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Comparison of the Efficacy and Tolerability of Herbal Medicines with 5-aminosalisylates in Inflammatory Bowel Disease: A Meta-analysis of Placebo Controlled Clinical Trials Involving 812 Patients

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Abstract: The use of herbal medicine for the management of Inflammatory Bowel Disease (IBD) is increasing. The aim of the present study is to compare the efficacy and tolerability of herbal medicines with 5-aminosalicylates (5-ASAs) in IBD by conducting a meta-analysis. For this purpose, electronic databases were searched for studies comparing efficacy and/or tolerability of herbal medicines with 5-ASAs in different types of IBD. The search terms were: "herb" or "plant" or "herbal" and "inflammatory bowel disease". Data were collected from 1966-2013 (up to Feb). The "clinical response", "clinical remission", "endoscopic response", "endoscopic remission", "histological response", "histological remission", "relapse", "any adverse events" and "serious adverse events" were the key outcomes of interest. Eight placebo controlled clinical trials met criteria and were included. Comparison of herbal medicine with 5-ASAs yielded the following results: a significant Relative Risk (RR) of 1.28 (95% Confidence Interval (CI): 1.07-1.54, p = 0.008) for clinical remission; a significant RR of 1.19 (95% CI = 1.01-1.39, p = 0.04) for clinical response; a non-significant RR of 0.85 (95% CI: 0.34-2.12, p = 0.73) for endoscopic remission; a non-significant RR of 1.14 (95% CI: 0.99-1.3, p = 0.07) for endoscopic response; a non-significant RR of 0.8 (95% CI: 0.05-13.72) for histological remission; a non-significant RR of 1.32 (95% CI: 0.64-2.9) for histological response; a non-significant RR of 1.05 (95% CI: 0.6-1.83, p = 0.87) for relapse; a non-significant RR of 1.31 (95% CI: 0.8-2.14, p = 0.28) for any adverse events; and a non-significant RR of 1.8 (95% CI: 0.13-24.5, p = 0.66) for serious adverse events. Overall, the efficacy and tolerability of herbal medicines in IBD is comparable to 5-ASAs, but the evidence is too limited to make any confident conclusion. Further high quality, large controlled trials are still needed.

Key words: Adverse events, 5-Aminosalisylates, efficacy, herbal medicine, inflammatory bowel disease, meta-analysis, relapse, evidence based medicine, systematic review

INTRODUCTION

Inflammatory Bowel Disease (IBD) is a group of inflammatory conditions of Gastro Intestinal (GI) tract with two major types of Ulcerative Colitis (UC) and Crohn's Disease (CD) and some atypical or intermediate forms like collagenous colitis and intractable colitis. Although, different drug categories are used for the conventional treatment of IBD (Abdolghaffari *et al*., 2012; Nikfar *et al*., 2010, 2011), the 5-aminosalisylates (5-ASA) are the main ones in this area (Nikfar *et al*., 2009; Rahimi *et al*., 2009b).

In the recent years, the use of complementary and alternative therapies especially herbal medicines for the treatment of IBD (Rahimi *et al*., 2009a, 2010) or even Irritable Bowel Syndrome (IBS), the other form of colitis (Nikfar *et al*., 2008; Rahimi and Abdollahi, 2012), have been increased. Besides many in vivo studies evaluating the effects of herbal medicines in the management of experimental colitis (Rahimi *et al*., 2013a; Baghaei *et al*., 2010; Abdolghaffari *et al*., 2010), there are several clinical trials comparing the efficacy and tolerability of these products with placebo and also 5-ASAs. In the present study, the studies compared herbal medicines with 5-ASAs in the management of IBD were collected and a meta-analysis was conducted to obtain conclusive results about the use of herbal medicines.

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MATERIALS AND METHODS

Data sources: PubMed, Scopus, Web of Science and Cochrane Central Register of Controlled Trials were searched for studies evaluating efficacy and/or tolerability of herbal medicines in any types of IBD. Data were collected from 1966-2013 (up to Feb). The search terms were: "herb" or "plant" or "herbal" and "inflammatory bowel disease". There was no language restriction. The reference list from retrieved articles was also reviewed for additional applicable studies.

Study selection: Controlled trials evaluating the efficacy and/or tolerability of herbal medicines in patients with any types of IBD were considered. "clinical response", "remission", "any adverse events" and "serious adverse events" were the key outcomes of interest. All published studies as well as abstracts presented at meetings were evaluated. Two reviewers independently examined the title and abstract of each article to eliminate duplicates, reviews, case studies and uncontrolled trials.

The reviewers independently extracted data on patients' characteristics, therapeutic regimens, dosage, trial duration and outcome measures. There was no disagreement between reviewers.

Assessment of trial quality: Jadad score which indicates the quality of the studies based on their description of randomization, blinding and dropouts (withdrawals) was used to assess the methodological quality of trials (Jadad and Enkin, 2007). The quality scale ranged from 0-5 points with a low quality report of score 2 or less and a high quality report of score at least 3.

Statistical analysis: Data from selected studies were extracted in the form of 2×2 tables by study characteristics. Included studies were weighted and pooled. Data were analyzed using StatsDirect software version 2.7.9. Relative Risk (RR) and 95% confidence intervals (95% CI) were calculated using Mantel-Haenszel, Rothman-Boice (for fixed effects) or Der Simonian-Laird (for random effects) methods. The Cochran Q test was used to test heterogeneity and $p<0.05$ considered significant. In case of heterogeneity or few included studies, the random effects model was used. Funnel plot was used as publication bias indicator.

RESULTS

The electronic searches yielded 1224 items; 698 from PubMed, 5 from Cochrane Central, 35 from Web of Science and 355 from Scopus. From these studies, 41 were scrutinized in full text.

Thirty four reports were considered ineligible. Thus, 8 trials were included in the analysis represented 812 patients (Fig. 1) (Tang *et al*., 2011; Gupta *et al*., 1997;

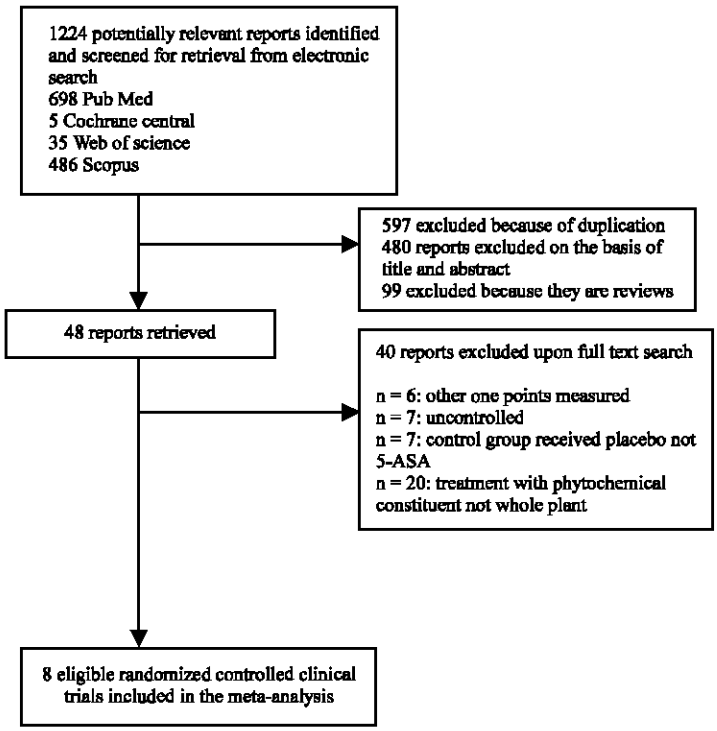


Fig. 1: Flow diagram of the study selection process

2001; Fernandez-Banares *et al*., 1999; Gong *et al*., 2012; Tong *et al*., 2010; Ling *et al*., 2010; Chen *et al*., 1994). From these 8 studies, 3 obtained Jadad score of 3 or more (Tang *et al*., 2011; Fernandez-Banares *et al*., 1999; Gong *et al*., 2012), 4 gained score of 2 or less (Gupta *et al*., 1997; 2001; Tong *et al*., 2010; Ling *et al*., 2010) and one with undetermined score because of its language was Japanese (Chen *et al*., 1994) (Table 1). Among studies

