. 82%; remission 21% vs.

16%) in patients with mild to moderate UC. In this study, there was no difference in the proportion of endoscopic remission in the two groups after 8 weeks (28% vs. 24%) [6].

Boswellia serrata (Burseraceae)

Boswellia (*Boswellia serrata)* belongs to the family of trees producing resin that are well-known for their good-smelling oil. *Boswellia* trees have a thick trunk that produces juice rich in carbohydrates, essential oils and acids called "boswellic acids". These acids seem to be the active component of the plant being responsible for its therapeutic capabilities.

The initial clinical studies suggested that *Boswellia serrata* resin could be effective in IBD. In 2002, the European Medicines Agency categorized *Boswellia serrata* gum resin extract in the category of "orphan drugs". *Serrata* gum resin extracts could influence the immune system in many ways. *Boswellia serrata* represses the formation of leukotriene via inhibition of 5-lipoxygenase with the action of two *boswellia* acids, namely 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid [7].

In the only available study, 30 patients with UC were randomized to receive either *Boswellia serrata* resin (900 mg/d in 3 doses, n=20) or sulfasalazine (3 g/d in 3 doses, n=10) for 6 weeks. Remission of the disease was achieved in 14 of 20 patients who received *Boswellia* gum resin, compared with 4 of 10 who received sulfasalazine [8]. Larger studies are urgently needed.

Jian Pi Ling (JPL)

JPL is considered as one of the current plant treatments in patients with UC. It consists of 9 components and is available in the form of tablets containing 0.75 g of dry herbal.

In a relevant study, 153 patients with UC were randomized in 3 groups. Group I: JPL tablet with Radix *Sophorae flavescentis* and *Flos sophorae* decoction; Group II: sulfasalazine and dexamethasone; Group III: placebo and enema decoction as in group I. The rate of remission after 3 months in group 1 was significantly higher (53%) compared with the rate of remission in the two other groups (28% and 19% respectively) [9]. However, the low rate of remission achieved in the two control groups raises questions about the real value of this study's results.

Tormentil extracts (*Tormentilla erecta-Rosaceae*) *Potentilla erecta* (*Tormentilla erecta*, *Potentilla tormentilla* widely known as tormentil or septfoil) is a plant belonging to the family of *Rosaceae*.

Tormentil extracts have antioxidative properties and thus, it might be used as a complementary therapy for chronic IBD. In a relevant study, 16 patients with active UC received Tormentil extracts in escalating doses of 1200, 1800, 2400 and 3000 mg/d for 3 weeks each. During therapy with 2400 mg Tormentil extracts per day, median clinical activity index and CRP improved from 8 (6 to 10.75) and 8 (3 to 17.75) mg/L at baseline to 4.5 (1.75 to 6) and 3 (3 to 6) mg/L, respectively. During therapy, clinical activity index decreased in all patients, whereas it increased during the washout period [10]. Tormentil extracts appeared safe up to 3000 mg/d.

Xilei-san

Xilei-san is a mixture of herbs of Chinese medicine that harbors significant anti-inflammatory properties. It seems to be effective in a number of inflammatory conditions including digestive disorders such as esophagitis.

In an 8-week randomized, double-blind study, the Xilei-san mixture was compared with dexamethasone enema in 35 patients with mild to moderately severe ulcerative proctitis for 12 weeks. A similarly significant clinical, histological and endoscopic response compared with the baseline values in the two groups was achieved [11].

In another controlled study, 30 patients with intractable ulcerative proctitis were randomized to receive either Xilei-san or placebo suppositories for 2 weeks. The number of patients who achieved an improvement in the clinical activity index as well as in the endoscopic and histological index, was higher in the group of Xilei-san compared with the group of placebo ($P<0.04$) [12]. The rate of recurrence after 6 months was lower in the arm of active treatment.

No significant side effects were observed in both studies.

Anthocyanin-rich bilberry preparation

Anthocyanins, which can be found in large quantities in bilberries (*Vaccinium myrtillus*) were shown to have antioxidative and anti-inflammatory effects.

In the only available study Biedermann *et al* [13] explored the possible therapeutic potential of bilberries in active UC. Thirteen patients with mild to moderate UC were treated with a daily standardized anthocyanin-rich bilberry preparation for 9 weeks. At the end of the 6th week 63.4% of patients achieved remission and 90.9% showed a response. A significant decrease in the Mayo score was also detected in all patients. Interestingly, the fecal calprotectin levels significantly decreased during treatment phase although an increase in the calprotectin levels and disease activity was observed after cessation of bilberry intake. No serious adverse events were observed. The results clearly indicate a therapeutic potential of bilberries in UC.

Fufangkushen colon-coated capsule (FCC)

FCC is a newly developed herbal drug for the treatment of UC patients with Chinese medicine pattern of damp-heat accumulating in the interior, consisted of *Sophorae flavescentis, Sanguisorba officinalis L., Indigo naturalis, Bletilla striata* and *Glycyrrhiza uralensis.*

In order to test the efficacy and safety of FCC in patients with active UC Gong *et al* [14] recently performed a double-blinded, randomized clinical trial comparing FCC with Huidi (HD, mesalazine enteric-coated tablets). In this study 320 active UC patients were assigned to two groups: 240 treated with FCC plus HD placebo treatment and 80 with HD plus FCC placebo for 8 weeks. At the 8th week, 72.5% of patients in FCC group and 65.0% of patients in HD group achieved a clinical response and 41.5% in FCC group vs. 41.25% in HD group clinical remission (no significant differences). The rate of mucosal healing at week 8 was also similar in the two groups. Similar safety profiles in the 2 groups were also seen. FCC seems to be equally effective and safe in the treatment of active UC compared with mesalazine.