Table 1: Characteristics of studies included in the meta-analysis

Study	Gong *et al*. (2012)
Scientific name of plant(s)	Sophorae flavescentis root, Sanguisorba officinalis root, Indigo naturalis leaf, Bletilla striata rhizome, Glycyrrhiza uralensis root
Study design	Randomized, double-blind, placebo-controlled
Method of randomization	3:1 ratio
Blindness	Double dummy
Withdrawal	35 in herbal group and 18 in mesalazine group
Quality score	5
Inclusion criteria	Patients who were 18-65 years of age at the time of informed consent; who had active UC defined by a Mayo score of 6-12 points (scores range from 0 to 12, with higher scores indicating more severe disease activity) and who meet the Chinese pattern diagnosis of damp-heat accumulation interior. The damp-heat accumulation interior pattern diagnosis can be identified based on the co-existence of 3major symptoms (diarrhea, mucous or bloody purulent stools, abdominal pain) and at least 2 secondary symptoms (tenesmus, buruing pain in anus, fever, anorexia, dry or bitter mouth, foul stools)
Exclusion criteria	Patients had quiescent UC; who were complicated with other severe diseases; pregnancy or lactation; male patients have desire for procreation; allergy to the drug; higher blood creatinine level, or blood alanine transaminase level higher than double of normal; who took any other investigational drugs within 3 months
Interventions	Group 1: 0.4 g colon-coated capsule prepared from extracts of above plants, 4 caps t.i.d + placebo tablet identical to mesalazine tablet 4 tabs 4 times daily. n = 234 (male/female: 123/111) Group 2: 0.25 g enteric-coated mesalazine tablet, 4 tabs 4 times daily + placebo capsule identical to herbal capsule, 4 caps t.i.d. n = 80 (male/female: 34/46)
Concomitant medications	-
Duration	8 weeks
Outcomes	(1) Clinical response (a decrease from baseline in the total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or absolute subscore for rectal bleeding of 0 or 1) (2) Clinical remission (a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point) (3) Mucosal healing (absolute subscore for endoscopy of 0 or 1)
Study	Tong *et al*. (2010)
Scientific name of plant(s)	Sophorae flavescentis root, Sanguisorba officinalis root, Indigo naturalis leaf, Bletilla striata rhizome, Glycyrrhiza uralensis root
Study design	Stratified, randomized, single-blind, positive drug parallel controlled
Method of randomization	ND
Blindness	Single-blind
Withdrawal	1 in herbal product and 1 in mesalazine group
Quality score	2
Inclusion criteria	Patients with the diagnosis fit to the diagnostic standard of UC, including chronic recurrent type, chronic persistent type, initiative type, but not the fulminating type, it should be in active stage, might be mild, moderate, or severe as the degree of severity; have symptoms of the damp-heat accumulation syndrome (DHAS) pattern; aged 18-65 years old (among them, women should receive strict contraception except for those who had entered menopausal period for over 3 months or had been sterilized); all cases enrolled should sign the written informed consent voluntarily
Exclusion criteria	Patients who are at remission stage; patients suffered from infective colitis as bacterial dysentery, amebic dysentery, chronic schistosomiasis, intestinal tuberculosis, etc; patients with severe complications like local stricture, intestine obstruction, intestinal perforation, rectal adenoma, toxic colonic dilatation, anal diseases, etc; women who are in pregnancy or lactation stage; patients with hypersensitive constitution or history of allergy to multidrugs, as sulfonamides, furosemide, sulfonyl, thiazinyl diuretics and carbonic anhydrase inhibitor; patients with primary diseases of heart, liver, kidney, lung or blood system, with asthmatic diseases, renal function abnormality, or alanine aminotransferase (ALT) level elevated to over twofold of the normal range; male patients who wished to possess reproductive function; patients who have participated in other clinical trials during the last three months
Interventions	Group 1: capsules from above herbs. n = 42 (male/female: 24/18). 4 capsules t.i.d. Group 2: Mesalazine enteric soluble tablet (0.25 g per tablet). n = 42 (male/female: 21/21). 4 tablets 4 times a day
Concomitant medications	ND
Duration	8 weeks
Outcomes	(1) Clinical efficacy (Markedly effective: complete disappearance of clinical symptoms with the basic normal feature shown by colonoscopy; Effective: basic disappearance of clinical symptoms with merely mild inflammation in mucous membrane or some pseudo-polyp formation shown by colonoscopic examination; and Ineffective: no improvement in either clinical symptoms or endoscopic/pathologic examination) (2) Endoscopic efficacy (Markedly effetive: pathologic changes recovered to the normal or with cicatrization of ulcerative focus or the recovery reached more than two grades; Effective: change recovery reached more than one grade; Ineffective: the symptom change did not reach the above criteria or even aggravated)
Study	Chen *et al*. (1994)
Scientific name of plant(s)	Sophorae flavescentis root, Sophora japonica flower and flower bud
Study design	Randomized, double-blind
Method of randomization	ND (the article was Japanese and we couldn't determine)
Blindness	Double-blind

Table 1: Continued

Study	Gong *et al.* (2012)
Withdrawal	ND (the article was Japanese and we couldn't determine)
Quality score	ND (the article was Japanese and we couldn't determine)
Inclusion criteria	Patients with intractable ulcerative colitis
Exclusion criteria	ND (the article was Japanese and we couldn't determine)
Interventions	Group 1: tablet + retention-enema from above herbs. n = 64 Group 2: sulfasalazine tablet + retention-enema of dexamethasone. n = 47 Group 3: placebo + retention-enema as that in group 1. N = 42
Concomitant medications	ND (the article was Japanese and we couldn't determine)
Duration	3 months
Outcomes	(1) Curative rate (2) Total effective rate
Study	**Ling *et al.* (2010)**
Scientific name of plant(s)	Plants for intake: Astragalus membranaceus root, Codonopsis pilosula root, Poria cocos sclerotium, Atractylodes alba rhizome, Coix lacrymajobi kernel, Angelica Sinensis root, Glehnia littoralis root, Aucklandia lappa, Hordeum vulgare germinated fruit, Crataegus pinnatifida fruit, Paeonia lactiflora root, Epimedium sp. Dried aerial parts, Lycium barbarum fruit, Pueraria sp. Root and Glycyrrhiza sp. root Plants for enema: Coptis sp. Rhizome, Phellodendron sp. bark, Pulsatilla chinensis root, Atractylodes sp. rhizome, Salvia miltiorrhiza root, Bletilla striata rhizome, Sanguisorba officinalis root, Chelidonium sp., Sophora Flavescentis root and Glycyrrhiza root
Study design	Randomized, controlled
Method of randomization	ND
Blindness	ND
Withdrawal	ND
Quality score	1
Inclusion criteria	Patients with IBD diagnosed as follows: (1) clinical symptoms: continuous or recurrent attacks of diarrhea, with mucous pus-bloody stool, abdominal pain, tenesmus and accompanied by different degrees of systemic symptoms and parenteral symptoms; (2) colonoscopic examination shows diffuse erosion or ulceration, pseudo polyp and bridge-shape membrane, etc.; (3) barium enema examination shows coarse irregular membrane with granular change, multiple small filling defects on the intestinal wall, lead pipe-like canal (disappearance of bags); (4) pathological examinations of the intestinal membrane shows diffuse infiltration of inflammatory cells, neutrophils and eosinophils in the membrane propria, crypt abscess formation, decreased goblet cells, with erosion, ulceration and granulation tissue on the membranous surface
Exclusion criteria	Women in the pregnancy or lactation period; allergic constitution, with comorbid severe diseases of the cardiocerebral vascular system, liver and kidney; mental disorders; severe intestinal complications such as intestinal obstruction, perforation, toxic colonic dilatation, intestinal tuberculosis, chronic amebic dysentery, colonic carcinoma, rectal carcinoma and anal diseases; not receiving any prescribed drug therapy; with factors that could influence the evaluation on the effectiveness or safety, such as incomplete patient' materials
Interventions	Group 1: decoction of above plants for intake (100 ml b.i.d.) + retention enema of above plants for enema (200 ml decoction for 45 min every day). n = 26 Group 2: Retention enema of above plants for enema (200 ml decoction for 45 min every day). n = 27 Group 3: Mesalazine+Smeda retention enema. n = 25
Concomitant medications	ND
Duration	30 days
Outcomes	Clinical efficacy (Completely cured: disappearance of clinical symptoms, with a generally normalized colonic membrane showed by colonoscopy; Effective: the disappearance of symptoms and colonoscopic examination only show mild inflammation or pseudopolyp formation; Ineffective: no clinical or endoscopic/pathologic improvement)
Study	**Tang *et al.* (2011)**
Scientific name of plant(s)	Andrographis paniculata
Study design	Randomized, double-blind, parallel-group
Method of randomization	in a 1:1 ratio
Blindness	double-dummy fashion
Withdrawal	2 patients in herbal extract group and 5 in the mesalazine group
Quality score	5
Inclusion criteria	Male or female patients, 18-65 years of age, with a diagnosis of mildly to moderately active UC confirmed by colonoscopy
Exclusion criteria	Pregnancy, lactation, stools positive for bacterial pathogens, renal or hepatic disease, a history of asthma, a bleeding or coagulation disorder, severe UC, severe complications of UC, Crohn's disease, cancer, a history of allergy or hypersensitivity to aminosalicylates or any component of herbal product, if they had received any medication for UC within 1 week of study including sulfasalazine, mesalazine, steroids and Chinese herbal medicines, if they had participated in any clinical study within 3 months
Interventions	Group 1: Capsules containing 200 mg ethanol / water (90 / 10 v/v) extract of Andrographis paniculata. n = 60 (male/female: 31/29). 2 caps t.d.s. Group 2: Mesalazine SR Granules. n = 60 (male/female: 27/33). 1500 mg t.d.s.
Concomitant medications	-
Duration	8 weeks
Outcomes	(1) Clinical remission (Remission: all symptoms disappeared; Partial remission: reduction of 50% of symptoms; Improvement: more than 25% reduction in symptoms) (2) Endoscopic remission (Remission: no inflammation; Partial remission: inflammation reduced by two grades; Improvement: inflammation reduced by one grade) (3) Histological improvement on biopsy