Table 2 Studies on herbal and plant product treatment of patients with active ulcerative colitis

Author/ year	CAM	No of patients	Comparisons	Treatment duration	Remission/response rate in the active treatment	Remission/ response rate in the control treatment	Conclusion
Sandborn *et al*, 2013	HMPL-004	224	Placebo	8 weeks	45 & 60 34 & 38	40 25	HMPL-004 at a dose of 1,800 mg/d achieved clinical response better than placebo
Biedermann *et al*, 2013	Anthocyanin-rich bilberry preparation	13	No comparative arm	9 weeks	63.4% remission, 90.9% response	No comparative arm	The results indicate a therapeutic potential of bilberries in UC
Zhang *et al*, 2013	Xilei-san enema	35	Dexamethasone enemas	8 weeks	-	-	Xilei-san enemas are comparable to dexamethasone enemas An alternative drug in the treatment of active UP
Fukunaga *et al*, 2012	Xileisan suppositories	30	Placebo suppositories	2 weeks	Higher number of patients in remission vs placebo		Significant clinical and endoscopic efficacy of Xilei San in patients with intractable U proctitis
Gong *et al*, 2012	Fufangkushen colon-coated capsule (FCC)	320 (240 with FCC plus HD)	Huidi (HD) mesalazine enteric-coated tablets 80 with HD plus FCC placebo	8 weeks	72.5% of patients in FCC group (170/234)	65.0% of patients in HD group (52/80) had achieved a clinical response (P>0.05)	Compared with HD, FCC is similarly effective and safe in the treatment of active UC
Tang *et al*, 2011	HMPL-004	120	Mesalazine	8 weeks	21 & 76 respectively	16 & 82 respectively	Efficacious alternative to mesalazine in active UC
Huber R *et al*, 2007	Tormentil extracts in escalating doses of 1200, 1800, 2400 and 3000 mg/d	16	-	3 weeks	During therapy with 2400 mg TE/d, CAI and CRP improved and CAI decreased in all patients	-	TE appeared safe up to 3000 mg/d
Langmead *et al*, 2004	*Aloe vera*	44	Placebo	4 weeks	30	7	Oral *aloe vera* produced a clinical response more often than placebo and reduced the histological disease activity
Ben-Arye *et al*, 2002	*Triticum aestivum*	23	Placebo	4 weeks	91	42	Effective and safe as a single or adjuvant treatment of active distal UC
Gupta *et al*, 2001	*Boswellia serrata*	30	Sulfasalazine	6 weeks	70	40	*Boswellia serrata* gum resin could be effective in the treatment of UC
Chen *et al*, 1994	Jian Pi Ling (JPL) tablet	153	Sulfasalazine (S), Placebo (P)	90 days	53	28 (S) 19 (P)	JPL seems to be the best therapeutic program

FCC, fufangkushen colon-coated capsule; JPL, Jian Pi Ling tablet; UC, ulcerative colitis; CRP, C-reactive protein; CDAI, Crohn's disease activity index

Table 2 shows the results of the effectiveness of herbal and plant products administration in the response and remission rate of patients with active UC.

Maintenance treatment of UC

So far, a small number of clinical trials have been published concerning the role of plant products in the maintenance treatment of UC patients. These studies are analyzed subsequently.

Curcumin

Curcumin is a biologically active phytochemical substance showing antioxidant, anti-inflammatory, anticarcinogenic, hypocholesterolemic, antibacterial, wound-healing, antispasmodic, anticoagulant, antitumor and hepatoprotective activities. Curcumin inhibits many cytokine pathways including interleukin (IL)-6, concurrently having a favorable safety profile. Its anti-inflammatory and antioxidant effect has been shown in numerous animal models.

Hanai *et al* [15] evaluated the usefulness of curcumin in 89 patients with quiescent UC. Forty-five patients received 1 g curcumin b.i.d. along with sulfasalazine or mesalamine, and 44 received placebo plus sulfasalazine or mesalamine for 6 months. Curcumin significantly improved both the clinical activity index and the endoscopic index. Recurrence rates were significantly lower in the curcumin group compared with placebo. Curcumin seems to be promising and safe medication for maintaining remission in patients with quiescent UC.

Plantago ovata (Plantaginaceae)

Plantago ovata is a small plant with characteristic flowers. The juice derived from the plant leaves, has been used in the treatment of peptic ulcer and pain accompanying inflammatory conditions. The plant has anti-inflammatory and anti-oxidative properties. It inhibits the protein kinase C, it down-regulates the expression of intercellular adhesion molecule-1 and inhibits the inflammation produced from 5-hydroxy-6,8,11,14-eicosatetraenoic acid and leukotriene B_4. The enzymatic dissolution of the seeds of Plantago ovata results in the production of short chain fatty acids that have favorable effects in patients with patients with UC.

In an open clinical study, 105 patients with UC in remission were randomized to receive either *Plantago ovata* seeds (10 g b.i.d.), mesalazine (500 mg t.i.d.), and *Plantago ovata* seeds with mesalazine in the same doses. The rate of recurrence after 6 months did not differ in the three groups (40% vs. 35% vs. 30%) [16]. There were few side effects mainly constipation and abdominal bloating.

Oenothera biennis

Oenothera biennis belongs to the group of *Oenothera* which can be found in North America and other tropical and subtropical countries. The evening primrose oil is the main product of the plant. The main constituent of *Oenothera biennis* seeds is the γ-linolenic acid.

The plant has been used as maintenance treatment in patients with UC with moderate results. In a placebo-controlled study, 43 patients with UC were randomized to receive MaxEPA (n=16), super evening primrose oil (n=19), or olive oil as placebo (n=8) for 6 months plus their regular maintenance treatment with 5-aminosalicylates (5-ASA). Treatment with super evening primrose oil increased the concentrations of dihomogamma-linolenic acid (DGLA) of red cell membrane ($P<0.05$) and the stool form during the first 6 months, compared to MaxEPA and placebo and this difference was continued 3 months after cessation of treatment ($P<0.05$). Evening primrose oil could offer some benefit in patients with UC [17].

Germinated barley foodstuff (GBF)

GBF represents the final product of dryness and fermentation of barley. It is based on recipes of traditional Chinese medicine having many beneficial physiological effects. GBF, which mainly consists of dietary fiber and glutamine-rich protein, is essentially a prebiotic that can reduce the clinical activity of UC over long-term as well as short-term administration [18].

In a relevant study, 59 patients with UC in remission were divided into two groups, control group (n=37) who received conventional treatment for 12 months and GBF group (n=22) who received conventional treatment plus 20 g of GBF daily. Significantly better activity index values were seen in the GBF group at 3, 6, and 12 months compared with control group. The cumulative recurrence rate in the GBF group with steroid tapering treatment was significantly lower compared with the value in the control group. No side effects related to GBF were noticed [19].

It seems that GBF is an effective and safe herbal in the maintenance treatment of UC having also the ability to taper steroid treatment.

Extract of myrrh, dry extract of chamomile flowers and coffee charcoal

It is well known that the herbal mixture of myrrh, dry extract of chamomile flowers and coffee charcoal has anti-inflammatory and antidiarrheal properties.

In the only one so far available randomized, double-blind, double-dummy study 96 patients with inactive UC were randomized to receive either the herbal preparation or mesalazine over a 12-month period. There was no significant difference in the relapse rate between the two groups (45% in the mesalazine group and 53% in the herbal group). No significant differences were also shown in relapse-free time, endoscopy and fecal biomarkers [20]. The herbal preparation was well tolerated and showed a good safety profile.

Table 3 shows the results of clinical trials with plant products of patients with UC in remission.

CD

Although the number of studies concerning the role of natural products in the treatment of active CD is quite small, their results are interesting. These studies are subsequently analyzed.

Active CD

Chios mustic gum (Pistacia lentiscus-Anacardiaceae)

Pistacia lentiscus var *Chia* belongs to the family of *Pistacia*. This tree is unique in the world because it produces a special resin (mastic gum). The mastic tree belongs to the family of *Anacardiaceae*. Mastic gum is a natural product produced by trees growing exclusively in the Greek island of Chios. Its aromatic and therapeutic characteristics are well-known for centuries. It contains a large number of antioxidant substances, most of which have been recently identified.

In a relevant study, the effectiveness of mastic on the clinical course and plasma inflammatory mediators of patients with active CD was evaluated. Recruited to a 4-week treatment with mastic caps (6 caps/d, 0.37 g/cap) were 10 patients and 8 controls. It was found that mastic treatment significantly

Table 3 Clinical trials with plant products in patients with ulcerative colitis in remission

Authors/ year	CAM	No of patients	Comparisons	Treatment duration	Remission on CAM (%)	Remission on placebo or active drug (%)	Conclusion
Langhorst *et al*, 2013	Herbal combination of myrrh, dry extract of chamomile flowers and coffee charcoal	96	Mesalazine	12 months	25/47 (53)	22/49 (45) (P=0.540)	Efficacy non-inferior to mesalazine
Hanai *et al*, 2006	Curcumin	89	Placebo	6 months	95	79	Promising and safe for maintaining remission in quiescent UC
Hanai *et al*, 2004	Germinated barley foodstuff (GBF) 20 g of GBF daily	59 patients Controls (n=37) GBF (n=22)	Control group: Conventional therapy alone for 12 months	12 months	Significantly better CAI values in the GBF group at 3, 6, and 12 months	Compared with the values in the control group	GBF appeared to be effective and safe as a maintenance therapy to taper steroids and prolong remission in UC
Kanauchi *et al*, 2003	Germinated barley foodstuff (GBF)	21	No placebo arm	6 months	Significant decrease in clinical activity index compared with control group (P<0.05)	No placebo arm	GBF may have a place in long-term management of UC
Fernandez-Banares *et al*, 1999	*Plantago ovata* seeds	105	Mesalazine	12 months	60	65	Similarly effective to mesalazine. Side effects: Constipation, abdominal bloating
Greenfield *et al*, 1993	*Oenothera biennis*	43	Evening primrose oil & olive oil	6 months	–	–	Evening primrose oil could offer some benefit in patients with UC

CAM, complementary or alternative medicine; CD, Crohn's disease; UC, ulcerative colitis; GBF, germinated barley foodstuff

decreased the CD activity index (CDAI) and the plasma levels of IL-6 and CRP [21].