Table 1: Continued

Study	Gong *et al.* (2012)
Scientific name of plant(s)	Boswellia serrata
Study design	open, non-randomized
Method of randomization	-
Blindness	-
Withdrawal	-
Quality score	0
Inclusion criteria	Patients with chronic colitis who presented with pain in lower abdomen, diarrhea with or without blood and mucus
Exclusion criteria	classical ulcerative colitis, colonic tuberculosis and malignancy, shigellosis as well as other infective pathologies
Interventions	Group 1: capsules containing 300 mg Boswellia resin. n = 20 (male/female:13/7). 1 capsule t.i.d. Group 2: tablets containing 1 g sulfasalazine. n = 10 (male/female: 4/6). 1 tablet t.i.d.
Concomitant medications	-
Duration	6 weeks
Outcomes	Clinical, endoscopic and histological remission Relapse within 1 year in patients went to remission
Study	**Gupta *et al.*, 1997**
Scientific name of plant(s)	Boswellia serrata
Study design	open
Method of randomization	-
Blindness	-
Withdrawal	-
Quality score	0
Inclusion criteria	Patients with grade II or III UC
Exclusion criteria	Colonic tuberculosis, amoebiasis, shigellosis
Interventions	Group 1: capsules containing 350 mg Boswellia resin. n = 34 (male/female:14/20). 1 capsule t.i.d. Group 2: tablets containing 1 g sulfasalazine. n = 8 (male/female: 4/4). 1 tablet t.i.d.
Concomitant medications	-
Duration	6 weeks
Outcomes	(1) clinical remission (2) endoscopic remission (3) endoscopic response
Study	Fernandez-Banares *et al.*, 1999
Scientific name of plant(s)	Plantago ovata
Study design	Open label, randomized, controlled
Method of randomization	parallel group design; Allocation sequence was computer-generated
Blindness	Open label
Withdrawal	Group 1: 15; Group 2: 16; Group 3: 10
Quality score	3
Inclusion criteria	18-70 years old patients with ulcerative colitis in remission for = 3 months, had a maximum extent of the disease ever recorded by endoscopy = 20 cm and had previously been taking oral mesalamine maintenance therapy
Exclusion criteria	Patients received in the month before trial entry oral or rectal steroids, rectal 5-aminosalicylic, or other drugs known to have an effect on colitis activity; no consent; uncooperative or unreliable patient; significant hepatic or renal disease; allergy to aspirin, other salicylates, or mesalamine; chronic intake of NSAIDs; and for women, pregnancy, not using adequate means of contraception, or breastfeeding
Interventions	Group 1: 20 g daily Plantago ovata seeds (10-g sachets b.i.d.). n = 35 (M/F: 16/19) Group 2: 1.5 g daily mesalazine (500-mg tablets t.i.d.). n = 37 (M/F: 24/13) Group 3: Plantago ovate seeds (10-g sachets b.i.d.) + mesalazine (500-mg tablets t.i.d.). n = 30 (M/F: 15/15)
Concomitant medications	-
Duration	12 months
Outcomes	(1) Relapse (an increase in bowel frequency with blood or mucus (activity index = 7 points) and evidence of active disease on sigmoidoscopy

included, 5 investigated the efficacy and/or tolerability of herbal medicines in UC (Tang *et al.*, 2011, Gupta *et al.*, 1997; Fernandez-Banares *et al.*, 1999; Gong *et al.*, 2012; Tong *et al.*, 2010), 1 in chronic colitis (Gupta *et al.*, 2001), 1 in intractable colitis (Chen *et al.*, 1994) and 1 in any type of IBD (Ling *et al.*, 2010). Four herbal products were used in included studies: *Andrographis paniculata* in one (Tang *et al.*, 2011), *Boswellia serrata* in 2 (Gupta *et al.*, 1997; 2001), *Plantago ovata* in one (Fernandez-Banares *et al.*, 1999) and traditional Chinese medicine in 4 studies (Gong *et al.*, 2012; Tong *et al.*, 2010; Ling *et al.*, 2010; Chen *et al.*, 1994). Induction of treatment was investigated in seven studies and duration of these studies is 4-8 weeks (Tang *et al.*, 2011; Gupta *et al.*, 1997; 2001; Gong *et al.*, 2012; Tong *et al.*, 2010; Ling *et al.*, 2010; Chen *et al.*, 1994). Maintenance of remission was evaluated in two studies and duration of these studies was 1 year (Fernandez-Banares *et al.*, 1999). The 5-ASAs used in included studies were sulfasalazine or mesalazine (Table 2). Scientific name of plant(s) used in herbal medicine, study design, inclusion and exclusion criteria, interventions, concomitant medications, patients'

Table 2: Investigated outcomes in studies included in the meta-analysis of the efficacy and safety of herbal remedies in any type of IBD compared to 5-aminosalisylates

				Patients reported AE		Clinical efficacy		Endoscopic efficacy		Histological efiicacy		Recurrence
Herbal product	IBD type	Study	Duration	Any AE	Serious AE	Clinical remission	Clinical response	Endoscopic remission	Endoscopic response	Histological remission	Histological response	Relapse
Andrographis paniculata	UC	Tang *et al.* (2011)	8 weeks	H: 7/53 M: 5/55	H: 2/53 M: 0/55	H:11/53 M: 9/55	H: 40/53 M:45/55	H: 15/53 M: 13/55	H: 39/53 M: 39/55	H: 0/19 M: 0/15	H: 10/19 M: 6/15	-
Boswellia serrata	Chronic colitis	Gupta *et al.* (2001)	6 weeks for evaluating induction of efficacy and 1 year for evaluation of recurrence	H: 2/20 S: ND	-	H:18/20 S: 6/10	-	H: 1/20 S: 0/10	H: 18/20 S: 7/10	-	H: 6/18 S: 2/6	-
Boswellia serrata	UC	Gupta *et al.* (1997)	6 weeks	-	-	H: 28/34 S: 6/8	-	H: 28/34 S: 6/8	H: 25/34 S: 6/8	-	-	-
Plantago ovata	UC	Fernandez-Banares *et al.* (1999)	12 months	H: 5/35 M: 4/37	-	-	-	-	-	-	-	H: 13/35 M: 13/37
TCM	UC	Gong *et al.* (2012)	8 weeks	H:38/234 M: 10/80		H:0/234 M: 0/80	H: 97/234 M: 33/80	H: 170/234 M: 52/80	H: 29/234 M: 44/80	-	-	-
TCM	UC	Tong *et al.* (2010)	8 weeks	H: 2/42 M: 2/42	-	H: 20/42 M: 15/42	H: 39/42 M: 30/42	H: 26/42 M: 17/42	H: 39/42 M: 31/42	-		-
TCM	Any type	Ling *et al.* (2010)	30 days	-	-	H: 17/26 M: 10/25	H: 24/26 M: 19/25	-	-	-		-
TCM	Intractable UC	Chen *et al.* (1994)	3 months	-	-	H: 34/64 S: 13/47	H: 55/64 S: 28/47	-	-	-		-

AE: Adverse events, H: Herbal remedy, IBD: Inflammatory bowel disease, M: Mesalazine, S: Sulfasalazine, TCM: Traditional Chinese medicine, UC: Ulcerative colitis

characteristics, duration of study and definition of outcomes investigated in each included study have been shown in Table 1. Results of investigated outcomes for each included study have been demonstrated in Table 2.

EFFICACY

Clinical remission: The summary for Relative Risk (RR) of clinical remission in IBD patients for seven included trials comparing herbal medicines with 5-ASAs (Tang *et al*., 2011; Gupta *et al*., 1997; 2001; Gong *et al*., 2012; Tong *et al*., 2010; Ling *et al*., 2010; Chen *et al*., 1994) was 1.28 with 95% CI = 1.07-1.54 (p = 0.008, Fig. 2a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (p = 0.38, Fig. 2b) and could be combined, thus the fixed effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for clinical remission in IBD patients was 2.42 (95% CI =-0.52 to 5.35, p = 0.09) and Kendall's tau = 0.43, p = 0.24 (Fig. 2c).

The summary for relative risk (RR) of clinical remission in UC patients for four included trials comparing herbal medicines with 5-ASAs (Tang *et al*., 2011; Gupta *et al*., 1997; Gong *et al*., 2012; Tong *et al*., 2010) was 1.06 with 95% CI = 0.85-1.33 (p = 0.61, Fig. 3a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (p = 0.65, Fig. 3b) and could be combined, thus the fixed effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for clinical remission in UC patients was 1.72 (95% CI =-1.7 to 5.15, p = 0.16 and Kendall's tau = 0.67, p = 0.33 (Fig. 3c).