In a subsequent study, the same group of investigators noticed that treating CD patients with mastic resulted in the reduction of TNF-α secretion. Migration inhibitory factor release was also significantly increased, meaning that random migration and chemotaxis of monocytes/macrophages were inhibited. It seems that mastic acts as an immunomodulator on peripheral blood mononuclear cells, acting as a TNF-α inhibitor and a migration inhibitory factor stimulator [22].

We strongly suggest that larger, double-blind, placebo-controlled studies are required in order to further clarify the role of this significant natural product in the treatment of patients with active CD.

Wormwood herb (Artemisia absinthium-Asteraceae)

Absinth wormwood is a herbaceous perennial plant with a distinctive smell of sage. It has traditionally been used to treat various digestive disorders. It is traditionally made by a distillation of neutral alcohol, various herbs, spices and water. The European Union permits a maximum thujone level of 35 mg/kg in alcoholic beverages where Artemisia species is a listed ingredient, and 10 mg/kg in other alcoholic beverages.

So far, two studies have been published concerning the possible therapeutic results of this herbal in patients with active CD. In the first one, 40 patients with CD receiving 40 mg of prednisone daily for at least 3 weeks were administered a herbal blend containing wormwood herb (3x500 mg/day) or placebo for 10 weeks. After 8 weeks, there was almost complete clinical remission in 65% patients as compared to none in the placebo group. This remission persisted until the end of the observation period. It was also noticed that wormwood had a steroid sparing effect and a positive effect on the quality of life of patients [23].

In the second study, 20 patients with active CD received dry powder of wormwood or placebo while being on their previous regular treatment. After 6 weeks, 8 of 10 (80%) of patients receiving wormwood and 2 of 10 (20%) receiving placebo achieved remission. Clinical response was noticed in 6 of 10 of the group of wormwood compared to none of the group of placebo [24]. The available data so far concerning this plant seem to be promising.

Cannabis (Cannabis sativa L. - Cannabaceae)

Cannabis sativa is an annual herbaceous plant in the *Cannabis* genus, a species of the *Cannabaceae* family. Although the main psychoactive constituent of *Cannabis* is tetrahydrocannabinol, the plant contains almost 60 cannabinoids. Differences in the chemical composition of *Cannabis* varieties may produce different effects in

humans. The marijuana plant cannabis is known to improve inflammatory processes, while experimental evidence suggests that the endogenous cannabinoid system inhibits colonic inflammation, leading to the conclusion that cannabis may have a therapeutic role in IBD.

In a retrospective observational study, disease activity, use of medication, need for surgery and hospitalization rate before and after cannabis use in 30 patients (26 males) with CD was investigated. Of the 30 patients, 21 significantly improved after treatment while the need for other medication was significantly reduced. Fifteen of the patients had 19 surgeries during an average period of 9 years before cannabis use, but only 2 required surgeries during an average period of 3 years of cannabis use [25]. In another study, a comparable proportion of UC and CD patients reported lifetime or current cannabis use [26].

During the forthcoming years, the plant might be widely used in the treatment of IBD patients. Changes in the relevant legislation, as well as the use of the plant after the patients' informed consent, would play a significant role in the adoption of this kind of treatment. It is, however, necessary to accurately confirm the safety and effectiveness of the plant by performing large clinical studies.

Boswellia serrata extract

Pilot clinical studies support the potential of *Boswellia serrata* gum resin extract for the treatment of IBD. Extracts from the gum resin of *Boswellia serrata* affect the immune system in different ways. It could suppress leukotriene formation via inhibition of 5-lipoxygenase by two boswellic acids, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.

In a randomized double-blind study, 102 patients with active CD randomized to receive Boswellia serrata extract (H15) or mesalazine. The mean reduction in the CDAI was 90 for H15 and 53 for mesalazine [27].

Tripterygium wilfordii Hook F

The traditional Chinese drug *Tripterygium wilfordii Hook F* (*TWHF*), a diterpene triepoxide, represents the main constituent of an extract obtained from *Tripterygium wilfordii*. Triptolide has multiple pharmacological properties (anti-inflammatory, immune modulating, antiproliferative and antiapoptotic).

In a study exploring the potential benefit of *Tripterygium wilfordii*, 20 patients with active CD received tablets containing T2 for 12 weeks. CDAI was significantly reduced during the first 8 weeks, while endoscopic improvement was noticed after 12 weeks. The inflammatory indices including CRP were also reduced [28].

Table 4 shows the results of the clinical studies regarding the role of plant therapy of active CD.

CD: maintenance treatment

Again a small number of studies have investigated the role of plant treatment in the prevention of recurrences in patients with CD.