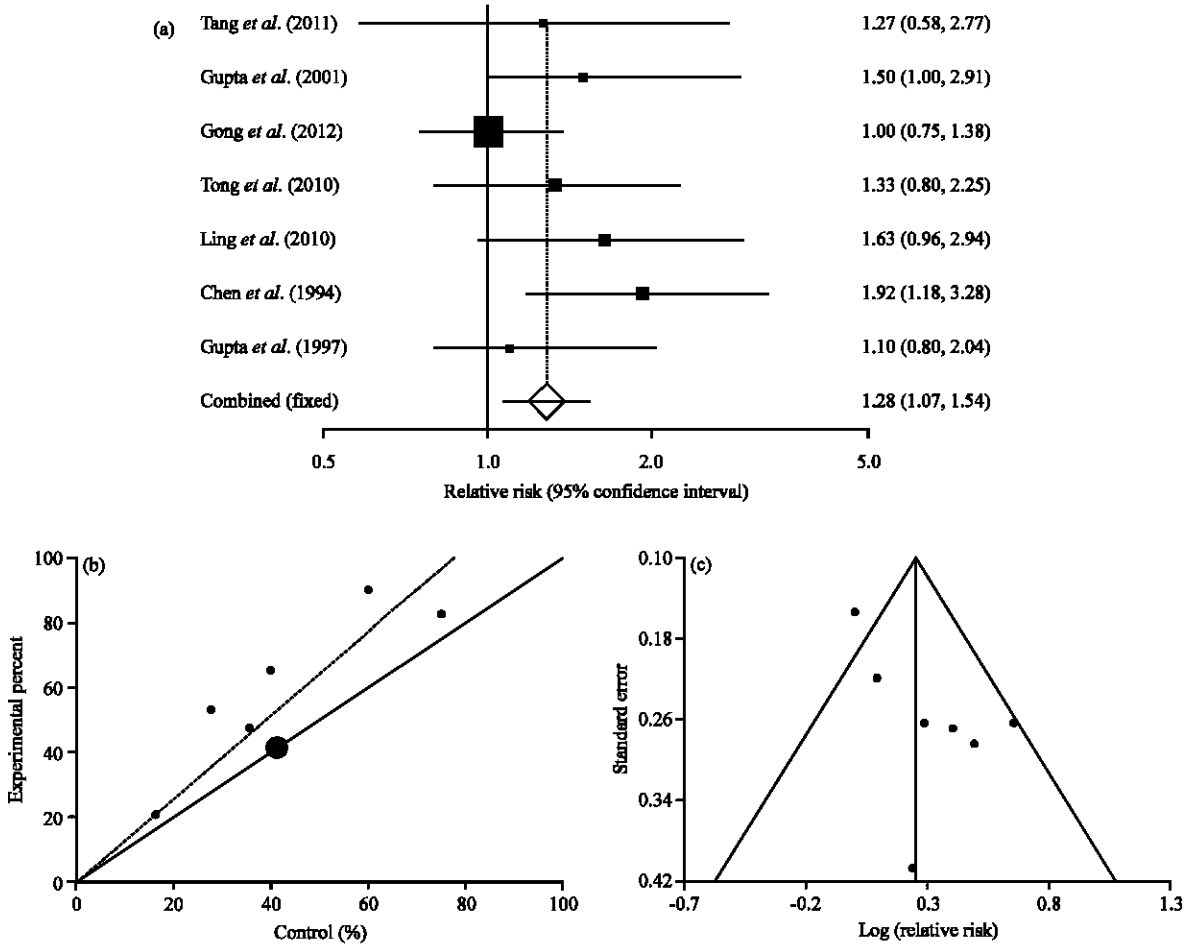


Fig. 2(a-c): (a) Individual and pooled relative risk for the outcome of "clinical remission" in the studies considering herbal medicines comparing to 5-ASAs therapy in IBD patients, (b) Heterogeneity indicators for the outcome "clinical remission" in the studies considering herbal medicines comparing to 5-ASAs therapy in IBD patients and (c) Publication bias indicators for the outcome of "clinical remission" in the studies considering herbal medicines comparing to 5-ASAs therapy in IBD patients

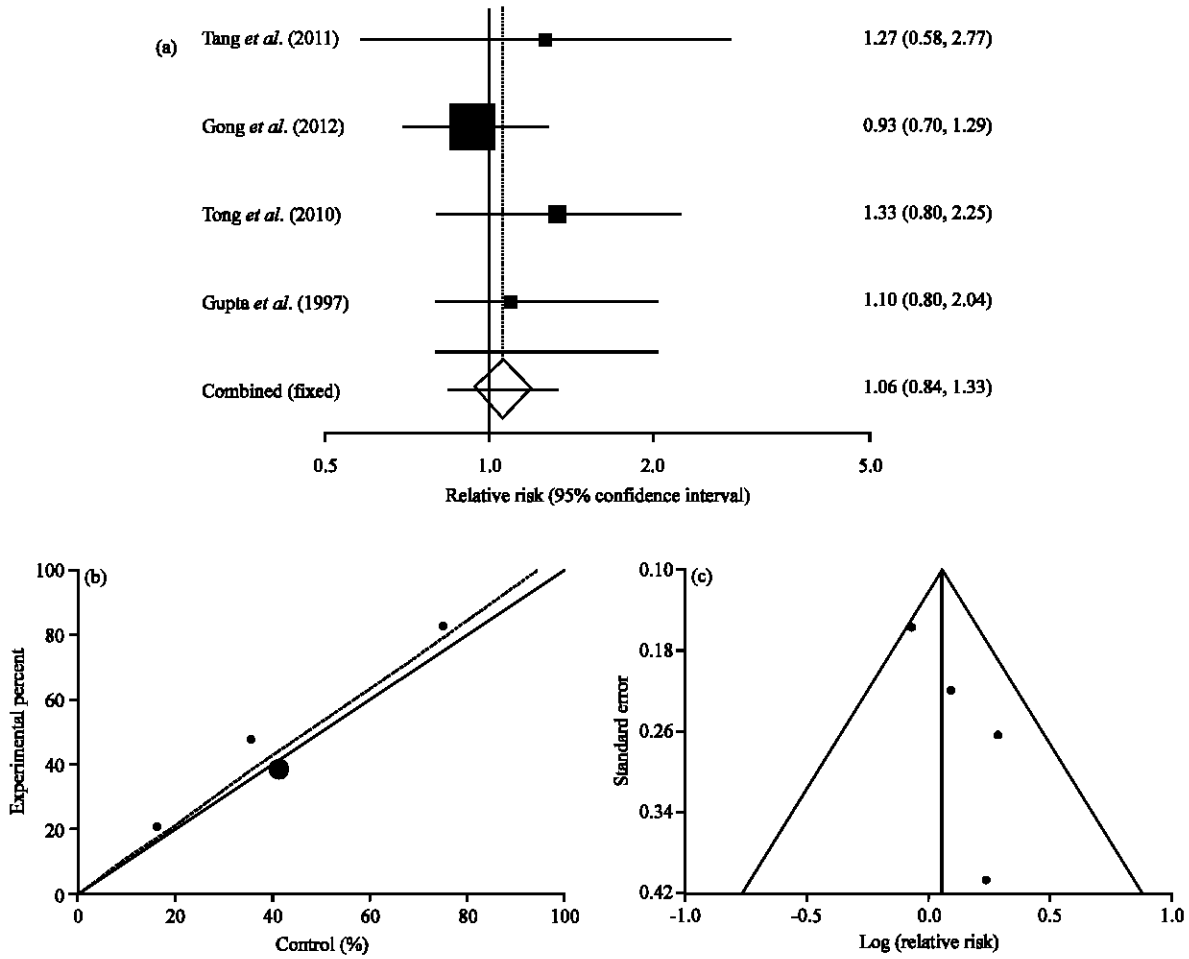


Fig. 3(a-c): (a) Individual and pooled relative risk for the outcome of "clinical remission" in the studies considering herbal medicines comparing to 5-ASAs therapy in UC patients, (b) Heterogeneity indicators for the outcome of "clinical remission" in the studies considering herbal medicines comparing to 5-ASAs therapy in UC patients and (c) Publication bias indicators for the outcome of "clinical remission" in the studies considering herbal medicines comparing to 5-ASAs therapy in UC patients

Based on plant type, RR of clinical remission was significant for TCM (1.29; 95% CI = 1.04-1.59, p = 0.02) and non-significant for *Andrographis paniculata* and *Boswellia serrata* (Table 3).

Clinical response: The summary for RR of clinical response in IBD patients for five included trials comparing herbal medicines with 5-ASAs (Tang *et al*., 2011; Gong *et al*., 2012; Tong *et al*., 2010; Ling *et al*., 2010; Chen *et al*., 1994) was 1.19 with 95% CI = 1.01-1.39 (p = 0.04, Fig. 4a). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (p = 0.03, Fig. 4b) and could not be combined, thus the random effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for clinical response in IBD patients was 6.72 (95% CI =-6.57 to 20, p = 0.21) and Kendall's tau = 0.6, p = 0.23 (Fig. 4c).

The summary for RR of clinical response in UC patients for three included trials comparing herbal medicines with 5-ASAs (Tang *et al*., 2011; Gong *et al*., 2012; Tong *et al*., 2010) was 1.1 with 95% CI = 0.91-1.33 (p = 0.32, Fig. 5a). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (p = 0.06, Fig. 5b) and could be combined but because of few included studies the random effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for clinical response in UC patients could not be calculated because of too few strata.

Table 3: Results obtained from sub-analysis of included studies based on plant type

			Patients reported AE		Clinical efficacy		Endoscopic efficacy		Histological efficacy		Recurrence
Herbal product	IBD type	Study	Any AE	serious AE	Clinical remission	Clinical response	Endoscopic remission	Endoscopic response	Histological remission	Histological response	Relapse
Andrographis paniculata	UC	Tang *et al.* (2011)	1.45 (0.52-4.12)	5.19 (0.48-57.24)	1.27 (0.58-2.77)	0.92 (0.74-1.13)	1.20 (0.64-2.26)	1.04 (0.81-1.32)	0.8 (0.05-13.72)	1.32 (0.64-2.9)	-
Boswellia serrata	Chronic colitis	Gupta *et al.* (2001)	-	-	1.24 (0.89-1.73) P = 0.2	-	1.11 (0.72-1.69) P = 0.64	1.13 (0.83-1.54) P = 0.45			1.00 (0.33-3.86)
	UC	Gupta *et al.* (1997)	-	-		-					-
Plantago ovata	UC	Fernandez-Banares *et al.* (1999)	1.32 (0.41-4.26)	-	-	-	-	-			1.06 (0.57-1.95)
TCM	UC	Gong *et al.* (2012)	1.26 (0.68-2.34) P = 0.45	0.35 (0.02-6.00)	1.29 (1.04-1.59) P = 0.02	1.25 (1.11-1.4) P = 0.0001	0.59 (0.09-3.85) P = 0.58	-			-
	UC	Tong *et al.* (2010)		-				1.26 (1.04-1.59)			-
	Any type	Ling *et al.* (2010)	-	-			-	-			-
	Intractable UC	Chen *et al.* (1994)	-	-			-	-			-

AE: Adverse events, IBD: Inflammatory bowel disease, TCM: Traditional Chinese medicine, UC: Ulcerative colitis

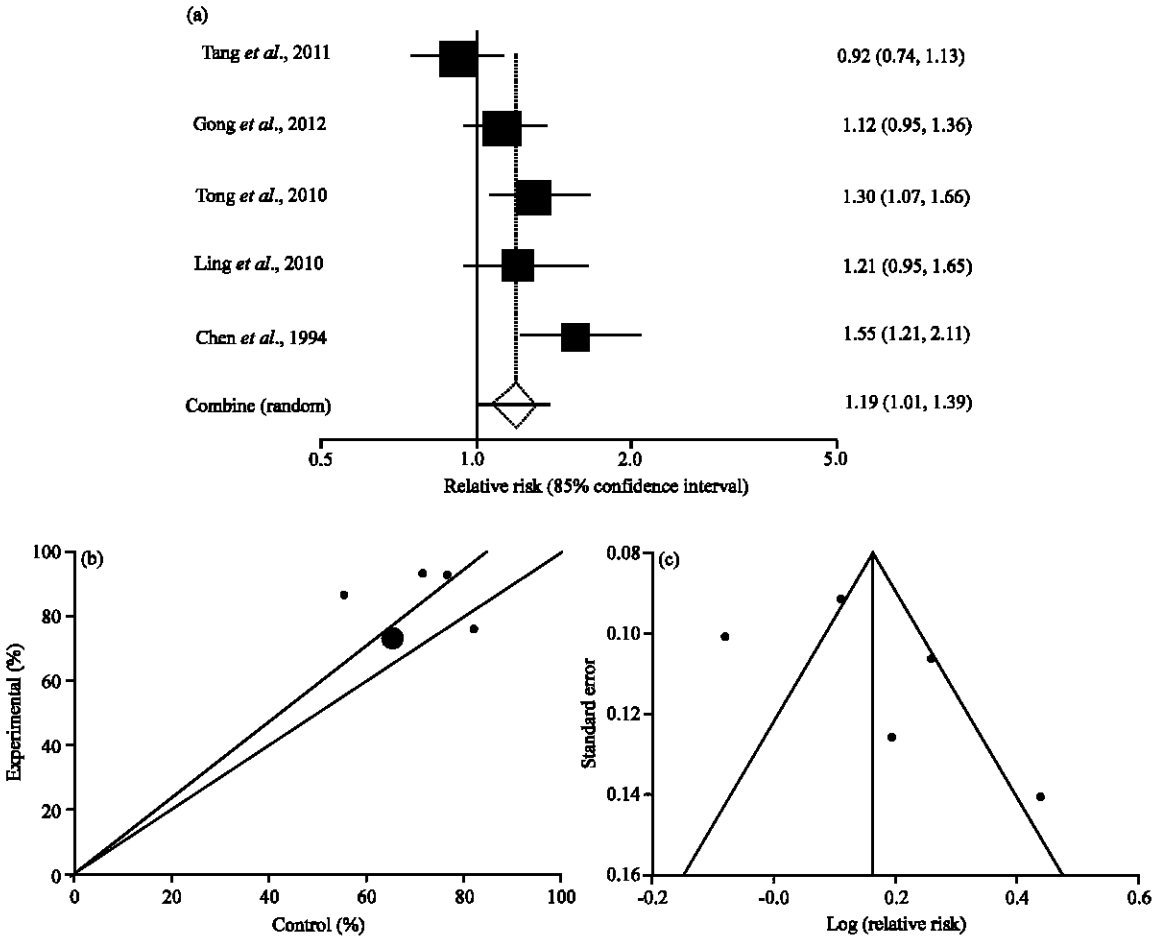


Fig. 4(a-c): (a) Individual and pooled relative risk for the outcome of "clinical response" in the studies considering herbal medicines comparing to 5-ASAs therapy in IBD patients (b) Heterogeneity indicators for the outcome of "clinical response" in the studies considering herbal medicines comparing to 5-ASAs therapy in IBD patients and (c) Publication bias indicators for the outcome of "clinical response" in the studies considering herbal medicines comparing to 5-ASAs therapy in IBD patients

Based on plant type, RR of clinical response was significant for TCM (1.25; 95% CI = 1.11-1.4, p = 0.0001) and non-significant for *Andrographis paniculata* (Table 3).

Endoscopic remission: The summary for Relative Risk (RR) of endoscopic remission in IBD patients for five included trials comparing herbal medicines with 5-ASAs (Tang *et al*., 2011; Gupta *et al*., 1997; 2001; Gong *et al*., 2012; Tong *et al*., 2010) was 0.85 with 95% CI = 0.34-2.12 (p = 0.73, Fig. 6a). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (p<0.0001, Fig. 6b) and could not be combined, thus the random effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for endoscopic remission in IBD patients was 1.79 (95% CI =-12.16 to 15.74, p = 0.71) and Kendall's tau = 0, p = 0.82 (Fig. 6c).

The summary for RR of endoscopic remission in UC patients for four included trials comparing herbal medicines with 5-ASAs (Tang *et al*., 2011; Gupta *et al*., 1997; Gong *et al*., 2012; Tong *et al*., 2010) was 0.81 with 95% CI = 0.31 to 2.13 (p = 0.67, Fig. 7a). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (p<0.0001, Fig. 7b) and could not be combined, thus the random effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for endoscopic remission in UC patients was 9.78 (95% CI =-48.2 to 67.77, p = 0.54 and Kendall's tau = 0.33, p = 0.75 (Fig. 7c).

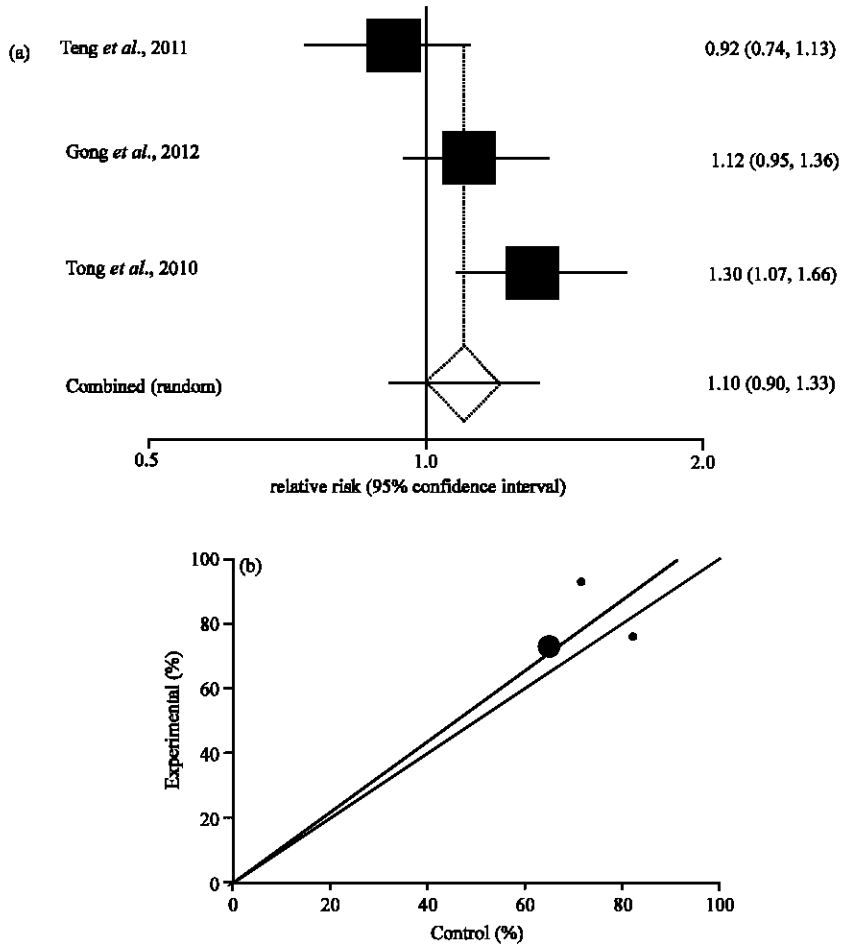


Fig. 5(a-b): (a) Individual and pooled relative risk for the outcome of "clinical response" in the studies considering herbal medicines comparing to 5-ASAs therapy in UC patients and (b) Heterogeneity indicators for the outcome of "clinical response" in the studies considering herbal medicines comparing to 5-ASAs therapy in UC patients

Based on plant type, RR of endoscopic remission was non-significant for *Andrographis paniculata*, *Boswellia serrata* and TCM (Table 3).