Boswellia serrata

In a double-blind, placebo controlled study investigating the efficacy of Boswelan in maintaining remission in CD, 82 patients were randomized to either Boswelan (n=42, 3×2 capsules/day; 400 mg each) or placebo (n=40). No differences in the two groups concerning the remission rates were noticed. Regarding safety, no disadvantages of taking the drug compared to placebo were observed [29]. This trial confirmed the good tolerability of Boswelan, although there were no significant differences versus placebo in maintenance of remission.

Tripterygium wilfordii

Two placebo controlled studies and one prospective, single-blind study, investigated the role of *Tripterygium wilfordii* in the prevention of postsurgical relapses in patients with CD.

In the first one 45 patients with CD were randomized to receive either *Tripterygium wilfordii* or mesalazine. No relapse

Table 4 Clinical studies of plant treatment of patients with active Crohn's disease

Author/year	CAM	Number of patients	Comparison	Duration	Remission with CAM (%)	Remission with control agent (%)	Conclusion
Gerhardt *et al*, 2001	*Boswellia serrata* extract H15	102	Mesalazine	-	36%	31%	Better results compared to mesalazine
Kaliora *et al*, 2007	Mastic gum	10	Healthy people	4 weeks	Significant reduction of CDAI and of plasma pro-inflammatory cytokines	Not applied	Effective and safe herbal
Ren *et al*, 2007	*Tripterygium wilfordii*	20	Placebo	12 weeks	–	–	Effective for the treatment of mild or moderately active CD
Omer *et al*, 2007	*Artemisia absinthium*	40	Placebo	10 weeks	65%	0%	The available data seem to be promising
Krebs *et al*, 2010	*Artemisia absinthium*	20	Placebo	6 weeks	80%	20%	Promising results
Naftali *et al*, 2011	Cannabis	30	No	3 months to 9 years	70%	-	Positive effect on disease activity

CDAI, Crohn's disease activity index; CAM, complementary or alternative medicine; CD, Crohn's disease

was noticed three months after operation. Again in 6 and 12 months after the operation the clinical relapse rate did not differ in the two groups (18% vs. 22% and 32% vs. 39%, respectively). No significant differences were observed in the rate of endoscopic recurrence after 12 months (46% vs. 61%) [30].

In the second study, 39 patients with CD were randomized two weeks after enterectomy to receive either *Tripterygium wilfordii* (*n*=21) or sulfasalazine (*n*=18). Clinical recurrence was noticed in 6% in the *Tripterygium wilfordii* group compared with 25% in the group of sulfasalazine. Again, endoscopic recurrence was observed in 22% in the group of *Tripterygium wilfordii* compared with 56% in the group of sulfasalazine. It seems that at least numerically, *Tripterygium wilfordii* is superior compared with sulfasalazine in the prevention from postsurgical recurrences of CD [31].

In the third study postoperative CD patients in remission were randomized to receive 1 mg/kg *Tripterygium wilfordii* polyglycoside daily, orally, or 4 g 5-ASA daily, orally, for 52 weeks. Twenty-one patients received *Tripterygium wilfordii* polyglycoside and 18 5-ASA [32]. The results showed that clinical and endoscopic recurrences were less common in the *Tripterygium wilfordii* polyglycoside group (n=4) versus the 5-ASA group (n=9).

Taking into account the results of the above mentioned studies it seems that *Tripterygium wilfordii* polyglycoside appears to be an effective, well-tolerated drug superior to oral 5-ASA, for preventing clinical and endoscopic recurrence in postsurgical CD.

Table 5 shows the results of the studies investigating the role of herbal treatment in the prevention of relapses of CD.

Discussion

Use of AM by the patients with IBD at least for a short period of time is quite frequent reaching a proportion of 50% while the use of herbals as treatment of either active or quiescent disease exceeds the proportion of 58% [33].

Clinical results

The available clinical studies showed that herbal treatment produces clinical remission or improvement in patients with mild or moderate IBD at least similar to that of drugs already used in the treatment of IBD patients, although a minority of studies did not noticed beneficial effects. For example, curcumin showed better results compared to placebo in the maintenance treatment of patients with UC. Other herbals, such as *Aloe vera* and *Boswellia serrata,* were effective in patients with active UC. In cases of proctitis, the wheat grass juice showed excellent results, while HMPL-004 was superior to placebo and equally effective with mesalazine in the prevention from recurrences in patients with UC. Patients with UC showed better results compared with patients with CD, although the number of clinical studies in patients with CD was quite smaller [34].

However, there are studies showing no positive results. The reasons are probably related to the poor design of studies, the small number of patients included, the variety of substances tested, the inadequate dose of the herbals, and the improper analysis and description of the results [35].

Treatment of patients with IBD either for active disease or maintenance is quite expensive. This cost could be unsustainable for most people in many countries. On the other hand, the cost of herbal therapy is probably similar or even smaller to the cost of conventional treatment of IBD.

Cellular/molecular/systemic effects of described plant preparations

A lot of clinical and especially experimental work has suggested that, individual chemical substances derived from the described plants and herbals may have antibacterial, antioxidant, antiinflammatory, and immunoreguratory properties. For example curcumin has antioxidant, anti-inflammatory, anticarcinogenic, hypocholesterolemic, antibacterial, wound-healing, antispasmodic, anticoagulant,

Table 5 Clinical studies of plant treatment of patients with Crohn's disease in remission

Authors/year	CAM	No of patients	Comparisons	Treatment duration	Remission on CAM (%)	Remission on placebo or active drug (%)	Conclusion
Tao *et al*, 2009	*Tripterygium wilfordii* (post-op CD)	45	Mesalazine	6 months 12 months	82% (6 months) 68% (12 months)	78% (6 months) 61% (12 months)	Effective and safe
Liao *et al*, 2009	*Tripterygium wilfordii* (post-op CD)	39	Sulfasalazine	–	94%	75%	Effective and safe
Holtmeier *et al*, 2010	*Boswellia serrata* extract (Boswelan, PS0201Bo)	108	Placebo	52 weeks	60%	55%	Good tolerability. Superiority versus placebo remission is not demonstrated
Ren *et al*, 2013	*Tripterygium wilfordii* (post-op CD)	39	Mesala zine	52 weeks	79%	53%	Effective, superior to oral 5-ASA, for preventing clinical and endoscopic recurrence in post-op CD

CD, Crohn's disease

Table 6 Cellular, molecular and systemic effects of described plant and herbal preparations

Herbal and plant	Cellular, molecular and systemic effects
Boswellia serrata (Boswellic acid)	Selective inhibition of 5-lipoxygenase Anti-inflammatory effects Direct inhibition of intestinal motility Reduction of chemically induced edema and inflammation in the intestine in rodents
Tormentil extracts	Antioxidative properties
Curcumin	Decreased activity 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-κB Binds to thioredoxin reductase and irreversibly changes its activity Increased activity IL-10, IL-4, Prostaglandin E2
Germinated barley foodstuff (GBF)	Increases luminal butyrate production by modulating the microfloral distribution Prebiotic action High water holding capacity
Oenothera biennis	The mature seeds contain 7-10% γ-linolenic acid (essential fatty acid)
Plantago ovata	Anti-inflammatory and anti-oxidative properties Inhibits protein kinase C Down-regulates the expression of intercellular adhesion molecule-1 Inhibits the inflammation produced from 5-hydroxy-6,8,11,14-eicosatetraenoic acid and leukotriene B_4
Anthocyanins	Antioxidative effects Anti-inflammatory effects
Xilei San	Anti-inflammatory effects
Aloe vera	*In vitro* inhibition of prostaglandin E2 and IL-8 secretion
Triticum aestivum	Antioxidant properties
Mastic gum	Anti-inflammatory Antioxidant

IL, interleukin

antitumor and hepatoprotective activities [36]. *Boswellia serrata* has significant immunoregulatory properties. Boswellic acids (the active moiety of *Boswellia*) reduces the levels of TNF-α by suppressing the biosynthesis of leukotrienes via inhibition of 5-lipoxygenase [37,38]. The extracts of wormwood (*Artemisia absinthium*) could reduce TNF-α and other proinflammatory cytokines. *Andrographis paniculata* inhibits *in vitro* the production of TNF-α, IL-1β and nuclear factor-κB. Moreover, the polysaccharide content of herbal and plant preparations suggests that they might also have prebiotic properties. Other herbal preparations such as GBF have prebiotic characteristics that could increase luminal butyrate production by modulating the microfloral distribution [18,39].

However, we must bear in mind that the results obtained from *in vitro* studies of an herbal preparation are not equally effective *in vivo*. This is because many factors including the amount of the active substance contained in the extract as well as interactions between individual constituents could interfere with the results obtained in IBD patients.

A summary of cellular and systemic effects of the described herbal and plants are shown in Table 6.

Safety of herbal treatment

Most of the published trials showed no side effects. In fact, the number and type of side effects were similar to those of placebo or mesalazine. This is quite important in patients with previous operations or patients who experienced significant side effects being on conventional treatment.

Curcumin and mastic gum probably represent the safest herbals. Curcumin is well tolerated without any serious toxicity and side effects. Several clinical studies have confirmed its safety in humans with no treatment-related toxicity up to 8,000 mg/day for 3 months. Only minor gastrointestinal adverse events, such as nausea and diarrhea, have been reported [40]. On the other hand, no side effects related to mastic gum consumption even after long-term use has been described.

Again, we must bear in mind that herbal therapy, in general, could carry risks and produce side effects similar to other forms of alternative therapy. Liver and renal failure has been described with some of them, fortunately not with those used in the treatment of IBD patients.

Toxic effects could also be associated with the inclusion of prescription medicines in some herbal preparations including corticosteroids, and glibenclamide [41]. Toxic products such as mercury, arsenic, and lead, can be found in some plant preparations.

However, the most important side effect of the use of herbal preparations is the abandonment of the drugs used in the treatment of IBD, a fact that may lead to severe or complicated IBD. On the other hand, patients with IBD initially consulting alternative doctors may be erroneously diagnosed as suffering from irritable bowel syndrome or other disease Finally, it must be stressed that the long-term safety of herbal treatment including possible mutagenicity and carcinogenicity has not adequately be explored. We suggest that future trials could combine a safe herbal product with conventional drugs thus improving treatment outcome without increasing toxicity.