Endoscopic response: The summary for RR of endoscopic response in IBD patients for four included trials comparing herbal medicines with 5-ASAs (Tang *et al*., 2011; Gupta *et al*., 1997; 2001; Tong *et al*., 2010) was 1.14 with 95% CI = 0.99-1.3 (p = 0.07, Fig. 8a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (p = 0.51, Fig. 8b) and could be combined, thus the fixed effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for endoscopic response in IBD patients was-0.61 (95% CI =-7.26 to 6.04, p = 0.73) and Kendall's tau =-0.33, p = 0.33 (Fig. 8c).

The summary for RR of endoscopic response in UC patients for three included trials comparing herbal medicines with 5-ASAs (Tang *et al*., 2011; Gupta *et al*., 1997; Tong *et al*., 2010) was 1.14 with 95% CI = 0.98-1.32 (p = 0.08, Fig. 9a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (p = 0.35, Fig. 9b) and could be combined but because of few included studies the random effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for endoscopic response in UC patients could not be calculated because of too few strata.

Based on plant type, RR of endoscopic response was non-significant for *Andrographis paniculata*, *Boswellia serrata* and TCM (Table 3).

Histological remission: The Relative Risk (RR) of histological remission in IBD (UC) patients for comparison of herbal medicines to 5-ASAs (Tang *et al*., 2011) was 0.8 with 95% CI = 0.05-13.72, a non-significant RR.

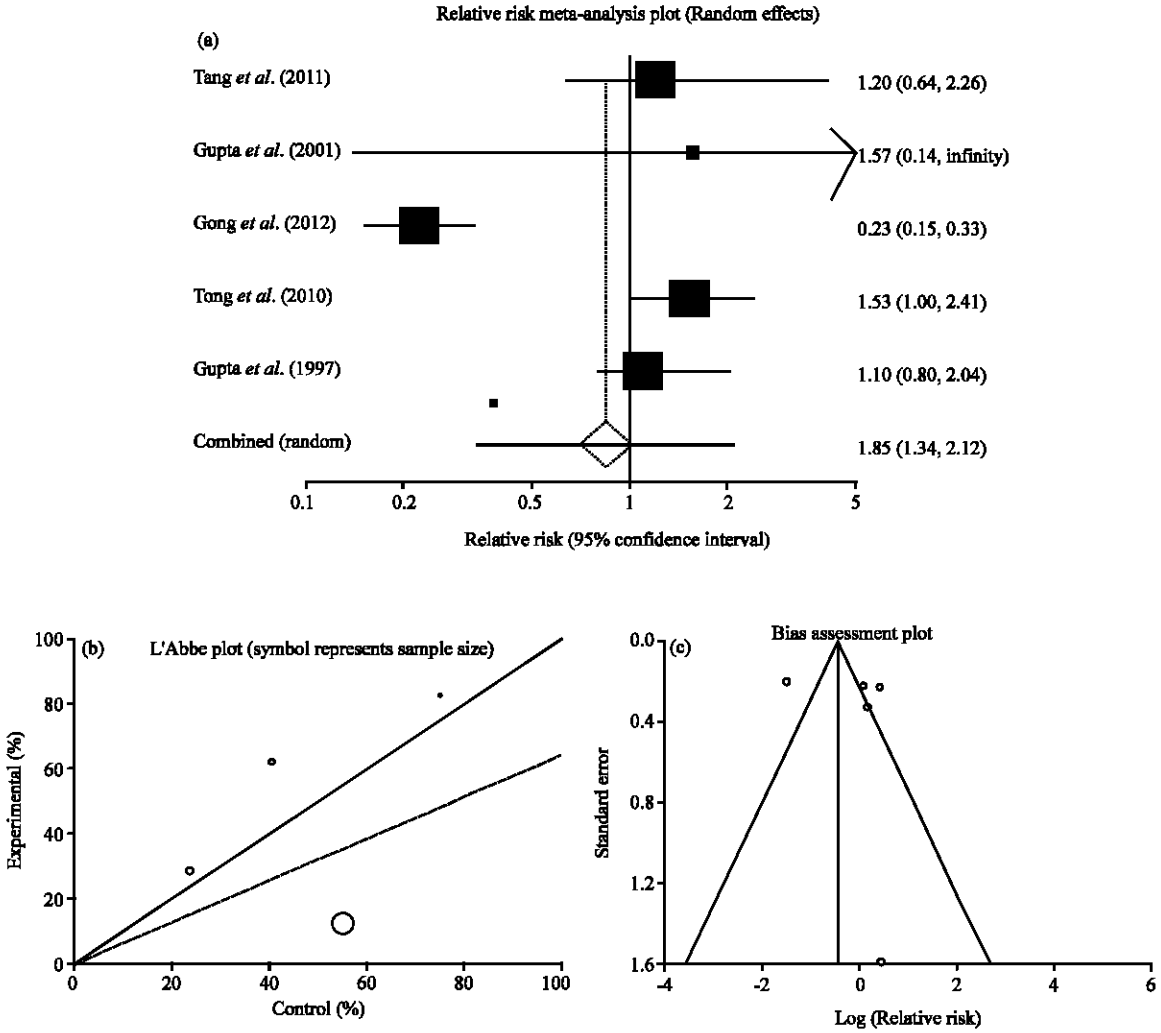


Fig. 6(a-c): (a) Individual and pooled relative risk for the outcome of "endoscopic remission" in the studies considering herbal medicines comparing to 5-ASAs therapy in IBD patients, (b) Heterogeneity indicators for the outcome "endoscopic remission" in the studies considering herbal medicines comparing to 5-ASAs therapy in IBD patients and (c) Publication bias indicators for the outcome of "endoscopic remission" in the studies considering herbal medicines comparing to 5-ASAs therapy in IBD patients

Histological response: The Relative Risk (RR) of histological response in IBD (UC) patients for comparison of herbal medicines to 5-ASAs (Tang *et al*., 2011) was 1.32 with 95% CI = 0.64 to 2.9, a non-significant RR.

Relapse: The summary for RR of relapse in IBD patients for two included trials comparing herbal medicines with 5-ASAs (Gupta *et al*., 2001; Fernandez-Banares *et al*., 1999) was 1.05 with 95% CI = 0.6-1.83 (p = 0.87, Fig. 10a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (p = 0.94, Fig. 10b) and could be combined but because of few included studies the random effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for relapse in IBD patients could not be calculated because of too few strata.

Based on plant type, RR of relapse was non-significant for *Boswellia serrata* and *Plantago ovata* (Table 3).

TOLERABILITY

Any adverse events: The summary for RR of any adverse events in IBD patients for five included trials comparing herbal medicines with 5-ASAs (Tang *et al*., 2011; Gupta *et al*., 2001; Fernandez-Banares *et al*., 1999; Tong *et al*., 2010) was 1.31 with 95% CI = 0.8-2.14 (p = 0.28, Fig. 11a). The Cochrane Q test for heterogeneity