A summary of the most important side effects reported so far are mentioned in Table 7.

Table 7 Safety of the main herbal and plants used in inflammatory bowel disease treatment

Herbal and plant	Side effects	Safety
Fufangkushen colon-coated capsule (FCC)	Mild or moderate degree of nausea, fatigue, abdominal pain and distension, anal pain, upper respiratory tract infection, dyspepsia, fever. Similar in active substance and mesalazine [15.9% vs. 12.5]	Satisfactory
Boswellia serrata	*Boswellia serrata* is rich in guggalsterones, that increase the thyroid function, leading to weight loss	Satisfactory
Tormentil extracts	Mild upper abdominal discomfort Incidence of side effects: 38% No discontinuation of the medication was needed	Satisfactory Safe up to 3000 mg/d
Wheat grass juice	No serious side effects were reported	Excellent Safe as a single or adjuvant treatment of active distal UC
Germinated barley foodstuff (GBF)	No side effects related to GBF were observed	Excellent
Oenothera biennis	Safety has not been evaluated in pregnant or nursing women	Satisfactory
Plantago ovata	Hypersensitivity, after inhaled or ingested psyllium Temporary gas and/or bloating	Satisfactory
Anthocyanins	No serious adverse events have been described	Satisfactory
Xilei San	Well tolerated topically without safety concerns	Satisfactory
Jian Pi Pian (Wan)	Safely used with few adverse effects	Satisfactory
Andrographis	Headache, fatigue, rash, bitter/metallic taste, diarrhea, pruritus, and decreased sex. Anaphylactic reaction in an HIV-positive patient	Moderate
Triticum aestivum L	The grain could cause poisoning in stock, though no toxic substance has been found Wheat can absorb toxic concentrations of selenium. However, "selenium" wheat rarely causes poisoning	Moderate
Mastic gum	No side effects have been reported	Excellent

Satisfactory: Side effects not different from an established active drug, Moderate: Larger number of side effects requiring close follow up during treatment, Excellent: No difference from placebo, UC, ulcerative colitis

Concluding remarks

The available data concerning the administration of extracts derived from plants and herbals give the gastroenterologist the excuse to explain to our patients the benefits of this therapy, concurrently providing evidence-based information about their use [42]. Pharmaceutical companies must aid to the current knowledge by supporting relevant studies even if their financial gain would be much lower compared to other kinds of treatment. Both international scientific societies and government organizations should take seriously the locally available opportunities of drug development by financially supporting relevant clinical studies. It is true that the cost of treatment of IBD patients is continuously raising and herbal treatment might represent a new effective and cheap treatment method [43]. Doctors must become more tolerant and open-minded about the benefits of AM. Finally, there is a need for more essential representation of AM in under- and postgraduate medical education.

References

1. Triantafillidis JK, Stanciu C (eds). Inflammatory bowel disease: etiopathogenesis, diagnosis, treatment. 4th Edition, "Technogramma", 2012 Athens, Greece.
2. Zollman C, Vickers A. What is complementary medicine? *BMJ* 1999;**19**:693-696.
3. Langmead L, Feakins RM, Goldthorpe S, et al. Randomized, double-blind, placebo-controlled trial of oral aloe vera gel for active ulcerative colitis. *Aliment Pharmacol Ther* 2004;**19**:739-747.
4. Ben-Arye E, Goldin E, Wengrower D, Stamper A, Kohn R, Berry E. Wheat grass juice in the treatment of active distal ulcerative colitis: a randomized double-blind placebo-controlled trial. *Scand J Gastroenterol* 2002;**37**:444-449.
5. Sandborn WJ, Targan SR, Byers VS, et al. Andrographis paniculata extract (HMPL-004) for active ulcerative colitis. *Am J Gastroenterol* 2013;**108**:90-98.
6. Tang T, Targan SR, Li ZS, Xu C, Byers VS, Sandborn WJ. Randomised clinical trial: herbal extract HMPL-004 in active ulcerative colitis - a double-blind comparison with sustained release mesalazine. *Aliment Pharmacol Ther* 2010;**33**:194-202.
7. Abdel-Tawab M, Werz O, Schubert-Zsilavecz M. Boswellia serrata: an overall assessment of in vitro, preclinical, pharmacokinetic and clinical data. *Clin Pharmacokinet* 2011;**50**:349-369.
8. 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.
9. Chen ZS, Nie ZW, Sun QL. Clinical study in treating intractable ulcerative colitis with traditional Chinese medicine. *Zhongguo Zhong Xi Yi Jie HeZa Zhi* 1994;**14**:400-402.
10. 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.
11. Zhang F, Li Y, Xu F, Chu Y, Zhao W. Comparison of Xilei-san, a chinese herbal medicine, and dexamethasone in mild/moderate ulcerative proctitis: a double-blind randomized clinical trial. *J Altern Complement Med* 2013;**19**:838-842.
12. 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.
13. 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.
14. Gong Y, Zha Q, Li L, et al. Efficacy and safety of Fufangkushen colon-coated capsule in the treatment of ulcerative colitis compared with mesalazine: a double-blinded and randomized study. *J Ethnopharmacol* 2012;**141**:592-598.
15. Hanai H, Iida T, Takeuchi K, et al. Curcumin maintenance therapy for ulcerative colitis: randomized, multicenter, double-blind, placebo-controlled trial. *Clin Gastroenterol Hepatol* 2006;**4**:1502-1506.
16. 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.
17. Greenfield SM, Green AT, Teare JP, et al. A randomized controlled study of evening primrose oil and fish oil in ulcerative colitis. *Aliment Pharmacol Ther* 1993;**7**:159-166.
18. Hanai H, Kanauchi O, Mitsuyama K, et al. Germinated barley foodstuff prolongs remission in patients with ulcerative colitis. *Int J Mol Med* 2004;**13**:643-647.
19. Kanauchi O, Mitsuyama K, Homma T, et al. Treatment of ulcerative colitis patients by long-term administration of germinated barley foodstuff: multi-center open trial. *Int J Mol Med* 2003;**12**:701-704.
20. 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.
21. Kaliora AC, Stathopoulou MG, Triantafillidis JK, Dedoussis GV, Andrikopoulos NK. Chios mastic treatment of patients with active Crohn's disease. *World J Gastroenterol* 2007;**13**:748-753.
22. Kaliora AC, Stathopoulou MG, Triantafillidis JK, Dedoussis GV, Andrikopoulos NK. Alterations in the function of circulating mononuclear cells derived from patients with Crohn's disease treated with mastic. *World J Gastroenterol* 2007;**13**:6031-6036.
23. Omer B, Krebs S, Omer H, Noor TO. Steroid-sparing effect of wormwood (Artemisia absinthium) in Crohn's disease: a double-blind placebo-controlled study. *Phytomedicine* 2007;**14**:87-95.
24. 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.
25. Naftali T, Lev LB, Yablecovitch D, Half E, Konikoff FM. Treatment of Crohn's disease with cannabis: an observational study. *Isr Med Assoc J* 2011;**13**:455-458.
26. Lal S, Prasad N, Ryan M, et al. Cannabis use amongst patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2011;**23**:891-896.
27. Gerhardt H, Seifert F, Buvari P, Vogelsang H, Repges R. Therapy of active Crohn disease with Boswellia serrata extract H15. *Z Gastroenterol* 2001;**39**:11-17.
28. Ren J, Tao Q, Wang X, Wang Z, Li J. Efficacy of T2 in active Crohn's disease: a prospective study report. *Dig Dis Sci* 2007;**52**:1790-1797.
29. Holtmeier W, Zeuzem S, Preibeta 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* 2010;**17**:573-582.
30. Tao QS, Ren JA, Ji ZL, Li JS, Wang XB, Jiang XH. Maintenance effect of polyglycosides of Tripterygium wilfordii on remission in postoperative Crohn disease. *Zhonghua Wei Chang Wai KeZa Zhi* 2009;**12**:491-493.
31. Liao NS, Ren JA, Fan CG, Wang GF, Zhao YZ, Li JS. Efficacy of polyglycosides of Tripterygium wilfordii in preventing postoperative recurrence of Crohn disease. *Zhonghua Wei ChangWai Ke Za Zhi* 2009;**12**:167-169.
32. 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.
33. Langhorst J, Anthonisen IB, Steder-Neukamm U, et al. Amount of systemic steroid medication is a strong predictor for the use of complementary and alternative medicine in patients with inflammatory bowel disease: results from a German national survey. *Inflamm Bowel Dis* 2005;**11**:287-295.
34. Langmead L, Chitnis M, Rampton DS. Use of complementary therapies by patients with IBD may indicate psychosocial distress. *Inflamm Bowel Dis* 2002;**8**:174-179.
35. Rahimi R, Mozaffari S, Abdollahi M. On the use of herbal medicines in management of inflammatory bowel diseases: a systematic review of animal and human studies. *Dig Dis Sci* 2009;**54**:471-480.
36. Ali T, Shakir F, Morton J. Curcumin and inflammatory bowel disease: biological mechanisms and clinical implication. *Digestion* 2012;**85**:249-255.
37. Dahmen U, Gu YL, Dirsch O, et al. Boswellic acid, a potent antiinflammatory drug, inhibits rejection to the same extent as high dose steroids. *Transplant Proc* 2001;**33**:539-541.
38. Singh P, Chacko KM, Aggarwal ML, et al. A-90 day gavage safety assessment of *Boswellia serrata* in rats. *Toxicol Int* 2012;**19**:273-278.
39. Bamba T, Kanauchi O, Andoh A, Fujiyama Y. A new prebiotic from germinated barley for nutraceutical treatment of ulcerative colitis. *J Gastroenterol Hepatol* 2002;**17**:818-824.
40. Cheng AL, Hsu CH, Lin JK, et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer Res* 2001;**21**:2895-2900.
41. Anonymous. Safety of traditional Chinese medicines and herbal remedies. *Curr Probl Pharmacovigilance* 2004;**30**:10-11.
42. Triantafillidis JK. The use of natural products in the treatment of inflammatory bowel disease (Editorial). *Ann Gastroenterol* 2008;**21**:41-43.
43. Joos S. Review on efficacy and health services research studies of complementary and alternative medicine in inflammatory bowel disease. *Chin J Integr Med* 2011;**17**:403-409.