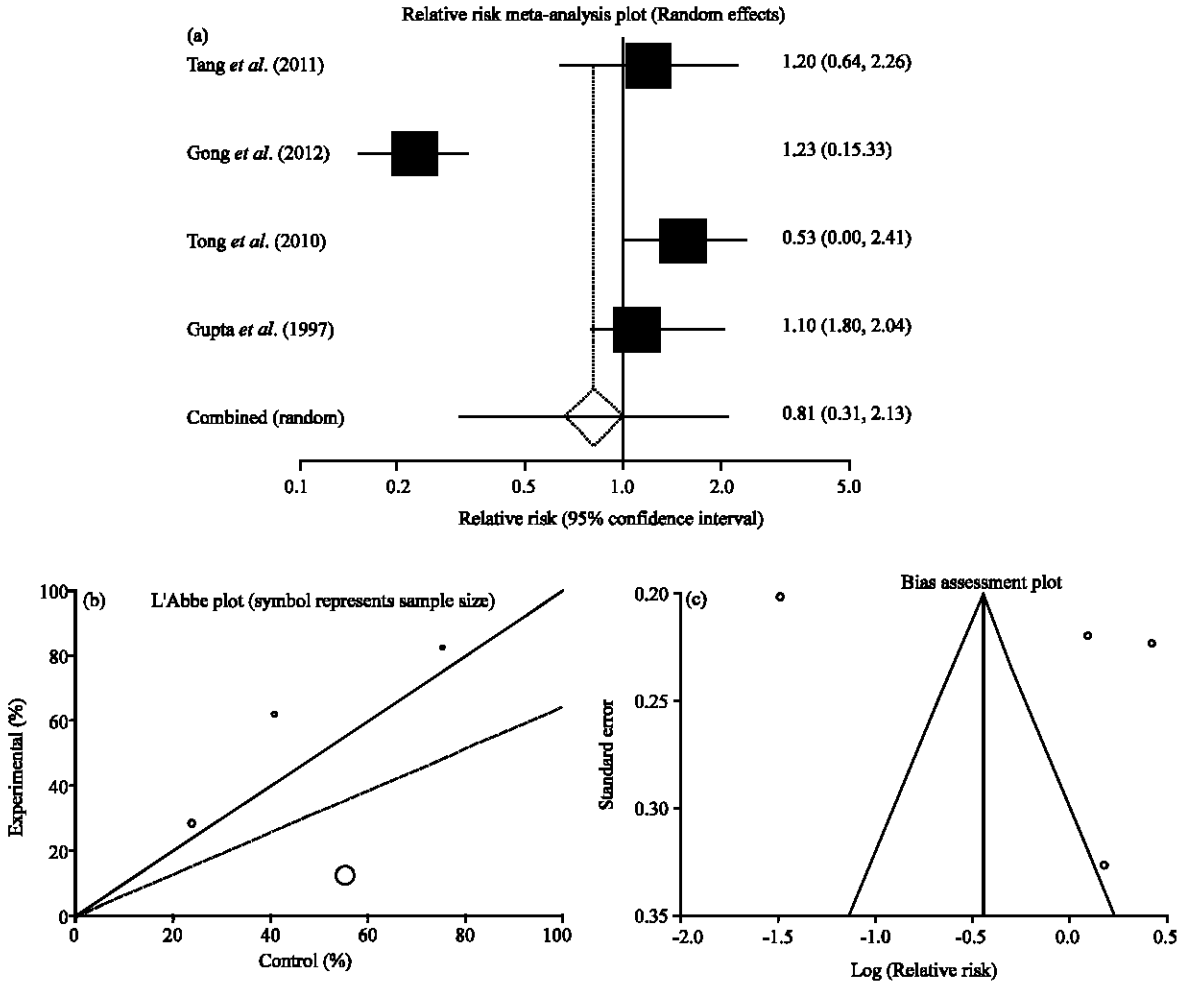


Fig. 7(a-c): (a) Individual and pooled relative risk for the outcome of "endoscopic remission" in the studies considering herbal medicines comparing to 5-ASAs therapy in UC patients, (b) Heterogeneity indicators for the outcome "endoscopic remission" in the studies considering herbal medicines comparing to 5-ASAs therapy in UC patients and (c) Publication bias indicators for the outcome of "endoscopic remission" in the studies considering herbal medicines comparing to 5-ASAs therapy in UC patients

indicated that the studies are not heterogeneous (p = 0.99, Fig. 11b) and could be combined, thus the fixed effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for any adverse events in IBD patients was -0.19 (95% CI = -1.47 to 1.08, p = 0.59) and Kendall's tau = -0.33, p = 0.33 (Fig. 11c).

Serious adverse events: The summary for Relative Risk (RR) of serious adverse events in IBD patients for two included trials comparing herbal medicines with 5-ASAs (Tang *et al*., 2011; Gong *et al*., 2012) was 1.8 with 95% CI = 0.13 to 24.5 (p = 0.66, Fig. 12a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (p = 0.28, Fig. 12b) and could be combined but because of few included studies the random effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for serious adverse events in IBD patients could not be calculated because of too few strata.

DISCUSSION

The 5-ASAs are usually considered as the first line treatment for IBD. Since, the use of herbal remedies for the treatment of chronic gastrointestinal disorders like IBD is increasing (Farzaei *et al*., 2013; Rahimi and Abdollahi, 2013; Rahimi and Abdollahi, 2012; Rahimi *et al*., 2009a,

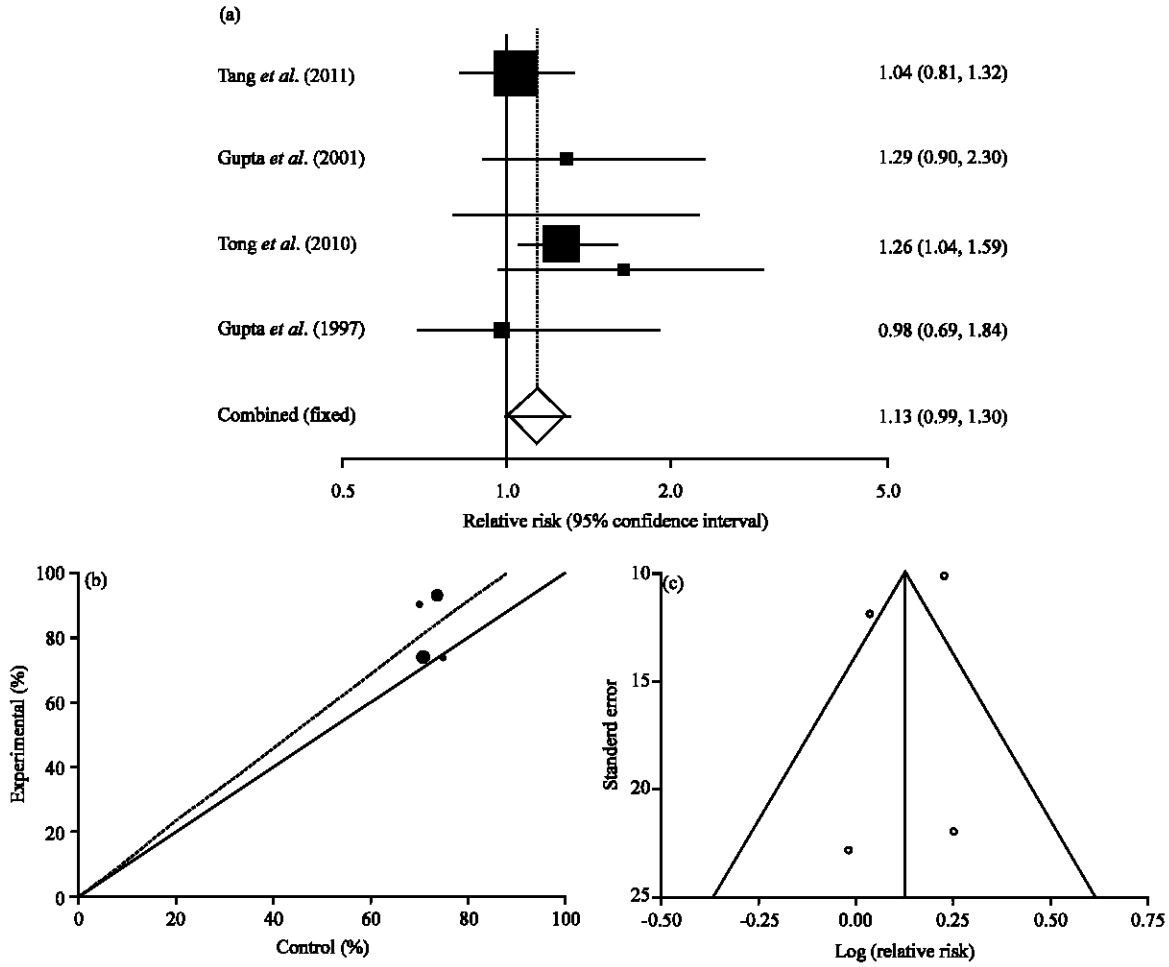


Fig. 8(a-c): (a) Individual and pooled relative risk for the outcome of "endoscopic response" in the studies considering herbal medicines comparing to 5-ASAs therapy in IBD patients, (b) Heterogeneity indicators for the outcome "endoscopic response" in the studies considering herbal medicines comparing to 5-ASAs therapy in IBD patients and (c) Publication bias indicators for the outcome of "endoscopic response" in the studies considering herbal medicines comparing to 5-ASAs therapy in IBD patients

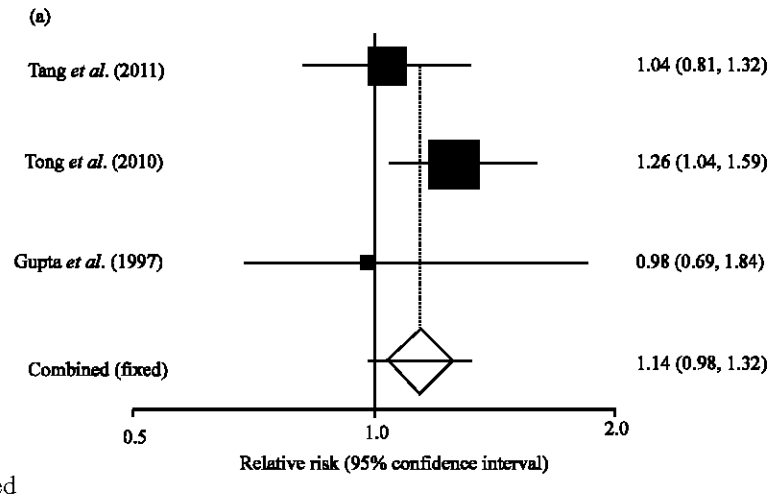


Fig. 9(a-b): Continued

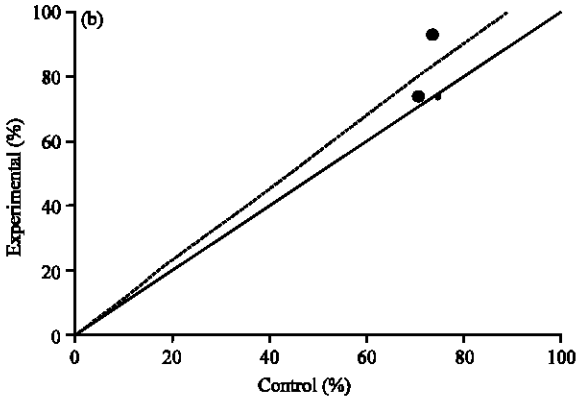
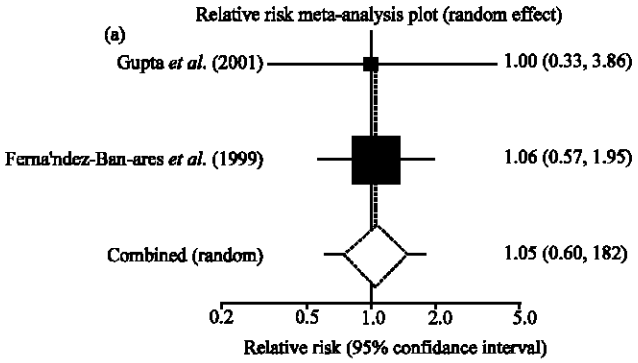


Fig. 9(a-b): (a) Individual and pooled relative risk for the outcome of "endoscopic response" in the studies considering herbal medicines comparing to 5-ASAs therapy in UC patients and (b) Heterogeneity indicators for the outcome "endoscopic response" in the studies considering herbal medicines comparing to 5-ASAs therapy in UC patients



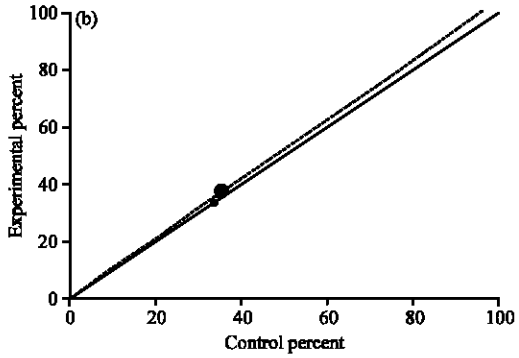


Fig. 10(a-b): (a) Individual and pooled relative risk for the outcome of "relapse" in the studies considering herbal medicines comparing to 5-ASAs therapy in IBD patients and (b) Heterogeneity indicators for the outcome of "relapse" in the studies considering herbal medicines comparing with 5-ASAs therapy in IBD patients

2013b), a meta-analysis was conducted to compare the efficacy of herbal remedies with 5-ASAs. The results of this meta-analysis showed that induction of clinical response and remission by herbal remedies is significant when compared with 5-ASAs. Regarding other outcomes endoscopic efficacy, histological efficacy, relapse, any adverse related to efficacy including events and serious adverse events, no significant difference was seen between herbal medicines and 5-ASAs.

The present meta-analysis may have been inevitably limited by small sample sizes of studies and heterogeneity. Because the included trials involved herbal medicines

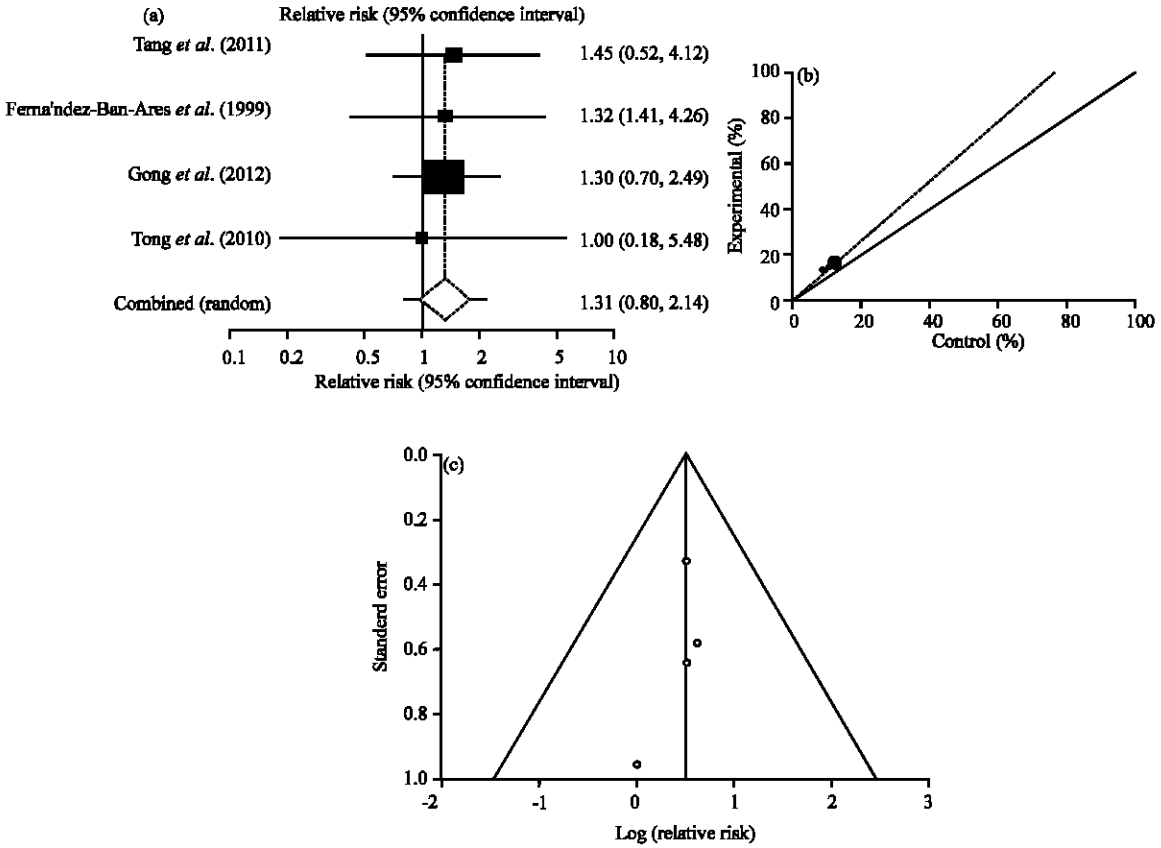


Fig. 11(a-c): (a) Individual and pooled relative risk for the outcome of "any adverse events" in the studies considering herbal medicines comparing to 5-ASAs therapy in IBD patients, (b) Heterogeneity indicators for the outcome "any adverse events" in the studies considering herbal medicines comparing to 5-ASAs therapy in IBD patients and (c) Publication bias indicators for the outcome of "any adverse events" in the studies considering herbal medicines comparing to 5-ASAs therapy in IBD patients

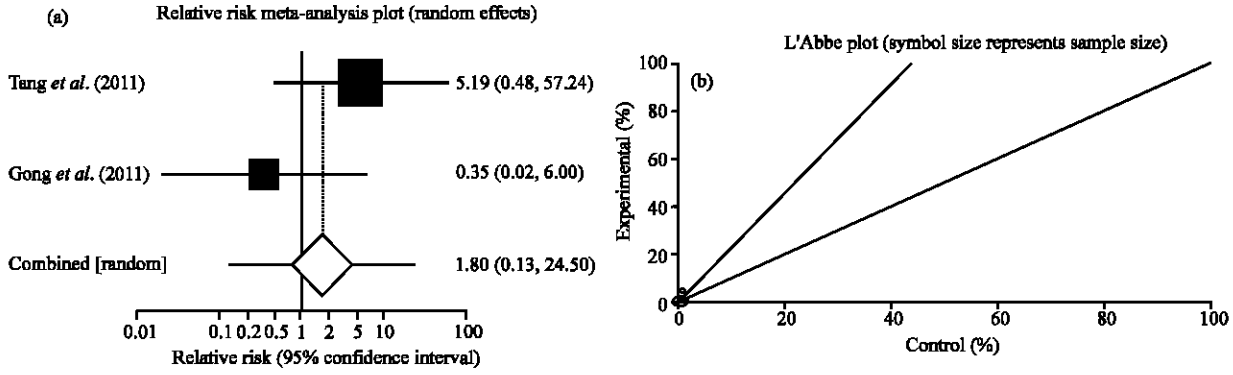


Fig. 12(a-b): (a) Individual and pooled relative risk for the outcome of "serious adverse events" in the studies considering herbal medicines comparing to 5-ASAs therapy in IBD patients and (b) Heterogeneity indicators for the outcome "serious adverse events" in the studies considering herbal medicines comparing to 5-ASAs therapy in IBD patients

containing different plants administered to patients with various subtypes of IBD, the trials were disaggregated. Thus, sub-analyses based on type of IBD and plant type were performed. The results of sub-analyses based on

IBD type showed that there is no significant difference between herbal medicines and 5-ASAs in inducing or maintaining efficacy in UC and chronic colitis. But inducing clinical response and remission by herbal medicines in patients with intractable colitis was significant compared to that of 5-ASAs. The sub-analysis based on type of herbal medicine conducted on 4 groups: *Andrographis paniculata*, *Boswellia serrata*, *Plantago ovata* and Traditional Chinese Medicine (TCM). TCM showed significant effect in induction of clinical response, clinical remission and endoscopic response in comparison with 5-ASAs. Other three groups did not show significant difference compared to 5-ASAs in any investigated outcomes.

CONCLUSION

Overall, it seems that efficacy and tolerability of herbal medicines in IBD is comparable to 5-ASAs, but the evidence is too limited to make any confident conclusions. Further high quality, large controlled trials are warranted to better conclusion.

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